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versa. "It's why we think this is an independent, interesting target," Chen added. A drug that alleviates Siglec-15–driven immunosuppression could be viable in patients who, with low or no PD-L1 expression, would not benefit from current checkpoint blockade.

Buoyed by preclinical results, Chen has been developing a Siglec-15 antibody, NC318, with Beltsville, MD–based biotech NextCure, for which he is the scientific founder. Preliminary findings from a phase I study of NC318 were highlighted during the Society for Immunotherapy of Cancer 2019 Annual Meeting in National Harbor, MD. Anthony Tolcher, MD, of NEXT Oncology in San Antonio, TX, reported that among 49 patients with a variety of tumor types, including non–small cell lung cancer (NSCLC), NC318 was safe and well tolerated. The main side effects were diarrhea and asymptomatic amylase and lipase elevations. Several cases of vitiligo—"considered a marker of immune activation," Tolcher said—were also observed.

Efficacy isn't always seen in phase I trials, but two patients with NSCLC responded to NC318—one completely, the other partially. Both had received prior chemotherapy and PD-1 blockade, to which the best response was stable disease that then progressed. Noting that they had low levels of PD-L1, Tolcher agreed that NC318 could become a valuable therapy for this subset of patients, "where there's a great unmet need" once disease progression occurs on standard treatment. Patients with several other tumor types experienced stable disease lasting at least 6 months.

Based on this early but encouraging efficacy, NC318 is undergoing phase II evaluation for NSCLC, as well as ovarian, head and neck, and triple-negative breast cancers. Chen hopes the data will hold up and pave the way for additional Siglec-15–targeted agents, potentially mirroring anti–PD-1 therapy's success.

"Some recent prospective drugs have been more about boosting systemic immune responses to higher levels, which could result in unwanted issues," he pointed out. Rather, "we believe normalizing defective immunity in the TME is something that can be done much more precisely, with minimal damage on the side." *–Alissa Poh* ■

## Bempegaldesleukin Ups Melanoma Responses

Preliminary findings of a phase I/II trial suggest that adding bempegaldesleukin (NKTR-214; Nektar Therapeutics) to the PD-1 checkpoint inhibitor nivolumab (Opdivo; Bristol-Myers Squibb) may lead to high overall and complete response rates, with relatively few side effects.

The data were presented by Adi Diab, MD, of The University of Texas MD Anderson Cancer Center in Houston, at the Society for Immunotherapy of Cancer (SITC) 2019 Annual Meeting in National Harbor, MD, in November.

Bempegaldesleukin is a CD122-preferential IL2-pathway agonist. In preclinical studies, it increased tumor-infiltrating lymphocytes, T-cell clonality, and PD-1 expression—and expanded and activated CD8+ T cells and natural killer (NK) cells—leading researchers to hypothesize that it might improve responses to a PD-1 inhibitor. "It is likely a synergistic mechanism" in which bempegaldesleukin and nivolumab "activate the T cells in somewhat distinct but complementary ways," says Douglas Johnson, MD, of Vanderbilt-Ingram Cancer Center in Nashville, TN, who was not involved in the trial.

The PIVOT-02 trial is testing bempegaldesleukin plus nivolumab in solid tumors. At SITC, researchers reported on 38 evaluable patients with newly diagnosed metastatic melanoma. After 18.6 months of follow-up, the combination had elicited responses in 20 patients, including 13 complete responses; median progression-free survival had not been reached. In total, 17.1% of patients experienced grade 3 or 4 adverse events, most commonly acute kidney injury or atrial fibrillation; 12.2% of patients discontinued one of the drugs due to side effects.

"It is very promising activity in terms of high response rates, high complete response rates, early signs of durable responses, and excellent progression-free survival," Johnson says. However, he adds that the results should be interpreted with caution given the study's small size.

Moreover, he emphasizes that immune checkpoint inhibitor monotherapy is associated with response rates of up to 40% to 45% in metastatic melanoma, so it is not clear how much bempegaldesleukin improves responses. "The gold standard is going to be randomized data comparing to nivolumab alone. That's really the only way to truly determine whether the combination is adding something over nivolumab monotherapy," he says.

Ryan Sullivan, MD, of Massachusetts General Hospital in Boston, who was also not involved in the trial, agrees. "I do think it's encouraging; I just think it's not game changing" without results from a larger, randomized trial, he says. He notes, however, that the combination is well tolerated compared with historical data on nivolumab monotherapy. "We're seeing clearly that there doesn't appear to be worse toxicity, and there may be some attenuation of the toxicity."

A phase III trial is now comparing the combination with nivolumab in melanoma; other trials will test bempegaldesleukin in other combinations and tumor types. In particular, Johnson and Sullivan want to know whether bempegaldesleukin, either alone or in combination with nivolumab, is active in patients who develop resistance to immune checkpoint inhibitors. The agent may be effective in these patients, Sullivan explains, because it increases NK cells, which selectively attack cells that have lost MHC class I—a common state in resistant cells.

If the combination demonstrates effectiveness, clinicians would have another therapeutic option, one that may lead to more individualized treatment. Eventually, Johnson says, he hopes that researchers can identify biomarkers, and use them to match patients with treatment regimens. "We're certainly not to that point yet," he says, "but you can envision if you have another therapy like this, you can start to refine which patient populations need which therapies." *–Catherine Caruso* ■

## Cancer Collaboration Aims to Boost Detection

Cancer Research UK (CRUK) has launched a collaboration among three institutions in the UK and two in the United States to improve early cancer detection.

Announced in October, the International Alliance for Cancer Early Detection (ACED) includes the UK's

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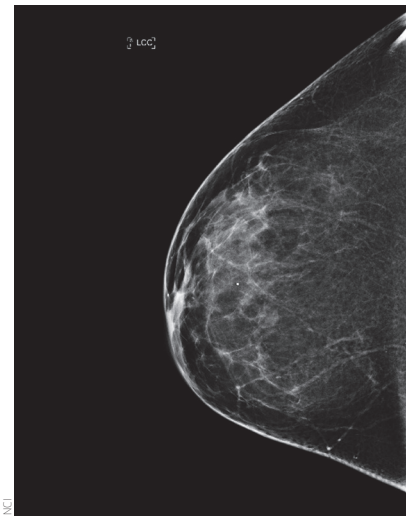


Routine mammography can uncover breast cancer at an early stage, but early-detection tests don't exist for many types of cancer. The International Alliance for Cancer Early Detection will help researchers develop technologies to spot other cancers at an early stage.

University of Cambridge, the University of Manchester, and University College London, which won a competition to join the partnership. The two U.S. institutions—the Canary Center at Stanford University in California and the Knight Cancer Institute at the Oregon Health and Science University (OHSU) in Portland—have long-standing programs focused on early detection, says Sanjiv Gambhir, MD, PhD, head of the Canary Center. CRUK will provide almost $52 million (£40 million) over the next 5 years, and the two U.S. centers could each add up to $10 million more.

Although screening is routine for a few types of cancer, such as colon and cervical cancers, there are no early-detection tests for many malignancies. One reason: Research on later stages of disease has traditionally received the lion's share of funding and attention, notes Robert Bristow, MD, PhD, who leads the ACED effort at the University of Manchester. Other obstacles have slowed early detection attempts, he says. For example, the people most likely to develop cancer are older, but they often have comorbidities that can make it difficult to determine whether a biomarker, such as inflammation, indicates cancer or another condition, he says.

Improving early detection would have a significant impact on patient survival. As CRUK notes, patients diagnosed with a stage I tumor are three times more likely to live for 5 years than patients whose cancers are discovered at stage IV. Early detection is "where the big wins will be," says Gambhir.

The ACED "is the first effort at this scale," says Sadik Esener, PhD, who heads the program at OHSU. The collaboration will enable researchers at the different institutions to jointly develop and test new technologies and approaches for early diagnosis. These technologies could include artificial intelligence and machine learning, microfluidics, imaging, and robotics.

Esener says that the partnership will allow researchers to tackle what he calls "the biggest problem" in the field. "In order to do research in early detection, you need very large cohorts of people." By promoting collaboration, the ACED will enable researchers at one institution who have devised a promising technology or discovered a potential biomarker to more easily recruit enough patients to validate it, he says.

Another possible benefit, says Bristow, is that the research may lead to more precise screening. Widespread screening can lead to overdiagnosis and worry people who are not at high risk. Through the ACED's work, scientists may discover biomarkers that pinpoint the patients most likely to develop particular cancers.

Alliance researchers haven't chosen which cancers to target first, says Gambhir. And although a few new detection methods could be available within a few years, he adds, the project is a long-term effort. "I hope the alliance will be around for decades, as early cancer detection is a very challenging problem to solve." –*Mitch Leslie* ■

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.

## NOTED

**Bristol-Myers Squibb completed its acquisition of Celgene.** The $74 billion deal was finalized after the companies won U.S. antitrust approval for their merger, with the understanding that Amgen would purchase Celgene's psoriasis drug apremilast (Otezla) for $13.4 billion.

**AbbVie signed a deal with Harpoon Therapeutics worth up to $2.4 billion.** The deal, which expands their existing partnership, allows AbbVie to license Harpoon's BCMA-targeting agent, HPN21, and up to six more targets.

**The FDA granted accelerated approval to zanubrutinib** (Brukinsa; BeiGene) to treat patients with mantle cell lymphoma who have received prior therapy. The approval was based on two single-arm studies in which the drug elicited an overall response rate of 84%. A Bruton tyrosine kinase inhibitor, zanubrutinib is the first drug developed in China to be approved by the FDA.

In the phase III POSIEDON trial, which included patients newly diagnosed with metastatic non–small cell lung cancer, AstraZeneca's PD-L1 inhibitor **durvalumab (Imfinzi) plus chemotherapy significantly prolonged progression-free survival** (PFS) compared with chemotherapy alone. A PFS benefit was also seen for durvalumab plus the CTLA4 inhibitor tremelimumab (AstraZeneca) and chemotherapy versus chemotherapy alone.

In its State of Lung Cancer report, The American Lung Association announced that **the 5-year survival rate in lung cancer has improved over the past decade,** from 17.2% to 21.7% (available at http://www.lung.org/). Per the report, more than 228,000 people will be diagnosed with lung cancer in 2019; Kentucky has the highest rate of disease, and Utah has the lowest.

**U.S. patients with cancer may have an elevated risk of dying from cardiovascular disease** (Eur Heart J 2019;0:1–9). Researchers compared 3.2 million patients diagnosed with cancer between 1973 and 2012 with the general population and found that patients diagnosed with cancer before age 55 were more than 10 times more likely to die from cardiovascular disease.

AACR American Association for Cancer Research

CANCER DISCOVERY

# Cancer Collaboration Aims to Boost Detection

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