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PEOPLE

CU Cancer Center

Dan Theodorescu, MD, PhD, started his position as director of the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles, CA, on July 1. He previously served as director of the University of Colorado Cancer Center in Aurora, where he was also a professor of surgery and pharmacology. Theodorescu is the founding co-editor-in-chief of *Bladder Cancer* and is a member of the editorial board of *Cancer Research*. In addition, he serves on the National Cancer Policy Forum of the National Academies. Theodorescu has studied the molecular mechanisms underlying bladder cancer, discovering genes that regulate tumor growth and metastasis.

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With Theodorescu's departure, **Richard Schulick, MD, MBA,** became director of the University of Colorado Cancer Center on July 1. He will continue to serve as the chair of the department of surgery at the University of Colorado School of Medicine. Previously, he was chief of the division of surgical oncology; a professor of surgery, oncology, and obstetrics and gynecology; and director of the pancreas cancer program at Johns Hopkins University in Baltimore, MD. Schulick has authored more than 300 publications and is the principal investigator on several clinical trials.

Pembrolizumab OK'd for Cervical Cancer

In June, the FDA approved the PD-1 inhibitor pembrolizumab (Keytruda; Merck) as a second-line treatment for patients with recurrent or metastatic cervical cancer whose tumors express PD-L1. It's the first such drug approved for a gynecologic cancer.

The FDA concurrently approved the PD-L1 IHC 22C3 pharmDx Kit (Dako) as a companion diagnostic.

Currently, patients with advanced cervical cancer receive chemotherapy, often in combination with bevacizumab (Avastin; Genentech), says Charles Drescher, MD, of Fred Hutchinson Cancer Research Center in Seattle, WA. However, few patients are cured by first-line treatment, and second-line options have been a "potpourri of dealer's choice of modestly active drugs," he says.

"Fortunately, in the U.S., cervical cancer is not a particularly common disease, and metastatic disease is even less common," he says, but a better second-line treatment option "is an urgent need for the population—there really are no [effective] alternatives."

Pembrolizumab was approved based on results of the ongoing phase II KEYNOTE-158 trial, a basket trial testing its activity in 11 types of advanced solid tumors. In the cervical cancer arm, 77 of 98 patients expressed PD-L1 with a combined positive score of at least 1 (the ratio of the number of PD-L1–expressing tumor and infiltrating immune cells to the total number of tumor cells). Patients were treated with the drug after chemotherapy and had an objective response rate (ORR) of 14.3%, with 11.7% partial responses and 2.6% complete responses. Of the patients who responded, 10 of 11 responded for at least 6 months.

"It's a whole new option that we just didn't have [before]," Drescher says, adding that because pembrolizumab is already approved for so many other indications, "its toxicity profile is well known, it's not hard to deliver, and it's available most anywhere, so I think that it'll be very rapid clinical uptake."

For Krishnansu Tewari, MD, of the University of California, Irvine, in Orange, who, on behalf of the NCI-sponsored Gynecologic Oncology Group, ran the trial that led to bevacizumab's approval in 2014, any option for patients at high risk for progression and death "is a good thing."

However, he notes that he is not overly impressed with the ORR and points out that although most women with squamous cervical cancer express PD-L1, that isn't necessarily true for patients with other histologies, such as adenocarcinoma.

"To an extent, it will change practice because we have nothing else, but we need to do better," he says, adding that researchers are exploring other options.

For example, the AIM2CERV study is evaluating the use of maintenance axalimogene filolisbac (ADXS11-001; Advaxis), a *Listeria*-based immunotherapy, following first-line therapy, and Iovance Biotherapeutics is conducting a phase II trial of LN-145, an adoptive T-cell therapy with autologous tumor-infiltrating lymphocytes. Additionally, Genentech is running clinical trials on its PD-L1 inhibitor atezolizumab (Tecentriq).

Other clinical trials are investigating combination therapy for cervical cancer, including pembrolizumab plus chemotherapy and radiation, and AstraZeneca's durvalumab (Imfinzi) plus tremelimumab and radiation.

"When the Gynecologic Oncology Group did the [bevacizumab] study, no one was doing any work in the cervix cancer field, and now there's probably 10 different studies going on," Tewari says. "Hopefully one of these new treatments will be even more effective." –*Catherine Caruso* ■

LOXO-292 Reins In RET-Driven Tumors

A selective and potent RET inhibitor, LOXO-292 (Loxo Oncology), is showing early signs of efficacy, yielding responses across a range of *RET* alterations and tumor types, and a favorable safety profile, according to interim phase I data presented on June 2 at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL (J Clin Oncol 36, 2018 [suppl; abstr 102]).

"It's very exciting to see a drug like this that's not only active but also highly tolerable," said lead trial investigator Alexander Drilon, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who made the presentation. "It really lends itself to prolonged dosing, especially considering that these patients can have long-term benefit with this treatment."

Gene fusions involving *RET* occur in approximately 10% of papillary thyroid cancers (PTC), 2% of non–small

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cell lung cancers (NSCLC), and a small fraction of other malignancies, whereas activating point mutations in *RET* are found in some 60% of medullary thyroid cancers (MTC), including hereditary and sporadic cases alike.

Several multikinase inhibitors with some activity against RET have been tried in these patients, with limited effect. Response rates tend to be low and off-target toxicities high, leading to a push to develop safer, more potent RET blockers.

Enter LOXO-292, "a purpose-built inhibitor of RET and nothing else," as Loxo CEO Josh Bilenker, MD, described it. "It can deeply inhibit the pathway as opposed to lightly tickle it, as a lot of repurposed drugs have been doing."

In April, Drilon and his colleagues reported on the first two patients to receive the drug; in each case, the *RET*-altered tumors regressed on LOXO-292 despite having received multiple prior therapies (Ann Oncol 2018 Apr 18 [Epub ahead of print]). The researchers also showed, in both cell lines and mouse models, that LOXO-292 has preclinical activity against various *RET* alterations, resistance mutations, and brain metastases.

At the ASCO meeting, Drilon provided a more detailed clinical picture of LOXO-292, offering data from the phase I trial for 61 response-evaluable patients with *RET*-altered cancers. For the 30 patients with *RET* fusion–positive NSCLC, tumor regression occurred regardless of *RET*'s fusion partner, with an overall response rate (ORR) of 77% and another 13% experiencing stable disease. Among other patients with *RET* fusions, all seven with PTC responded and both patients with pancreatic cancer had stable disease. In the *RET*-mutant MTC cohort, the ORR in 22 patients was 45%, with another 41% experiencing stable disease. Only two patients experienced serious adverse events, and the other side effects were mostly benign and infrequent.

Notably, at the time of data analysis, more than 90% of the trial participants remained on therapy—an indicator that "disease control was durable in many cases," Drilon said.

The data for LOXO-292 compare favorably to interim phase I results for another early clinical-stage *RET*-targeted agent, BLU-667 (Blueprint Medicines). As reported at the American Association for Cancer Research Annual Meeting 2018 in April, that drug was well tolerated, with a 50% ORR among patients with NSCLC and a 40% ORR among those with MTC.

"Both of these drugs look like they're very promising," said Justin Gainor, MD, of Massachusetts General Hospital in Boston, MA, who has been involved in testing both agents. "We are seeing higher response rates than what we've seen with the multikinase inhibitors, and it does look like the toxicity profiles are more favorable." *–Elie Dolgin* ■

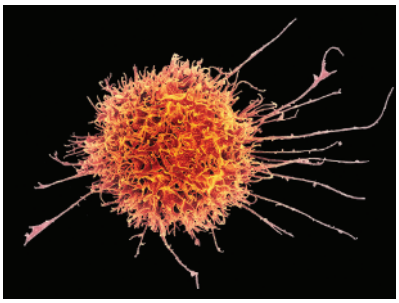
Antibiotics Protect against Liver Tumors in Mice

Researchers have known for some time that the gut microbiome affects tumor development in the liver. Recently, scientists uncovered the first compelling explanation for this phenomenon. By treating mice with antibiotics, they showed that depleting commensal bacteria enhances certain primary bile acids in the liver (Science 2018;360:eaan5931). This change signals natural killer T (NKT) cells to accumulate there, inhibiting tumors.

"Most studies on the microbiome and cancer are based on correlations," says Tim Greten, MD, of the NIH, senior author of the article. "Here we show a clear mechanism for how commensal bacteria use bile acids as a messenger to regulate natural killer T cells in the liver."

Investigators found that the protective effects of antibiotic treatment—a "cocktail" of vancomycin, neomycin, and primaxin—were similar in mouse models of primary hepatocellular carcinoma (HCC) and mouse models of liver metastasis from melanomas, lymphomas, or thymomas. "The effect is completely independent of the tumor type," says Greten. "The genetics are irrelevant."

What mattered was the location of the tumor. Antibiotics protected against liver tumors—both primary and metastatic—but they did not protect against tumor formation elsewhere in the body. For example, antibiotics did not slow the growth of subcutaneous tumors in mice. Further, lung metastases increased in treated mice after they were injected with melanoma or lymphoma cells. Christian Jobin, PhD, of the University of Florida in Gainesville, says that the fact that the rate of lung metastasis was not reduced "really highlights the specific impact of microbes on carcinogenesis."



NIAID

Using antibiotics to reduce commensal bacteria increases primary bile acids in the liver. The bile acids signal natural killer T cells (above) to accumulate there and attack tumors.

The researchers found that after antibiotics depleted commensal bacteria from the gut microbiome in mice, levels of some secondary bile acids, such as ω-MCA, in the liver fell. This relieved inhibition of the cytokine CXCL16, a potent recruiter of NKT cells. At the same time, levels of certain primary bile acids that were shown to induce CXCL16, such as T-β-MCA, increased. This resulted in the accumulation of hepatic NKT cells and a reduction in liver tumors. Consistent with this bile-mediated mechanism, when mice were treated with antibiotics for just a week and subsequently inoculated with *Clostridium scindens*, a commensal bacterium that produces secondary bile acids, the protective effect against liver tumors disappeared.

Eiji Hara, PhD, of Osaka University in Japan, says that previous research in mice had established that secondary bile acids can promote liver cancer by damaging DNA, but the idea that they can also cause cancer by preventing NKT cells from accumulating in the liver is new. Moreover, he says that the opposing roles of primary and secondary bile acids demonstrated in the study is both novel and surprising.

Greten says that the next step is to investigate how these findings apply to humans. In the current study, his team demonstrated that certain primary bile acids correlated with CXCL16 expression in tumor-free liver tissue from patients with HCC or cholangiocarcinoma, whereas certain secondary bile acid levels were inversely correlated with the cytokine, as in mice. Now they are

AACR American Association for Cancer Research

CANCER DISCOVERY

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