[human papillomavirus] vaccination would also reduce the number of females developing cervical cancer," says Songiso.

McCormack says that the WHO is providing a road map for governments to tackle the two most commonly fatal cancers in young women via its Cervical Cancer Elimination Initiative and the Global Breast Cancer Initiative. She adds that researchers have planned to follow the children of deceased women in the cohort of patients with breast cancer in Africa that prompted this study—to see how their lives have been affected compared with children whose mothers survived the disease. Another project will focus on the intergenerational impact of fathers' deaths from cancer.

"At younger ages, men have lower risks of death from cancer than women—[and at] ages when they might leave kids behind—but they can father children for much longer than women so it will be important to extend this work to paternal orphans," McCormack says. *–Aaron Tallent* ■

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BTK Inhibitor Options Expand for CLL/SLL

In a head-to-head comparison, zanubrutinib (Brukinsa; BeiGene), a second-generation covalent inhibitor of Bruton tyrosine kinase (BTK), outperformed ibrutinib (Imbruvica; Janssen/Pharmacyclics) in patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Findings from the phase III trial, ALPINE, were presented during the 2022 American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, LA, December 10–13.

Ibrutinib, the first drug in this class, "has been transformative" for CLL/SLL, observed lead investigator Jennifer Brown, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA. "However, it does have properties limiting its use, with up to 23% of patients discontinuing treatment due to toxicity."

Enter zanubrutinib, "designed with greater specificity for BTK," Brown said, as well as improved pharmacokinetics and pharmacodynamics "that should result in more sustained, complete inhibition, potentially increasing efficacy." In ALPINE, 652 patients were randomly assigned to receive 160 mg of zanubrutinib twice daily or 420 mg of ibrutinib once a day. An interim analysis, published in November, indicated a higher objective response rate with the newer agent—78.3% versus 65.5% (J Clin Oncol 2022 Nov 17 [Epub ahead of print]).

At ASH, Brown disclosed that the estimated 2-year progression-free survival (PFS) was 79.5% with zanubrutinib and 67.3% with ibrutinib. In a high-risk subgroup—patients who lack part of chromosome 17 (17p deletion), which contains *TP53*—the magnitude of PFS benefit, 77.6% versus 55.7%, "was quite remarkable," she said.

Patients with the 17p deletion generally respond well to the BCL2 inhibitor venetoclax (Venclexta; AbbVie/Genentech), but "they probably do even better with BTK inhibition, when we look at how long remission lasts," said John Byrd, MD, of the University of Cincinnati in Ohio. "There hasn't been a trial directly comparing both types of agents in this population, however."

Zanubrutinib had fewer side effects necessitating dose reductions or treatment discontinuation than ibrutinib, Brown reported. The rate of atrial fibrillation, a known ibrutinib toxicity, was lower with zanubrutinib, 5.2% versus 13.3%, "and whereas there were six fatal cardiac events in the ibrutinib arm, none occurred with zanubrutinib."

Zanubrutinib is currently indicated for Waldenström macroglobulinemia, mantle cell lymphoma, and marginal zone lymphoma. Besides a strong performance in ALPINE, it has also proven superior to chemoimmunotherapy as a first-line treatment in the SEQUOIA trial (Lancet Oncol 2022;23:1031–43). As such, "we hope its approval is imminent" for CLL/SLL, Brown noted. Meanwhile, the drug has joined its second-generation counterpart acalabrutinib (Calquence; AstraZeneca)—which is greenlighted by the FDA—as a preferred CLL/SLL therapy, according to recently revised National Comprehensive Cancer Network Guidelines.

"Ibrutinib was a great drug," Byrd remarked, "but both acalabrutinib and zanubrutinib are safer. I think my patients who are already on ibrutinib can continue treatment unless problems develop. For patients who haven't had a BTK inhibitor, however, I'll choose either of the newer drugs."

Meanwhile, BTK candidates continue to emerge. For instance, NX-2127 (Nurix Therapeutics), which degrades rather than suppresses BTK and has shown early phase I efficacy, was also reported on at ASH. Reversible inhibitors are on the way too: Nemtabrutinib (Merck) and pirtobrutinib (Loxo/Lilly) are being evaluated in the phase II BELLWAVE-001 and phase III BRUIN-CLL-314 trials, respectively. Such options will be key to countering disease progression, Byrd said, "because existing agents have an overlapping mechanism of action, so resistance to one likely means resistance to the others." *–Alissa Poh* ■

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Cardiac Antigen Implicated in ICI-Linked Myocarditis

Inflammation of the heart is a rare but serious drug-related toxicity associated with immune checkpoint inhibitors (ICI). Two independent studies have now found that autoreactive cytotoxic T cells directed against the cardiac muscle–specific antigen α-myosin underpin the life-threatening side effect.

The conclusions come mainly from mouse models, with supportive human data from just a few patients. But if they hold up to scrutiny, the findings could usher in new strategies to prevent or treat the condition, says Justin Balko, PharmD, PhD, of Vanderbilt University Medical Center in Nashville, TN, who co-led one of the studies with Javid Moslehi, MD, from the University of California, San Francisco.

For instance, a diagnostic test for autoantibodies against α-myosin could help predict which patients have an elevated risk for ICI-related myocarditis. Or a therapy that induces