approval for neoadjuvant use will lead to the approval of other drugs in that setting.

“I believe it could be the new model, at least for HER2-amplified and triple-negative breast cancers, where pCR has been shown to correlate with outcome,” said Rita Nanda, MD, associate director of breast medical oncology at the University of Chicago Hospitals.

FDA officials were more cautious. Pazdur said pertuzumab’s accelerated approval “could be a model—potentially, it is.” But he and Mikkael Sekeres, MD, chair of FDA’s Oncologic Drugs Advisory Committee and director of the Cleveland Clinic's leukemia program, both stressed that the case file on pertuzumab contained much more than the results of one phase II trial with an endpoint of pCR. The regulators also considered the results of the phase III CLEOPATRA trial that led to pertuzumab’s 2012 approval in the metastatic setting—results that showed a clinically meaningful effect on overall survival and an acceptable toxicity profile. Also, Genentech has already accrued 4,800 patients for its confirmatory APHINITY trial of pertuzumab in the adjuvant setting.

“We looked at the surrogate endpoint [pCR] as reasonably likely to translate to a clinically meaningful endpoint,” said Sekeres. But because of the unique circumstances, it was “not a precedent-setting decision.”

Asked what it would take for pCR to become an acceptable endpoint for future drug trials, Sekeres said, “We’d be more confident if we saw those [pCR] results translate into progression-free, disease-free, event-free, or overall survival.”

Breast cancer patients who have a pCR have a greater chance of long-term survival than those who don’t. However, the strength of that association is not known.

In May 2012 FDA issued draft guidance suggesting that pCR could be used as an endpoint in neoadjuvant early-stage high-risk breast cancer trials for accelerated approval under certain conditions. The agency also established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) to conduct a pooled analysis of data from more than 12,000 patients enrolled in neoadjuvant trials with long-term follow-up. The aim was to assess the correlation between pCR and disease-free or overall survival and the subtypes of early-stage breast cancer in which pCR is most likely to predict clinical benefit. The analysis will be published shortly in The Lancet, but preliminary results were presented at the San Antonio Breast Cancer Symposium in December 2012.

“The association between pCR and long-term outcomes is strongest in patients with more aggressive subtypes—triple-negative disease or HER2 positive, hormone receptor negative,” said Patricia Cortazar, M.D., the FDA official who wrote the study. However, she added, the magnitude of pCR improvement that predicts long-term clinical benefit could not be determined.

Several neoadjuvant studies presented at the 2013 San Antonio meeting looked at the same question. The European NeoALTO trial showed that the improved pCR rates seen in hormone receptor–negative, HER2-positive patients who received a combination of two HER2-targeted drugs did seem to translate into better long-term outcomes. But the trial was statistically underpowered to demonstrate such an outcome definitively.

Another trial being watched is I-SPY 2, a phase II study to identify new agents that show promise in treating patients with certain biomarker signatures. As of December 2013, I-SPY 2 had “graduated” two drugs expected to go on to phase III trials: veliparib, for triple-negative breast cancer, and neratinib, for HER2-positive, hormone receptor–negative tumors. In both cases, women who received the investigational drug in addition to a standard neoadjuvant regimen had much higher pCR rates than those in the control arm. Because of its statistically innovative “adaptive randomization” design, I-SPY 2 identifies drugs highly likely to perform well in patients with certain disease subtypes—so well that the confirmatory phase III trial may need to enroll as few as 300 patients.

Donald Berry, PhD, professor of biostatistics at the University of Texas M. D. Anderson Cancer Center in Houston, and one of the principal investigators of I-SPY 2, believes that such trials in the neoadjuvant setting are the future of drug development. “We’ve stopped doing adjuvant trials,” he said. “They’re huge, cumbersome, and slow—the antithesis of what cancer research needs to be.

“We’ve made great progress [in treating early breast cancer], which has led to big improvements in survival. The statistical implication is that we need bigger studies. We’ve been designing studies with 3,000, 5,000, or 10,000 patients in the adjuvant setting. This is not a tenable strategy. It’s too expensive. And by the time we get the results, the world has moved on.”

© Oxford University Press 2014. DOI:10.1093/jnci/dju072
First published online March 7, 2014

Fifty Years Later, Many Teens Still Smoke

By Mike Fillon

January 11 marked 50 years since US Surgeon General Luther Terry’s warning linking cigarette smoking to lung cancer. Although the report caused many smokers to quit and others not to start smoking, teens still use and become addicted to nicotine at alarming rates.

The Campaign for Tobacco-Free Kids estimates that 3,500 U.S. youngsters try their first cigarette every day. Youth use of cigarettes and other nicotine-laced products is a good news–bad news dilemma. According to the 2012 National Youth Tobacco Survey released in November 2013 by the Centers for Disease Control
and Prevention, although the rate of youth cigarette smoking has decreased, popularity of other tobacco products—including cigars, electronic cigarettes, and water pipes (aka hookahs, nargilehs, or shisha pipes)—has increased. Further, the Campaign for Tobacco-Free Kids estimates that 18.1% of high school students still smoke and nearly 1,000 kids become regular smokers each day. In a 2012 report, the U.S. Surgeon General concluded that to entice youngsters—and skirt restrictions—tobacco companies are marketing new products, including cheap, sweet, colorfully packaged small cigars that come in fruit and candy flavors that appeal to kids who might shun cigarettes. That's in addition to the growing craze of water pipes, which are popular at parties, and electronic cigarettes, or e-cigarettes.

To combat teen smoking, New York City Mayor Michael Bloomberg signed a bill on Nov. 19, 2013, raising the city's minimum cigarette-buying age to 21 years. The belief is that restricting teens' access to cigarettes greatly reduces the number of individuals who will get hooked on nicotine as adults.

Findings of a study by researchers at Washington University School of Medicine in St. Louis bear out this assertion: States with more restrictive limits on teens purchasing tobacco also have lower adult smoking rates, especially among women.

“Our study shows that if we can get people through adolescence without them experiencing the reinforcing effects of nicotine, they may be less likely to become addicted later on,” said lead author Richard A. Grucza, PhD, MPE, associate professor in the department of psychiatry.

Cavazos-Rehg, PhD, assistant professor of psychiatry at Washington University School of Medicine, and the marketing is far ahead of the potential dangers of these alternative products.

“Even many adults have a misconception that these newer products are automatically safer than cigarettes,” she said.

Appearing in the June 13, 2013, online issue of the American Journal of Public Health, the Grucza study analyzed adult smoking data from the 1998 through 2006–2007 ongoing National Cancer Institute survey monitoring smoking behavior in all 50 states. Participants included 105,519 adults, aged 18–34 years at the time of the survey. Researchers noted whether subjects ever smoked, whether they smoked currently, and whether they smoked more than 10 cigarettes per day. The team also looked at the smoking restrictions in place in states when subjects were aged 17 years. Grucza said they used age 17 because in most states, for anyone under 18 to buy tobacco products was illegal.

The researchers focused on nine smoking-related policies. In states with enforcement policies, 17-year-olds not only had more difficulty buying cigarettes but also were less likely to smoke when they reached their 20s or 30s. As revealing as their results were, Grucza believes the results would be even more profound if the age were raised to 21 years. However, the researchers noted inconsistent enforcement among states.

“Our study shows that if we can get people through adolescence without them experiencing the reinforcing effects of nicotine, they may be less likely to become addicted later on.”

“We predicted that if youth smoking initiation is delayed as assumed in the model, within 7 years it would result in a large drop in youth smoking prevalence from 22% to less than 9% for the 15- to 17-year age group. Our study was simulation, and New York will hopefully determine whether we’re right.”

Billimek noted that another frequently used and effective tool to curb cigarette use in New York and other jurisdictions is raising the excise tax on cigarettes. Although this measure is effective, he said, the burden unfairly hits poor people the most.

“As a proportion of disposable income, excise taxes represent a larger burden to poor people than to more affluent individuals.”

**Not Just Cigarettes**

In the final days of his term as mayor, Bloomberg also signed a bill banning e-cigarettes anywhere use of conventional cigarettes is prohibited in New York City. E-cigarettes do not burn tobacco leaves. Rather, they vaporize a blend of propylene glycol and/or vegetable glycerin, with tobacco-derived nicotine and flavoring.

The long-term effects of smoking e-cigarettes have yet to be studied, said Patricia Cavazos-Rehg, PhD, assistant professor of psychiatry at Washington University School of Medicine, and the marketing is far ahead of the potential dangers of these alternative products.

“All the new approaches are more dynamic and engaging, so that less than an entire 20-cigarette pack could not be sold, and prohibiting distribution of free cigarettes at public events.

One researcher monitoring the law requiring that cigarette buyers in New York be at least 21 years old is John Billimek, Ph.D., assistant adjunct professor at the Health Policy Research Institute at the University of California, Irvine. He cowrote a study in the March 2007 issue of Health Policy that presented results of a 75-year dynamic simulation model investigating long-term benefits of raising the legal purchase age of cigarettes to 21 years.

“We predicted that if youth smoking initiation is delayed as assumed in the model, within 7 years it would result in a large drop in youth smoking prevalence from 22% to less than 9% for the 15- to 17-year age group. Our study was simulation, and New York will hopefully determine whether we’re right.”

Billimek noted that another frequently used and effective tool to curb cigarette use in New York and other jurisdictions is raising the excise tax on cigarettes. Although this measure is effective, he said, the burden unfairly hits poor people the most.

“As a proportion of disposable income, excise taxes represent a larger burden to poor people than to more affluent individuals.”

**Allure of “Forbidden Fruit”**

Brian A. Primack, MD, PhD, associate professor of medicine and pediatrics at the University of Pittsburgh, believes anything that cuts tobacco use or delays starting the habit is a plus. But he also sees the need for a new approach to educating young people about smoking—besides the adverse health effects.

“We run the risk of making smoking more alluring, and for rebellious youth,
who don’t want to appear like ‘goody-two-shoes,’ that can be a huge problem.”

To overcome this obstacle, Primack is investigating using media literacy programs as education tools. Instead of only teaching kids that cigarettes are dangerous to their health, these tools show young people how the media glamorizes tobacco use to their detriment.

The PDQ (Physician Data Query) is the National Cancer Institute's source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:


The PDQ Adult Brain Tumors Treatment summary was recently updated to:

1) Include new prognostic information for patients with glioblastoma, specifically regarding O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status; a subset study of an EORTC-NCIC trial provided strong evidence that epigenetic silencing of the MGMT DNA-repair gene promoter by DNA methylation was associated with increased overall survival (OS) in patients with newly diagnosed glioblastoma.

2) Add the results of a multicenter, randomized phase III trial conducted by the Radiation Therapy Oncology Group, European Organization for Research and Treatment of Cancer, and the North Central Cancer Treatment Group (RTOG 0525/ NCT00304031) that compared standard adjuvant temozolomide treatment with a dose-dense schedule to test whether protracted temozolomide enhances treatment response in patients with newly diagnosed glioblastoma. All patients were treated with surgery followed by radiation therapy and concurrent daily temozolomide. Patients were then randomly assigned to receive either standard adjuvant temozolomide or dose-dense temozolomide. Patients were then randomly assigned to receive either standard adjuvant temozolomide or dose-dense temozolomide. No survival advantage was found for the use of dose-dense temozolomide versus standard-dose temozolomide in newly diagnosed glioblastoma patients, regardless of MGMT status. The efficacy of dose-dense temozolomide for patients who have recurrent glioblastoma, however, is yet to be determined.

3) Update the summary to include final data from two multicenter, phase III, randomized, double-blind placebo-controlled trials of bevacizumab in patients with newly diagnosed glioblastoma (RTOG 0825/ NCT00884741 and the Roche-sponsored AVAglio/NCT00943826). Patients in both studies were randomly assigned to receive standard therapy (chemoradiation with temozolomide) or standard therapy plus bevacizumab. OS and progression-free survival (PFS) were co-primary endpoints in both trials, and the outcomes were similar. Bevacizumab did not improve OS in either study and the PFS result in the AVAglio study was statistically significant and associated with clinical benefit because bevacizumab-treated patients remained functionally independent longer (9.0 months vs. 6.0 months) and the length of time before their Karnofsky Performance Scale deteriorated was longer (HR, 0.65; \( P < .0001 \)). Furthermore, the period before corticosteroids were initiated was longer for the bevacizumab-treated patients (12.3 vs. 3.7 months; HR, 0.71; \( P = .002 \)), and a larger proportion of patients was able to discontinue corticosteroids if they were already taking them (66% vs. 47%). However, the PFS result in the RTOG 0825 trial did not meet the pre-specified significance level (\( P = .004 \)). Of note, there was significant crossover in both trials (approximately 40% of RTOG 0825 patients and approximately 30% of AVAglio patients received bevacizumab at the first sign of disease progression).

The two trials had contradictory results in health-related quality of life (HRQoL) and neurocognitive outcomes studies. In the mandatory HRQoL studies in the AVAglio trial, bevacizumab-treated patients experienced improved HRQoL, but bevacizumab-treated patients in the elective