However, there was no significant increase in overall survival with sotorasib. "It's not going to cure anyone," says Roy Herbst, MD, PhD, deputy director and chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital in New Haven, CT, who also noted that "it's incredibly expensive."

A 1-month supply of sotorasib costs about $20,000, whereas docetaxel runs just a few hundred dollars. Insurance companies generally cover the expense, but given that difference and the lack of a survival benefit, should sotorasib be prescribed?

Herbst says yes. "I think we should use it because it's much less toxic." It can also be taken orally at home, eliminating the need for regular intravenous infusions. Even so, "we need more science," Herbst adds.

The next step should be "looking at drug combinations and trying to understand what genomic alterations are implicated in resistance or potential benefit to sotorasib in NSCLC tumors that harbor *KRAS*$^{G12C}$," says Abdul Rafeh Naqash, MD, of the Stephenson Cancer Center at the University of Oklahoma in Norman, who was not involved in the study. "Teasing out these signals will be crucial to find the right patients for the appropriate combination approaches."

"It is important to recognize that non–small cell lung cancer is very heterogeneous, even within this group of patients that all have *KRAS*$^{G12C}$ mutations," says Melissa Johnson, MD, of Sarah Cannon Research Institute in Nashville, TN, and a CodeBreaK 200 investigator. "Some have secondary *STK11* and *KEAP* co-alterations, while others have a secondary *p53* mutation. In prior studies with chemotherapy and immunotherapy, it was these co-mutations which predicted a different prognosis. Those subgroup analyses from CodeBreaK 200 are ongoing."

Additional clinical trials are evaluating KRAS inhibitors in combination with other treatments. A phase II trial is assessing sotorasib and RMC-4630 (Revolution Medicines), a SHP2 inhibitor, as a second-line therapy for *KRAS*$^{G12C}$-mutated NSCLC. The phase III KRYSTAL-7 study is evaluating adagrasib (Krazati; Mirati) plus the PD-1 inhibitor pembrolizumab (Keytruda; Merck) compared with pembrolizumab plus chemotherapy as an initial treatment for inoperable, locally advanced or metastatic NSCLC with a *KRAS*$^{G12C}$ mutation and a PD-L1 tumor proportion score of less than 50%. Adagrasib received FDA approval in December for advanced *KRAS*$^{G12C}$-mutated NSCLC.

Other questions about sotorasib, adagrasib, and KRAS inhibitors in development need to be answered as well, says Johnson. For example: Does the extent of the disease correlate with response? How might radiation therapy augment the drugs' activity? Another area ripe for exploration is whether the agents can be administered as initial therapy for patients with newly diagnosed or early-stage disease.

"We are beginning to ask research questions about how to incorporate these drugs earlier in a patient's disease course, but you've got to start somewhere," Johnson says. *–Aaron Tallent and Suzanne Rose* ■

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## NOTED

**The U.S. Centers for Disease Control and Prevention called for all adults to be screened for hepatitis B** infection at least once, saying that testing "is cost-effective compared with risk-based screening" because most people living with the infection don't know that they have it (MMWR Recomm Rep 2023;72:1–25). A cure is not available, but early diagnosis and treatment of infections reduce the risk of liver cancer and other conditions.

As of September 2024, **mammography facilities must tell patients whether they have dense breasts,** according to a final rule issued by the FDA. Dense breast tissue makes it more difficult to spot breast cancer on a mammogram and raises the risk of developing the disease.

**An FDA advisory panel voted 11–2 in favor of approving polatuzumab vedotin** (Polivy; Roche) as an initial treatment for diffuse large B-cell lymphoma based on the findings of the phase III POLARIX trial. The drug, a first-in-class anti-CD79b antibody–drug conjugate, would be combined with rituximab, an anti-CD20 monoclonal antibody, and chemotherapy. The final decision rests with the FDA.

Clinical trial data show that immune checkpoint blockade can prompt lymph nodes to produce cancer-fighting T cells, suggesting that **leaving lymph nodes near a tumor intact could boost the drugs' effectiveness** (Cell 2023;186:1127–43).

**Drugmakers that raised prices faster than the rate of inflation on 27 medicines will be fined,** the Biden administration announced, and will have to pay back the difference to Medicare. Six of the drugs treat blood cancers, one treats lung cancer, one treats bladder cancer, and one is used to prevent chemotherapy-induced nausea and vomiting.

Novartis announced that **the FDA approved dabrafenib (Tafinlar) with trametinib (Mekinist) for children age 1 and older with low-grade glioma** with a *BRAF*$^{V600E}$ mutation. The agency also OK'd new oral formulations of both drugs for patients who cannot swallow pills. This is the first approval of a systemic therapy as an initial treatment for children with this condition.

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