

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 (Erbix; 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.