Nanda noted that “the degree of PD-L1 positivity and response [to pembrolizumab] didn’t appear to correlate, so PD-L1 alone may not be the most appropriate biomarker.” Research is under way to investigate the relationship between outcome and PD-L2 expression, and a phase II trial to further evaluate pembrolizumab in TNBC will begin enrolling patients in the first half of 2015.

“This was a small study,” said Eric Winer, MD, director of Dana-Farber Cancer Institute’s Breast Oncology Center in Boston, MA, “but the fact that a handful of patients responded durably to pembrolizumab is a signal suggesting, ‘Look into this further,’ which is where the next study, and the one after that, should go.”

**Somatic Mutations May Predict Blood Cancers**

Two teams of researchers independently discovered that somatic mutations in the DNA of peripheral blood cells associate with an individual’s risk of developing hematologic cancers later in life.

In both studies, researchers conducted whole-exome sequencing of DNA in blood samples taken from individuals not known to have cancer or blood disorders. They found that more than 10% of individuals over age 70 carried somatic mutations common in hematologic cancers, resulting in an overall 5% risk of a cancer diagnosis within 5 to 10 years. Most of the mutations occurred in three genes recognized as drivers of blood cancers: *DNMT3A*, *ASXL1*, and *TET2*.

One study, led by Siddhartha Jaiswal, MD, PhD, clinical fellow at Massachusetts General Hospital in Boston, analyzed more than 17,000 DNA samples from patients enrolled in type 2 diabetes and heart disease studies to determine whether it is possible to detect early somatic mutations that may initiate hematologic cancers (N Engl J Med 2014;371:2477–87).

After realizing that somatic mutations were concentrated in cancer genes, Genovese’s team examined patients’ medical histories and found that those with the mutations had a higher risk of blood cancer than healthy controls. They detected the somatic mutations in 42% of study participants who were diagnosed with a blood cancer more than 6 months after the DNA samples were taken.

Researchers emphasize that it is premature to screen otherwise healthy people for premalignant somatic mutations, because the absolute risk of progressing to cancer is very low, and there is no way to prevent the development of cancer. However, the studies may have immediate implications for cancer diagnostics.

“When you suspect someone might have a malignancy like myelodysplastic syndrome, screening for these mutations can have negative predictive value,” says Jaiswal. “However, the

The findings corroborate earlier studies in mouse models, he says, which show that loss of *TET2* or *DNMT3A* results in an increase in blood stem cells and a selective growth advantage.

After a median follow-up period of 8 years, Jaiswal’s group assessed DNA samples and found that carrying a mutation was also associated with all-cause mortality.

“We found that individuals with mutations were about 40% more likely to die in the follow-up period, and the causes extended beyond cancer to cardiovascular disease,” says Jaiswal. “When we looked deeper, we found that people with the mutations were 2 to 2.5 times more likely to have cardiovascular events than people without the mutations.”

A second study, led by Giulio Genovese, PhD, a computational biologist at the Broad Institute of MIT and Harvard in Cambridge, MA, set out to examine somatic mutations that may contribute to risk for schizophrenia using a database of DNA samples from more than 12,000 people, about half of whom had schizophrenia or bipolar disorder; the rest served as controls (N Engl J Med 2014;371:2477–87).

After realizing that somatic mutations were concentrated in cancer genes, Genovese’s team examined patients’ medical histories and found that those with the mutations had a higher risk of blood cancer than healthy controls. They detected the somatic mutations in 42% of study participants who were diagnosed with a blood cancer more than 6 months after the DNA samples were taken.

Researchers emphasize that it is premature to screen otherwise healthy people for premalignant somatic mutations, because the absolute risk of progressing to cancer is very low, and there is no way to prevent the development of cancer. However, the studies may have immediate implications for cancer diagnostics.

“When you suspect someone might have a malignancy like myelodysplastic syndrome, screening for these mutations can have negative predictive value,” says Jaiswal. “However, the
Drug Combo Beneficial in Colorectal Cancer

The BRAF V600E mutation, well documented in melanoma, is also present in approximately 8% of patients with colorectal cancer. However, whereas BRAF inhibitors like vemurafenib (Zelboraf; Genentech) are highly effective for the treatment of melanoma, their benefit as monotherapy in BRAF-mutant colorectal cancer is limited at best.

“This type of metastatic colorectal cancer has a very poor prognosis compared to BRAF-wild-type disease,” says Josep Tabernero, MD, PhD, director of the Vall d’Hebron Institute of Oncology in Barcelona, Spain.

At the recent 2014 Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, sponsored by the European Organization for Research and Treatment of Cancer, the NCI, and the American Association for Cancer Research, Tabernero presented data from a multicenter phase I study in which patients were treated with a combination of encorafenib (LGX818; Novartis), an investigational BRAF inhibitor, and the EGFR inhibitor cetuximab (Erbitux; Bristol-Myers Squibb). The researchers also tested a combination of encorafenib, cetuximab, and a third drug, alpelisib (BYL719; Novartis), an investigational PI3K inhibitor.

The decision to target BRAF and EGFR simultaneously was spurred by research showing that BRAF inhibition in colorectal cancer cell lines leads to rapid feedback activation of EGFR, resulting in constitutive signaling through the MAPK-ERK pathway and continued tumor cell proliferation. “This finding could explain the limited efficacy of BRAF inhibitor monotherapy in these patients,” Tabernero says.

In addition, “according to TCGA [The Cancer Genome Atlas] data, the PI3K pathway is dysregulated in roughly 30% of cases, so we decided to add alpelisib to the combination.”

Fifty-four patients with BRAF-mutant colorectal cancer enrolled in the study; 26 received encorafenib and cetuximab, and 28 received encorafenib, cetuximab, and alpelisib. The objective response rates for the two-and three-drug combinations were 23% and 32%, respectively. The median progression-free survival (PFS) was 3.7 months for patients on dual therapy and 4.3 months for those given the trio. Although not directly compared in this study, Tabernero notes that these PFS times are almost double those seen with standard therapy. The dual therapy’s main adverse effects included fatigue and infusion reactions; adding alpelisib also caused nausea and diarrhea.

So far, the study’s findings “suggest that PI3K activation may not play a clinically significant role,” Tabernero says. However, he adds, these are only preliminary efficacy data, and the question of PI3K’s significance remains to be definitively resolved.

The trial is now enrolling patients into a phase II expansion cohort. Investigators are also collecting tumor and blood samples from patients before and after treatment to assess the drugs’ pharmacodynamic effects, while a comprehensive genomic analysis is under way to potentially identify predictive biomarkers.

“We’re encouraged by what we’ve found so far,” Tabernero says. “This study is an example of how understanding tumor biology is highly relevant when it comes to improving therapeutic strategies.”

PD-1 Inhibitors Effective in Hodgkin Lymphoma

Two immunotherapy drugs are showing promise for treating patients with Hodgkin lymphoma (HL) who failed to respond to other therapies, according to results from phase I trials presented at the annual meeting of the American Society of Hematology in San Francisco, CA, in December.

Both studies tested programmed death 1 (PD-1) inhibitors in patients with classic HL. In one trial of 23 patients who received nivolumab (Opdivo; Bristol-Myers Squibb), the objective response rate was 87%, with 17% achieving a complete response and 70% a partial response; the remaining 13% had stable disease (N Engl J Med 2014 December 6 [Epub ahead of print]). In another trial of 29 patients treated with pembrolizumab (Keytruda; Merck), the overall response rate was 66%, with 21% achieving a complete response and 45% a partial response after 12 weeks (available at https://ash.confex.com/ash/2014/webprogram/Paper75615.html).

About half of the responses seen in the nivolumab trial occurred within 8 weeks of starting treatment, says Philippe Armand, MD, PhD, an oncologist at Dana-Farber Cancer Institute in Boston, MA, and senior author of the study. While the median overall survival had not yet been reached, 48% of patients were still in remission at the time the data were analyzed, some for over a year.

“Most patients have had ongoing responses but it’s too early to get a sense of durable responses,” says Armand. “At the time of data lock, one patient was still in complete remission without any further treatment, but we still don’t know how long the effects will last or whether you can stop the drug at some point.”

Based on the study results, the FDA designated nivolumab as a breakthrough therapy for HL, and a large phase II study is under way. In December, the drug received FDA approval for inoperable or advanced melanoma.

In the pembrolizumab trial, some patients who did not achieve complete or partial response experienced stable disease, notes first author Craig Moskowitz, MD, clinical director of the Division of Hematologic Oncology at Memorial Sloan Kettering Cancer Center in New York, NY. Twenty of the 29 patients are still undergoing treatment.

“Almost all patients had evidence of tumor shrinkage,” says Moskowitz. “Including patients with stable disease, we saw a clinical benefit rate of 86%.”

Classic HL frequently harbors amplification of chromosome 9p24.1 that leads to increased expression of PD-L1 and PD-L2, which then engage the PD-1 receptor to temporarily shut down the immune response, says Armand.
Somatic Mutations May Predict Blood Cancers


Updated version

Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2015-001

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/5/2/101. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.