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tumor lysis syndrome—metabolic abnormalities that can occur when dying cells release their contents into the bloodstream—patients received venetoclax in a stepwise dosing schedule. "The goal was 400 mg, but we were already seeing tumor-cell destruction when we started with 20 mg," Stilgenbauer said. "This highlights venetoclax's dramatic efficacy; there aren't many other therapeutic agents that can achieve a response at only 5% of the target dose."

"These results will change the treatment landscape for a high-risk patient population," said Robert Hromas, MD, chair of medicine at the University of Florida in Gainesville. "It's an enormously exciting time to be working in the blood cancer field. When Rudolf Virchow coined the word 'leukemia' 150 years ago, his principle was 'as the cell goes, so goes the disease, so goes the patient.' Today, it's really 'as the gene goes, so goes the cell, so goes the disease'—we have the ability to define and selectively target molecular defects, and I think that, for the first time, we can begin talking about curing CLL."

Andrew Zelenetz, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, noted the "completely different, accelerated pace" of drug approvals for CLL, with four therapies in the last 2 years: obinutuzumab (Gazyva; Genentech), ofatumumab (Arzerra; GlaxoSmithKline), ibrutinib (Imbruvica; Pharmacyclics/Janssen), and idelalisib (Zydelig; Gilead Sciences). Venetoclax has been designated a Breakthrough Therapy by the FDA, and Zelenetz thinks it will "almost certainly be approved" in 2016.

"The challenge now will be figuring out how to use these therapies in novel, creative ways that reduce toxicity, shorten treatment durations, and ultimately eliminate this disease," he said. *–Alissa Poh* ■

Tracing Melanoma's Genetic Progression

The process by which some benign skin lesions, or nevi, transform into melanomas remains unclear. A new study illuminates the genetic evolution of melanoma and strengthens the case for a controversial category of intermediate lesions that are midway between nevi and melanomas [N Engl J Med 2015;373:1926–36].

In this study, Boris Bastian, MD, PhD, of the University of California, San Francisco, and colleagues analyzed 37 melanoma samples—each including malignant tissue and its precursor lesion—and identified 150 distinct areas that represented different stages of disease progression. They asked eight pathologists to independently classify these areas as benign, intermediate but likely benign, intermediate but likely malignant, or melanoma. Although the pathologists usually agreed on areas at the benign and melanoma ends of the spectrum, they often disagreed on areas that were in the middle.

To find out if these histologic categories carried different genetic alterations, the researchers sequenced 293 cancer-causing genes in the melanoma samples. They observed that lesions unanimously classified by the pathologists as benign had only one driver mutation, *BRAF* V600E. Mutations in *CDKN2A* and genes that encode members of the SWI/SNF complex, such as *ARID1A*, occurred later, followed by mutations in *TP53* and *PTEN*.

This analysis also shed light on whether intermediate lesions represent a separate category or whether they reflect the limitations of pathologists' ability to discriminate lesion types. Bastian and colleagues found that lesions classified by at least two pathologists as intermediate were genetically distinct. Unlike benign nevi, they carried *TERT* mutations and either *NRAS* mutations or the *BRAF* V600K alteration.

"Our study shows that there is something between benign and malignant," says Bastian, adding that testing for these mutations could provide a better way to distinguish such lesions. "It's a step toward an objective diagnosis of melanoma," he says.

Essentially, lesions can follow several pathways to become melanomas, the researchers propose. Alterations that activate the MAPK pathway—*BRAF* V600E, *BRAF* V600K, or *NRAS* mutations—are the earliest to emerge. *TERT* mutations then switch on telomerase and enable the lesions to escape replicative senescence. By the time lesions have progressed to invasive melanomas, they've accrued *CDKN2A* mutations that disable the G1-S cell-cycle checkpoint.

"I think this is a landmark paper for melanoma," says David Polsky, MD, PhD, of the New York University Langone Medical Center in New York City, who wasn't connected to the study. "Here, they show that there is an intermediate stage in tumor development."

"It adds to our knowledge of the molecular events that are occurring as some melanomas develop from nevi," says Douglas Grossman, MD, PhD, of the University of Utah Health Sciences Center in Salt Lake City.

However, before any of the mutations could be clinically useful, Grossman cautions, researchers need to determine which ones influence outcomes for patients. *–Mitch Leslie* ■

ESR1 Mutations Prevalent in Some Breast Cancers

Mutations in the estrogen receptor 1 (*ESR1*) gene are highly prevalent and associated with worse overall survival in women with advanced, metastatic estrogen receptor (ER)–positive breast cancer, according to data presented at the 2015 San Antonio Breast Cancer Symposium in Texas, held December 8–12. The results shed light on why some tumors resist hormonal therapy and may aid in developing more personalized treatments.

Researchers analyzed cell-free DNA in blood samples from 541 of the 724 women enrolled in the phase III BOLERO-2 trial. All of the participants were postmenopausal women with advanced, metastatic ER-positive breast cancer that had progressed after treatment with an aromatase inhibitor. In that trial, adding the mTOR inhibitor everolimus (Afinitor; Novartis) to the standard hormonal therapy exemestane improved overall survival (OS), leading to FDA approval of everolimus for this use in 2012.

In this new study, almost 30% of the blood samples from BOLERO-2 tested positive for the *ESR1* mutations D538G (15.3%), Y537S (7.8%), or both (5.5%); these mutations have been observed in animal models of the disease and are known to promote resistance to estrogen-deprivation therapy. In these patients, median OS

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