presence of a mutation alone is not sufficient to make a cancer diagnosis in the absence of other clinical data. If there is no detectable mutation, it's much more likely that the person does not actually have a malignancy." ■

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.

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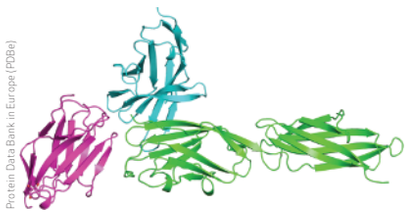

Crystal structure of the PD-1/PD-L1 complex.

"When we analyzed 10 patient biopsies," says Armand, "all of the tumors had this genetic amplification and increased expression of ligands PD-L1 and PD-L2, which seems to be the basis for vulnerability to PD-1 blockade in these patients."

Pembrolizumab has been approved for metastatic melanoma and has shown promise for treating other cancers.

Overall, the results suggest that PD-1 inhibitors should be tested in patients with other types of lymphoma, such as large cell lymphoma, says Moskowitz.

"The safety profile of these drugs is quite good, with very little grade 3 or 4 toxicity," he says. "Our results should encourage continued research with PD-1 inhibitors for a variety of patients with HL." ■

Blinatumomab Knocks Out Residual Disease

A novel immunotherapeutic given to adults with acute lymphoblastic leukemia (ALL) before relapse showed promising results in a phase II trial presented in December at the American Society of Hematology Annual Meeting in San Francisco, CA.

The trial assessed Amgen's blinatumomab (Blincyto), a bispecific T-cell engager that directs T cells to kill malignant B cells. The agent was approved in December to treat relapsed or refractory Philadelphia chromosome–negative precursor B-cell ALL.

Researchers wanted to see if the drug would also be effective in treating patients who are in remission but have trace amounts of disease in their bone marrow, putting them at high risk for disease recurrence.

The 113 trial participants were deemed to be at high risk for recurrence based on a PCR test that detected a small amount of residual disease. (Conventional cytology is typically used to examine bone marrow smears.)

The participants received continual infusion of blinatumomab for 4 weeks, followed by a 2-week break. Responders could receive up to four cycles of treatment or have a stem cell transplant after the first cycle. At the end of the trial, no minimal residual disease was detected in 78% of participants.

"If positive long-term results are confirmed, [blinatumomab] may really change the standard of care of ALL in the future," says first author Nicola Gökbuget, MD, coordinator of the German ALL study group and an investigator at the University Hospital Frankfurt, Germany.

Most side effects—mild to moderate flu-like symptoms—related to the activation of the immune system, although some patients had neurologic symptoms. Two patients died during the trial.

It appears that the drug "tips the balance in favor of the immune system over the tumor cell," says Catherine Bollard, MD, a professor of pediatrics at George Washington University, who moderated the press conference at which the trial results were presented.

Bollard says she was surprised by the drug's effectiveness as a single agent, but that it makes sense in the context of what scientists are learning about the relationship between cancer and the immune system. Cancer needs many different strategies to override the immune system, she says, but blocking any one of them may be enough to give the immune system the advantage.

Gökbuget says the first part of the trial was very promising, but she's restraining her enthusiasm until after follow up. "We want to see whether the achievement of a molecular response will result in a better long-term outcome," she explains.

Researchers will also need to confirm the effectiveness of PCR detection before applying for federal approval to prescribe the drug this way, Gökbuget says. ■

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

NOTED

- The U.S. Congress reached a deal on a $1.013 trillion budget package to fund the federal government through September 2015. **The budget includes an increase of just $150 million (0.5%) for NIH over fiscal year 2014,** to $30.084 billion, and an increase of just $27 million (0.54%) for NCI, to $4.950 billion, amounts that do not keep pace with inflation.
- **The FDA approved Gardasil 9** (Merck), a vaccine for the prevention of certain diseases caused by nine types of human papillomavirus (HPV), five more than Gardasil. Approved for use in females ages 9 through 26 and males ages 9 through 15, Gardasil 9 has the potential to prevent approximately 90% of cervical, vulvar, vaginal, and anal cancers.
- **The FDA also approved ramucirumab (Cyramza; Eli Lilly) to treat patients with metastatic non–small cell lung cancer** whose tumor has progressed during or after treatment with platinum-based chemotherapy. The drug was first approved in 2014 to treat patients with advanced stomach cancer or gastroesophageal junction adenocarcinoma.
- The American Cancer Society's annual cancer statistics report finds that **a 22% drop in cancer mortality over two decades led to the avoidance of more than 1.5 million cancer deaths** that would have occurred if peak rates persisted (CA Cancer J Clin 2015 January 5 [Epub ahead of print]). While cancer death rates have declined in every state, the report finds substantial variation in the magnitude of these declines from state to state.
- **An FDA advisory panel unanimously recommended approval of the investigational biosimilar filgrastim** (Sandoz) for all of the same indications as its reference product, Neupogen (Amgen), a granulocyte colony-stimulating factor analog used in cancer treatment. This is the first time that a generic biologic drug has been recommended for approval.
- In an updated policy statement, **the American Society of Clinical Oncology called for greater access to and education about phase I clinical trials** (J Clin Oncol 2014 December 15 [Epub ahead of print]). Barriers to clinical trial participation, such as the lack of insurance coverage for routine care in clinical trials, should be addressed, according to the statement.

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