THE CANCER LETTER

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KRAS Finding Changes Oncology Practice But Poses Profound Regulatory Dilemma

By Paul Goldberg

In the clinic, the role of KRAS mutations in selection of colorectal cancer patients for treatment with Erbitux and Vectibix is hardly controversial.

However, at FDA, the KRAS findings have pointed to a series of interlocking regulatory dilemmas over the role of diagnostics in determining which patients stand to benefit from cancer therapeutic agents.

In fact, the controversy over labeling of the two agents has become a regulatory test case that may determine whether "personalized medicine" is something tangible or just another Washington policy talk-fest.

The role of KRAS mutations was settled at last year's annual meeting of the American Society of Clinical Oncology, when researchers presented multiple studies demonstrating that patients with advanced tumors who had KRAS mutations would not benefit from the ImClone drug Erbitux (cetuximab). The same effect was observed with the Amgen's drug Vectibix (panitumumab).

"That's about as clean a case as you can make for that specific biomarker

(Continued to page 2)

In Brief:

UCSF Brain Tumor Center Wins $1 Million From Pediatric Brain Tumor Foundation

UCSF BRAIN TUMOR CENTER was awarded a three-year, $1 million institute award from the Pediatric Brain Tumor Foundation of the United States. The grant will fund studies on stem cell neurobiology, aberrant cell-signaling pathways, and the development of siRNA molecules as therapeutic agents for pediatric brain tumors. . . . **SHARMILA MAKHIJA** joined Emory University School of Medicine and the Emory Winship Cancer Institute as director of gynecologic oncology. Makhija was associate professor of gynecology/oncology and associate scientist in the UAB Comprehensive Cancer Center. . . . **ELLEN STOVALL** is serving as acting president and CEO of the National Coalition for Cancer Survivorship, the coalition announced last week. Stovall will serve in those positions until the Board of Directors selects a successor to **Cathy Bonner**, who served as president and CEO during the last half of 2008. Stovall, the organization's senior health policy advisor, served as NCCS president and CEO from 1992 to 2008. The firm of Isaacson Miller will help the NCCS Board conduct a national search. . . . **RICHARD BESSER** was appointed acting director of CDC, succeeding **Julie Gerberding**. Besser was the agency's director of the Coordinating Office for Terrorism Preparedness and Emergency Response.

FDA's Concern: Data-Dredging In Drug-Diagnostic Applications

(Continued from page 1)

in that specific patient population for those specific drugs," said Richard Schilsky, a GI oncologist, chairman of Cancer and Leukemia Group B and president of ASCO. "Those drugs don't work in patients who have RAS-mutated tumors, and they shouldn't be used."

Response to the findings was swift. NCI required changes in ongoing clinical trials to require KRAS mutational analysis, the National Comprehensive Cancer Network changed its guidelines, ASCO issued a "provisional clinical opinion," and the European regulators restricted the use of both Vectibix and Erbitux to metastatic colorectal cancer patients who express non-mutated KRAS.

Though the sponsors of the two agents asked FDA to change the label, U.S. regulators didn't move as fast as the Europeans. Instead, they saw a reason to pause and formulate the criteria for joint labeling of diagnostics and therapeutics. To air the controversy, the agency consulted the Oncologic Drugs Advisory Committee on Dec. 16, 2008.

Though the sponsors presented data on the role of KRAS mutations in Erbitux and Vectibix, ODAC wasn't asked to make approval recommendations. The meeting was about criteria.

"We have asked these sponsors to present this data to provide a context for the questions posed to the committee," Richard Pazdur, director of the FDA Office of Oncology Drug Products, said at the meeting. "The KRAS presentations provide a real-world situation faced by FDA in which considerations of the type and extent of data needed to support labeling claims must be made."

No votes were taken. If any take-home message emerged from ODAC's deliberations, it was that in this emerging and complex field of science and the law, regulators shouldn't be guided by rules of thumb.

Regulatory Dilemma

The drugs in question were first approved for tumors characterized by the presence of another target, the epidermal growth factor receptor.

However, subsequent studies showed that characterization of patients for a signaling pathway molecule with respect to KRAS mutation predicted response to the agent. Alas, confirmation of this hypothesis emerged after the initial approval of the agents in the U.S.

In Europe, initial response to the Vectibix regulatory submission was negative—unless the sponsor, Amgen, was able to provide predictive advice for patients most likely to respond.

Anticipating this possibility, Amgen's clinical researchers had prospectively collected tumor tissue from every patient enrolled in the registration, which made it possible to conduct an analysis for KRAS mutation, sources said. Other studies of both Vectibix and Erbitux were conducted retrospectively.

The findings were consistent in multiple studies, but retrospective studies traditionally mean trouble for applicants.

Should FDA accept such studies? If so, under what circumstances? How would the agency safeguard against "data dredging," scientifically suspect and long-verboten efforts by sponsors of failed trials to perform post hoc analyses and zero in on subsets that produce desired results?

Precedents offered little guidance. Though diagnostic tests have occasionally been specified on labels for therapeutics, the agency hasn't formally and explicitly stated what evidence it requires for getting a diagnostic assay on the label of a therapeutic.

Genentech's drug Herceptin (trastuzumab)—the closest thing to a precedent—was approved in conjunction with an immunohistochemistry test in 1998, but the two weren't designed to work together from the outset. In fact, the assay used in the trials differed from the assay that finally appeared on the label.

The requirements for EGFR testing by

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immunohistochemistry were specifically mentioned in the labels for the two drugs in question. Erbitux is approved for EGFR-expressing tumors, and the Vectibix label specifically mentions testing.

"It's worth noting that the FDA has approved genotyping assays before," said Leonard Saltz, a colorectal cancer expert at Memorial Sloan-Kettering Cancer Center. "The UGT-1A1 assay is in the label for irinotecan (Camptosar), even though many of us feel that this test is not useful in clinical practice." The test is not recommended in the NCCN guidelines. Saltz consults for and receives support from ImClone, BMS, and Amgen, and consults for two assay-makers, Genomic Health Inc. and Genzyme Corp.

FDA's dilemma is all the more profound because the questions raised in the case of Erbitux and Vectibix edge into the broader controversy over the approval mechanisms and levels of evidence required for getting a diagnostic assay on the market.

Historically, it has been difficult to demonstrate the contribution a particular diagnostic can provide in the clinical management of patients with therapeutic agents.

"The tension is that the regulatory standard for the assay is even more rigorous than the regulatory standard for the drug," Schilsky said in an interview. "For the drug, you have to show that the drug works in the population for whom you are making the claim. For the assay, you have to show that the assay discriminates between those in whom the drug will work and those in whom the drug will not work.

"To meet that standard, you may have to have a much larger clinical trial than you would have if you were just studying the drug. The issue always is, can you just study the drug in the marker-positive population, and if the drug works, you can get a label for use of the drug in the marker-positive population? That usually works for the drug.

"But to get a labeling claim for the assay, what the people at the FDA Center for Devices and Radiological Health like to see is not only that the assay identifies the group in which the drug will work, but that the assay identifies the group in which the drug will not work.

"And that requires you to include both marker-positive and marker-negative patients in your trial in order to get the requisite level of precision on testing the assay, which can increase the size of the clinical trials," Schilsky said.

Of course, historically there has been another way to deal with this daunting scientific challenge: you can open a reference laboratory and seek certification under the Clinical Laboratory Improvement Amendments and regulated by the Centers for Medicare & Medicaid Services. FDA's jurisdiction over CLIA-certified labs is a matter of some debate, and the agency generally has chosen not to exert its authority in this area.

Many tests offered by such reference labs and called "home brews" have been widely accepted in oncology and are commonly being used to select patients to receive drugs and determine coverage.

The standard for CLIA approval of these tests relates to "test validity," that is, the technical performance of the test. Such approval doesn't consider the "clinical validity," or clinical meaning, of the test. While some home brews have also gone through more rigorous testing to establish a higher level of clinical evidence, they represent an exception, industry insiders say.

With the advent of more complex tests, which may make it possible to match patients with drugs, the controversy is becoming increasingly urgent.

Last December, Genentech Inc. filed a citizen's petition with FDA demanding that the agency promulgate and enforce a single set of standards for all such assays.

The petition is posted at http://www.regulations.gov/fdmspublic/ContentViewer?objectId=09000064807d4a7e&disposition=attachment&contentType=pdf.

The petition reflects Genentech's recognition that a multitude of assays is determining utilization of therapeutics. Advocates of personalized medicine note that the petition also reflects recognition by a drug sponsor that drug usage today is gated by indications of use related to biology, as opposed to historical classifications of cancer.

Philosophies differ on how assays should best be developed, validated, reimbursed, and integrated into clinical practice.

Some players say that stronger regulations would be stifling and impede rapid advances in development of tests. This view would leave the current CLIA-based regulation unchanged.

Critics of this approach warn against reliance on incompletely or inaccurately validated assays, arguing that unverified assays are the 21st century equivalent of snake oil. Unverified information would drain scientific rigor from the practice of medicine, thereby harming patients.

When assays and drugs are linked, the potential for doing harm increases. "The assay used to test for KRAS mutation is pretty straightforward, and it's hard to screw it up, but that's not necessarily the case for all assays," said Schilsky. "If you are going to use an assay

to determine whether or not a patient should get a drug, the risk is that the assay is false-positive. In the Erbitux example, you would exclude a patient from getting the drug, because the assay read-out is that there is a mutation when there isn't one. Or, if it's a false-negative, you run the risk of giving the drug to somebody who isn't going to benefit from it."

Multiplicity of Standards

"There is not a debate on whether this is the right thing for patients," said Steven Shak, chief medical officer of Genomic Health. "The question is how do the regulatory agencies in the U.S. show flexibility in managing this new information?"

Shak said FDA isn't the sole authority evaluating assays and shaping the way they are used. "One message here is that FDA has a role within the larger context of groups and organizations that help to ensure quality patient care," Shak said.

One of them is CLIA. Some states, including New York, review assays as well. "There is an ASCO group that establishes guidelines for tumor tests that has been very effective," Shak said. "If ASCO doesn't recommend the use of a test, it's unlikely that payers are going to pay for it."

Assays that haven't gone through FDA approval are commonplace in oncology.

Genomic Health's Oncotype DX, a multi-gene expression test supported by clinical evidence to predict the likelihood of chemotherapy benefit as well as recurrence in early-stage breast cancer, is among them.

The test is widely accepted. Results of a study validating its use were published in The New England Journal of Medicine, and guidelines from both ASCO and NCCN support the test's use. Altogether, 7,500 physicians have ordered more than 75,000 tests, and both Medicare and private insurers are now paying for it, the company said.

"Estrogen receptor testing has, for the most part, not been done with FDA-approved tests," Shak said. "There finally is one now, but we have always relied on laboratory-developed tests and the efforts, still ongoing, by ASCO, [College of American Pathologists], and CLIA to ensure quality testing for ER."

In many cases—including HER2 testing—the quality of a lab determines accuracy of the test.

"We did an incredible job at Genentech on [Herceptin], but now, sitting here a decade later, we look at the issue of testing, and there is still incredible controversy and concern about whether we are selecting the right patients for Herceptin treatment," said Shak, who ran Genentech's Herceptin development program before co-founding Genomic Health.

"In fact, the issue is not only whether it should be FISH or IHC or an improved technology," Shak said. "It's most importantly what is the quality of laboratories and the standards they use to ensure quality of either IHC or FISH or any testing technology. And that's not FDA; that's CLIA.

"And over the past decade since Herceptin, where are the new companion diagnostics for the newer cancer drugs that give physicians the data they need to determine which drug works for which patient?"

The biomarker field needs to be standardized, said George Sledge, professor of medicine and pathology at Indiana University and incoming president-elect of ASCO, who has consulted with Genentech.

"The idea of bouncing forth between CLIA and FDA is crazy," Sledge said. "There need to be some standard rules, whether they are standard CLIA rules or standard FDA rules. The situation where you have two portions of the medical establishment within the government warring over who gets to regulate these things is absurd."

Sledge said he favors standards that would require correlation with outcomes. "Without it, it's all meaningless," he said.

As a doctor who uses predictive assays in breast cancer, Sledge says he is perplexed by the regulatory status of OncotypeDX when compared with a similar assay, MammaPrint, developed by the Netherlands Cancer Institute. Both are multi-gene assays based on the principle that each gene tested adds something to the overall result.

While OncotypeDX went through CLIA, MammaPrint went through FDA. "MammaPrint went to FDA for the seal of approval rather than doing it as a home brew," Sledge said.

Their prize: upon review, MammaPrint was specifically prohibited from claiming that the assay was useful in terms of predicting response to therapy. To make things even more convoluted, the two assays aren't backed by the same quality of evidence. MammaPrint was validated in fewer and smaller studies than OncotypeDX and isn't recommended in ASCO and NCCN guidelines.

"Everyone in the field basically agrees that both MammaPrint and Oncotype did a good job," Sledge said. "They are both measuring pretty much the same thing, but they are being marketed under totally different guidelines, one saying we predict response, the other

being explicitly told that they can't say that they are predicting response."

The problem of regulating assays will likely get more difficult as assays become more complex. "Looking at estrogen receptor, or HER2, or KRAS in a population is pretty simple," Sledge said. "If you are looking at something like Oncotype or MammaPrint, where you have either a 21-gene or a 70-gene assay, the idea of having to prove from the regulatory standpoint that every single gene is valuable in the assay would not be fun."

The science and regulations will have to evolve to address these problems, said David Parkinson, president and CEO of Nodality Inc. of South San Francisco, a privately held company developing complex cancer diagnostics.

"The new generations of tests are going to be more complicated, but also more valuable from the perspective of the information they provide regarding specific therapeutic approaches in a particular patient," Parkinson said. "There will be a real need for educating the various parties affected by the introduction of these new tests, including clinicians, with respect to their clinical meaning, and regulators and payers with respect to the need for policy changes in the regulatory approval and reimbursement of these complex new 'patient management tools.'

"It is a misnomer to characterize these complex new tests as similar to classic 'diagnostics.' These tests are designed to enable to more effective use of therapeutics, in effect to inform clinical decision-making," Parkinson said.

"The questions are going to keep showing up, and regulators are going to have to confront them," Parkinson said. "How do you develop these tests? How do you ensure consistency in the development of appropriate levels of clinical evidence? How do you make sure that the system values these tests appropriated so that companies are motivated and able to provide the resources and accept the timelines necessary to develop them? How do you make sure that therapeutic companies and the diagnostic companies work in concert?

"The potential benefits to patients with cancer are extraordinary, but without concerted attention and policy changes to enable this area of technology to flourish, progress will be slow," Parkinson said.

Many physicians are perplexed to see a clinical no-brainer present a profound regulatory challenge. "This unfortunate dilemma places common sense and a large body of basic and clinical science in conflict with the regulatory process," said Louis Weiner, director, Lombardi Comprehensive Cancer Center. "While an FDA decision to approve the KRAS biomarker test could create a thorny precedent for future biomarker submissions, common sense and patient benefit should be the highest priorities of this particular regulatory process. If so, the answer seems to be quite clear."

"Retrospective Prospective"

In opening remarks at the ODAC hearing Dec. 16, Pazdur described the methodology used in the Erbitux and Vectibix studies as "retrospective prospective," a term that emerged in literature over the past two or three years.

The text of Pazdur's opening remarks follows:

The selection of a drug based on biomarker profile is desirable because it may limit drug exposure to patients who will benefit from drug treatment, may avoid drug use in patients who may be harmed by drug treatment, or may enhance safe use by optimizing drug dosing.

In the ideal case, the development of the assay methodology for a biomarker should be an integral part of the clinical drug development program. The clinical studies required to establish the drug's efficacy and those needed to establish the prognostic and/or predictive value of the biomarker should occur in tandem.

However, there are multiple examples of "retrospective" or post-hoc biomarker assessment. The worst example involves a retrospective re-analysis of a "failed" clinical trial—that is a trial that did not met its primary endpoints and an attempt to salvage the trial is made by examining non-prespecified subgroups. FDA discourages such practices and should not be considered during this advisory meeting discussion.

However, FDA also recognizes that there may be legitimate reasons for the lack of consideration of biomarkers early in drug development, primarily due to advances in the scientific knowledge of a drug or disease occurring during drug development. In today's meeting, the FDA seeks guidance regarding how to incorporate new scientific information without compromising our mandate to ensure that marketed drugs show substantial evidence of efficacy and are safe.

FDA and commercial sponsors during this meeting will present a recent example of retrospective biomarker analyses intended to support changes to product labeling. ImClone, the license holder for cetuximab (Erbitux) and Amgen, the license holder for panitumumab (Vectibix), will describe the results of retrospective analyses assessing efficacy outcomes determined by KRAS genomic status.

We have asked these sponsors to present this data to provide a context for the questions posed to the Committee. The KRAS presentations provide a "real-world" situation faced by FDA in which considerations of the type and extent of data needed to support labeling claims must be made. The issues posed to the committee during the afternoon discussions deal with general considerations of incorporating retrospectively identified biomarkers in regulatory decisions rather than the specifics of the KRAS example.

As previously stated, an ideal scenario is one in which the relationship of the biomarker to potential action of the drug is recognized early—indeed, such a relationship might be the motivation for starting the drug's development. In this setting, many milestones for development of the in vitro diagnostic or IVD might be reached in an orderly manner.

The identity of the biomarker should be established early, along with reliable means for its measurement. If the biomarker has an impact on the natural course of disease (prognosis), such a relationship might be elucidated.

Through pre-clinical studies and early clinical trials, support might grow for applicability of the biomarker as an indicator of drug effect. Formulation of an intended use for the biomarker might emerge, and resources are committed to complete the analytical validation of a fully specified IVD. When a definitive efficacy trial for an investigational drug is undertaken, its design might incorporate a test of the IVD, so that conclusions can be drawn concerning both the drug's safety and efficacy and effectiveness of the IVD. With a trial that is successful from all perspectives, the drug will be approved and the test will be clinically validated and approved for prediction of drug effect.

For many reasons, the ideal scenario is unusual. When a definitive efficacy trial has been conducted and completed without reference to the biomarker, then there may be interest to retrospectively examine the biomarker in available clinical trial specimens. The follow-up for patients accrued to an efficacy trial is already in hand. The patients who accrued to the completed trial included both patients who were "positive" and patients who were "negative" for the biomarker of interest—a likely requirement for gaining insight on a predictive claim for the IVD.

There are many issues to be addressed with this strategy of retrospectively examining biomarker data. Some of the points of the discussion should include the following.

—The chance of erroneously concluding that there is a real treatment effect when in fact it is not true, or the chance of concluding there is no treatment effect when in fact one actually exists, are two critical concerns for the design and interpretation of study results of any clinical trial. There are many examples of subpopulation findings that are spurious. To address this problem, it is necessary to control the chances of making these false conclusions, usually by pre-specifying the hypotheses and the number of subgroups for which a treatment effect in the subpopulation is sought as a primary objective of the trial.

—An additional issue to be discussed with the anticipated use of retrospective analyses is replication—that is the likelihood for reproducing a treatment effect identified in a subpopulation in a single clinical trial in another independent study.

—A third consideration in using retrospective biomarker analysis is that the required sample size for the biomarker negative subpopulation should be sufficient to detect a treatment effect, if it exists, considering that the effect may not be of the same magnitude as in the biomarker positive subpopulation

—The minimum performance characteristics (e.g., sensitivity, specificity, reproducibility) of the assay used to define patient subgroups and the consequences of that performance for correct decision making and inferences from the study must be understood. In addition, the proportion of patients whose biomarker specimens are available for analysis needs to be considered in any request for a retrospective analysis of a completed trial.

—Clarity on whether the biomarker is being considered a prognostic and/or predictive marker and the consequences of these definitions on study design planning, sample size, and ability to draw conclusions must be understood.

—Lastly, there should be an understanding if randomization has been preserved in a retrospective analysis, especially in small sample size subpopulation identified after completion of a clinical study.

In today's meeting we will discuss the concept of a prospective retrospective study. A working definition follows. In a completed or post-interim-analysis trial genomic samples were collected prior to treatment initiation, whether or not full ascertainment, the genomic hypothesis is 'prospectively specified' prior to diagnostic assay testing. However, the clinical outcome data without biomarker information have already been (partially) collected, unblinded, and analyzed. The biomarker data analysis might be arguably prospectively performed, which is a retrospective analysis.

In essence, in a prospective retrospective study, the classification factor or biomarker is not known at the time of study initiation, and the study is, at first, not analyzed with that factor as part of the hypothesis (retrospective aspect). The initial hypothesis and endpoints for the study are not changed, except if pre-specified as part of a planned adaptive study design. The controls of the false positive conclusion from the study are appropriately dealt with. The randomization is not stratified on a biomarker status as one of the hypotheses to be tested. Biomarker should be ascertained at baseline on all subjects randomized to treatment groups

FDA is seeking ODAC's deliberations on issues raised in using biomarkers after trials have been initiated or completed. In particular, the committee should discuss the conditions where a prospective retrospective clinical study design may provide evidence for treatment effects that are limited to biomarker classified subpopulation, thereby being judged as evidence of a predictive biomarker. In addition, if a retrospective analysis can be performed to show benefit in a subset and it is considered acceptable that randomization on biomarker status was not done, what level of evidence should be considered for reproducibility of the finding.

As stated previously, our purpose of presenting KRAS data is to provide an illustrative example of the complexities in decision-making regarding retrospective analyses. We view the discussions at today's ODAC to be an educational dialog examining the incorporation of new scientific information without compromising our mandate to ensure that marketed drugs show substantial evidence of efficacy and are safe.

Criteria for Retrospective Prospective Studies

According to the FDA briefing document, the agency told the sponsors that they could submit data for retrospective studies, provided that they meet the following criteria:

—"The trial was adequate, well-conducted and well-controlled;

—"The sample size was sufficiently large to be likely to ensure random allocation to each of the study arms for factors (i.e., KRAS status) that were not used as stratification variables for randomization;

—"Tumor tissue was obtained in ≥ 95% of the registered and randomized study subjects and an evaluable result (wild type or mutant KRAS) is available for ≥ 90% of the registered and randomized study subjects;

—"Prior to analysis, FDA has reviewed the assay methodology and determined that it has acceptable analytical performance characteristics [e.g., sensitivity, specificity, accuracy, precision] under the proposed conditions for clinical use;

—"Genetic analysis is performed according to the qualified assay method by individuals who are masked to treatment assignment and clinical outcome results;

—"Prior to analysis of clinical outcomes based on the genetic testing, agreement with FDA has been reached on the analytic plan for hypothesis testing for proposed labeling and promotional claims."

In discussion, several ODAC members said these criteria seemed unnecessarily limiting. Objections focused on the agency's definition of data dredging and its requirement that tumor tissue samples should have been collected from at least 95 percent of patients.

Richard Simon, chief of the NCI Biometric Research Branch, who served as a "temporary voting member" of the committee, said that internal consistency of the data suggests that the finding isn't a fluke.

"We've had this sort of conventional wisdom: never trust subset analysis unless the overall results are positive, and that has sort of protected us against data dredging," Simon said. "That is actually sort of an irrational rule of thumb in terms of what we're really talking about, and we don't need that to protect us against data dredging.

"We need to distinguish data dredging from the kind of KRAS situation we were seeing today. But if we continue to use this rule of thumb, never look at a trial unless it's met its [overall endpoint], that leads to clearly erroneous conclusions. And so that rule of thumb really needs to be sort of given up, and we need to independently make sure we're not talking about a data dredging situation."

"We need to distinguish the kind of prospective-retrospective design and the conditions for doing it that were presented this morning by the FDA. [The FDA conditions] are very useful, and we need to not lump those kinds of analyses together with the sort of typical data dredging analyses.

"It needs to have enough patients, both in the test positive and the test negative subsets, to be interpretable, and you have to have a test that is analytically validated on archived tissue.

"But I can conceive of situations where you could do an analysis—even though the trial was big enough and the proportion positivities were appropriate and you had arranged for archived tissue, and you could actually do, to me, just as believable analysis if information arose during the course of the trial from external sources as if you had set it up from the start that way.

"That may not be the typical situation, but I don't think because it wasn't done completely prospectively that that precludes being able to reach reliable conclusions—if other things are right.

"It was alluded to this morning that this term kept popping up, stratified, randomized stratified by the prospective--by the predictive biomarker, meaning that if, by stratified, we mean that the randomization is balanced by the predictive biomarker, that is not, to me, a viable objection.

"That is not, to me, an essential. You can do a perfectly valid randomization test without prospective stratification and all of the prospective stratification—if you know the predictive biomarker in advance, then prospective stratification is valuable because it assures that you will have tissue and assays for all of the patients who go into the trial.

"But it doesn't really do anything to improve the validity of the analysis. All it improves is the balance between the number allocated to treatment versus the number allocated to control for, say, the test positive patients. It doesn't improve the balance of those with regard to unknown covariates.

"So there is, I think, a lot of confusion about the supposed benefits of prospective stratification, at least as it applies to sort of providing a basis for inference. I think key issues are sample size, multiplicity control [and] having a focused analysis."

Another temporary member of the committee, Derek Raghavan, director of the Cleveland Clinic Taussig Cancer Institute, said regulators should refrain from setting hard-and-fast rules.

"We want to be careful that we don't box [FDA] into a little corner where, with our information, we set a bar that's so high from our advice that they can't make sensible decisions," Raghavan said. "One of the attractive features about ODAC is it doesn't have lawyers on it and so we can actually think about patient welfare.

"One of the things I've felt has been lost today, because it's probably one of the very first times I've seen it at the FDA, is two companies have come here to try to create a situation where they sell less product. That seems like kind of an important thing.

"Perhaps the way we need to think about this is in terms of, yes, we need to set rigor, we need to have good assays, we need to have well powered studies. But we might create a fudge factor that would let Dr. Pazdur, et al, look at the numbers of sets of data, the overall numbers.

"If you think about our clinical trial domain, we've come up with a crooked trick of meta analysis that allows us sometimes to glean information from rather poorly executed studies, where the numbers are small. That's not a replacement for a very well designed randomized trial.

"But the point I'm making is I think if we set rules that have common sense in them and allow the FDA some discretion to look at what was the intent of the study--as Mike Link said, I think, were you able to glean a useful quantum of reproducible information, even though the study wasn't designed to do it. And as I've been hearing the discussion, I've been a little uneasy that we're starting to raise the bar with a lot of clever terms that will actually stop common sense from being implemented, and that would be a shame."

Gregory Curt, a non-voting ODAC member who represents the pharmaceutical industry, said the requirement that 90 to 95 percent of all tissue should be preserved is "a bridge too far."

"Even in trials where we've required tissue as a prerequisite for coming on study, the actual attrition that occurs in the percentage of patients in whom you can interrogate tissue is actually far less than that," said Curt, AstraZeneca Oncology's U.S. Medical Science Lead for Emerging Products.

ODAC Acting Chair Janice Dutcher agreed. "It sounds like a laudable goal, but something that needs a lot of work and we have to deal with the practical aspects of IRBs and pathology departments and dollars and freezers and a lot of stuff," said Dutcher, associate director,clical affairs, at the cancer center of the Montefiore Cancer Center.

Materials from the ODAC meeting are posted at http://www.fda.gov/ohrms/dockets/ac/cder08.html#OncologicDrugs.

The requirement to collect all specimens doesn't appear to be entirely out of the realm of possibility.

NCI-funded cooperative groups receive funds for collecting and storing all biospecimens. Also, in the case of KRAS studies, NCI pays for assays used to determine whether patients have the KRAS mutation.

However, funds for analysis specimens have to come either from separate grants or from the industry.

"Most studies that have been done on specimens collected on cooperative group trials have been funded through mechanisms other than the cooperative group budgets," Schilsky said in an interview. "We have funding to collect the specimens, but we don't have funding to analyze the specimens.

"But you can't learn anything until you actually do research on them."

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