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FDA Approves Iressa For Third-Line Treatment Of Non-Small Cell Lung Cancer

FDA earlier this week approved Iressa (gefitinib) tablets for third-line treatment of non-small cell lung cancer.

According to the label, the agent should be used following platinum-based and docetaxel chemotherapy.

Though lung cancer is the second most common cancer that affects both men and women, only one NSLC patient out of 10 lives long enough to receive a third-line treatment, and about one in 10 of these patients

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Did Iressa Data Merit Approval? Experts Discuss Implications For Drug Development, Lung Cancer Treatment, Reimbursement

The Cancer Letter asked a group of experts to address 10 questions about the FDA approval of Iressa. The experts are:

—**Richard Pazdur**, a gastrointestinal oncologist and director of the FDA Division of Oncology Drug Products.

—**Thomas Fleming**, chairman of the University of Washington Department of Biostatistics.

—Richard Schilsky, associate dean for clinical research at the University of Chicago, chairman of the Cancer and Leukemia Group B, and former ODAC chairman.

—Paul Bunn, a lung cancer expert, director of the University of Colorado Cancer Center, president of ASCO, and a former ODAC chairman. He was not involved in Iressa studies.

—David Johnson, Cornelius Abernathy Craig Chair in Oncology and Director of Oncology at Vanderbilt-Ingram Cancer Center, and a former member of ODAC. Johnson served as chairman of the steering committee that oversaw the IMPACT trials, consulted with AstraZeneca. Johnson is president-elect of ASCO.

—**John Ruckdeschel,** a lung cancer expert and director of Karmanos Cancer Institute. He was not involved in several Iressa studies.

—Chandra Belani, professor of medicine at the University of Pittsburgh School of Medicine and co-director, Lung and Thoracic Cancer Program at the University of Pittsburgh Cancer Institute. Belani was involved in clinical development of Iressa.

—**Mace Rothenberg**, a gastrointestinal cancer expert, is the Ingram Associate Professor of Cancer Research at Vanderbilt.

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FDA, AstraZeneca Agree On Post-Marketing Trials

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may stand to benefit from Iressa, lung cancer experts say.

Granting accelerated approval to Iressa, FDA accepted the company's claim that the agent appears to cause tumor shrinkage in 10 % of patients, who would ordinarily not be expected to benefit from any treatment.

Clinicians and the company note that some of these patients appear to benefit dramatically. In fact, testimony by a number of patients appears to have swayed several members of the FDA Oncologic Drugs Advisory Committee to recommend approval for Iressa (**The Cancer Letter**, Nov. 8, 2002).

Since no one understands how the agent works on the molecular level, it's impossible to determine prospectively who these one in 10 responders may be.

Also, it's unclear whether tumor shrinkage associated with Iressa would lead to a benefit for patients. ODAC rejected the company's quality-of-life data, stating that such data are meaningless in a single-arm clinical trial (**The Cancer Letter**, Sept. 27, 2002).

One key word, "targeted," was conspicuously absent from AstraZeneca's announcement of Iressa's approval May 5.

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Though the agent was initially described as a small-molecule, targeted treatment that blocks tyrosine kinases, including the one associated with Epidermal Growth Factor Receptor, the company has been cautious about hypothesizing on the basic science underpinnings of the agent's activity.

"From a clinical perspective, a targeted therapy that does not have a measurable target is not a targeted therapy," said Richard Pazdur, director of the FDA Division of Oncology Drug Products.

"I wish the term 'targeted therapy' had never been coined, at least in conjunction with drugs like Iressa," agreed David Johnson, a lung cancer expert at Vanderbilt University, who was involved in clinical development of the agent.

Indeed, Iressa may be as targeted as 5-fluorouracil, a drug that's older than many oncologists who pump and infuse it. "We can do better with 5-FU," said Richard Schilsky, an associate dean for clinical research at the University of Chicago and Chairman of the Cancer and Leukemia Group B.

"If patients are carefully selected based on tumor thymidylate synthase and dihydropyrimidine dehydrogenase expression, we can increase the 5-FU response rate from 15% to 50% without changing a single thing about the treatment," Schilsky said to **The Cancer Letter**.

"So, our 21st Century medicine, with respect to Iressa, is no better than what we can accomplish with a drug from a half-century ago!"

Physicians involved in clinical trials and the treatment of lung cancer said FDA appropriately applied accelerated approval criteria when it approved Iressa. The accelerated approval mechanism allows the agency to clear drugs on the basis of "surrogate endpoints" that are "reasonably likely" to predict patient benefit.

At least on paper, accelerated approvals can be withdrawn if companies fail to conduct post-marketing studies to demonstrate benefit. However, FDA officials acknowledge that they would be unlikely to withdraw active drugs from the market, even if pharmaceutical companies fail to deliver solid proof of benefit (**The Cancer Letter**, March 21.)

If that's the case, an accelerated approval from FDA equals a full approval, said biostatistician Thomas Fleming, chairman of the University of Washington Department of Biostatistics.

"We don't know whether Iressa provides a clinical benefit, and if it does, to whom," Fleming said. "It is ethically and scientifically imperative to

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determine whether it has a favorable benefit-to-risk profile in the labeled population, and if such trials do not provide timely evidence establishing benefit, Iressa should be promptly withdrawn from the market."

Several experts noted that Iressa's target was not determined as thoroughly as the target of Herceptin, a monoclonal antibody for breast cancer.

"There seemed to be a race to market for the targeted therapies," said John Ruckdeschel, a lung cancer expert and director of Karmanos Cancer Institute. "I think the company failed to do the proper subset analyses to validate the targets. This is in stark contrast to Herceptin, where before the drug was generally released, we knew what subsets it worked in, and we knew how to test for them."

The scientific problems involved in developing an agent like Iressa are profound. "The answers are not easy or obvious," said Paul Bunn, a lung cancer expert and director of the University of Colorado Cancer Center.

"If we are successful, the efficacy rates will be very high—similar to what has been seen with Gleevec for gastrointestinal stromal tumor and Herceptin for breast cancer," said Chandra Belani, a lung cancer expert at the University of Pittsburgh Cancer Institute.

AstraZeneca has agreed to compare Iressa with best supportive care in the third-line indication. The trial, which would be powered to evaluate survival, would be have to be conducted outside the U.S., since patients here would be unlikely to accept randomization, especially after Iressa becomes commercially available.

Another study will compare Iressa with Taxotere (docetaxel) in lung cancer resistant to one previous chemotherapy regimen, and the third trial will evaluate Iressa's effect on cancer symptoms in patients with lung cancer resistant to all available chemotherapy.

After having conducted several Iressa trials, NCI no longer allows its cooperative groups to conduct randomized trials of Iressa until the agent's mechanism of action is known or until patient screening criteria are found, documents indicate. On April 10, the NCI Cancer Therapy Evaluation Program declined to approve a proposed phase III trial comparing Iressa with Taxotere in second-line refractory stage IIIB/IV non-small cell lung cancer.

"With the results of the two INTACT phase III trials and phase II IDEAL trials, CTEP has had to consider its portfolio of studies with the small molecule EGFR inhibitors," Scott Saxman, a CTEP official, wrote in a memo addressed to the program's protocol and information office.

"The low response rates seen in the phase II trials, coupled with the negative results demonstrated by the phase III trials, strongly suggests that there is a small, as yet unidentified, population of patients with NSCLC who have the appropriate target for these agents," Saxman wrote.

"It is likely, therefore, that if there is a survival advantage for these agents, it will not be detected by continuing to conduct studies that dilute this effect by including both 'sensitive' (i.e. patients whose tumors have the target) with 'insensitive' patients (i.e. patients who tumors do not have the target and thus have no chance of benefit)," he wrote.

"While CTEP has remained committed to studying these agents both as single agents in the adjuvant setting and as maintenance therapy in patients with locally advanced disease, further large scale studies will need to await the identification of predictive factors that will allow selection of the appropriate patient population to be treated with these agents."

Schilsky disagrees with this approach.

"Unfortunately, the NCI has put up a major roadblock to studying the drug further by taking the position that they will not support phase III trials in lung cancer with Iressa until its biology is better understood," he said to **The Cancer Letter**.

"The only way we may ever really learn how to use it is to do well-conducted, large-scale trials with correlative science endpoints and sufficient sample size to sort out which groups are most likely to benefit."

Reimbursement for Iressa is likely to present a tangle of problems. Iressa is an oral drug, which means oncologists would not be reimbursed for administering it. Patients may not be reimbursed, either.

The Centers for Medicare and Medicaid Services recently began "national coverage analyses" of two cancer therapies that received accelerated approval from FDA.

In hospital outpatient prospective payment system regulations that went into effect Jan. 1, CMS reserved the right to deny reimbursement to any agent that "received marketing approval based on the use of surrogate endpoints" (**The Cancer Letter**, March 21).

"CMS must determine whether the cost of the therapy is outweighed by the benefit," said Mace

Rothenberg, a gastrointestinal oncologist at Vanderbilt and the principal investigator on the pivotal trial of Eloxatin, one of the agents now scrutinized by CMS.

"It is quite possible that Iressa might set a precedent by being approved by FDA for one indication, but reimbursed by CMS for a much narrower indication—if at all," Rothenberg said. "I believe that CMS is likely to request that additional studies be performed in order to identify more precisely those patients most likely to benefit from Iressa."

Biostatistician Fleming said CMS and other payers may be able to accomplish something FDA cannot: add rigor to the system of drug development.

"If CMS or private insurers did not pay, might we see some level of restoration of a sense of urgency on the part of the sponsors and investigators to complete the subsequent clinical endpoint trials in a timely and reliable manner?" Fleming said.

This may be the sort of help drug companies would rather do without.

Iressa Cleared For Narrow Indication Of Third-Line NSCLC; What Happens Next?

(Continued from page 1)

CL: What are your thoughts on this drug's usefulness? Should it have been approved?

PAZDUR: Does this drug have activity? The answer is yes. We believe the drug has a 10 % response rate, with 95% confidence interval ranging from 6 to 17%.

The median duration of response was seven months. The FDA looked at the x-rays of the responding patients who were entered in the clinical trial. Some patients had significant reductions in tumor size. Certain groups may have higher response rates. These include women, non-smokers, and patients with adenocarcinomas.

These observations were also present in the Japanese clinical trials and the expanded access program. These subgroup findings are exploratory and will be examined prospectively in randomized trials. For the FDA to approve this drug under accelerated approval (Subpart H), we needed to be convinced that the findings were reasonably likely to predict clinical benefit.

The emergence of the Japanese post-marketing experience caused us to devote significant time evaluating safety issues, especially interstitial lung disease. This toxicity was not discussed adequately at the ODAC meeting. We had to have a major submission looking at the Japanese post-marketing experience, the expanded access program, and reexamining randomized first-line trials.

The incidence of ILD is about 1%. The uncontrolled nature of single-arm trials, the expanded access program, and post-marketing trials from Japan made evaluation and attribution sometimes difficult to assess. Interestingly, the randomized trial in the first-line setting showed a 0.7% incidence of ILD and there was no difference in this toxicity between placebo or Iressa-treated patients.

FLEMING: It should not have been approved. What do we know about established benefit-to-risk of Iressa?

Regarding symptoms, the sponsor provided only uncontrolled data that didn't provide substantial evidence of benefit.

Regarding objective response rate in the indicated third-line setting, the sponsor provided two trials. The 0016 study had only 17 patients who were third-line patients, and only one of those was a responder.

So the essence of the data came from a single study, their 0039 trial, which yielded a 10 % response rate in 139 patients, but most of those responses were in very favorably selected patients, with slow-growing adenocarcinomas, and a large fraction of those having had measurable disease in only one or two lesions. The data on response is not compelling.

Regarding survival, there were two outstanding trials, randomizing 2,000 patients yielded consistent and compelling evidence that Iressa didn't provide survival benefit in a very closely related clinical setting.

Is there benefit? In a very small subgroup, less than 10 percent of treated patients. I think that is unclear, but there is a substantial risk that Iressa's toxicity, including interstitial lung disease, could ultimately mean that the agent has an unfavorable benefit-to-risk profile in the aggregate population that would be likely to receive it.

The results are sufficiently unimpressive that the lower bound of the 0039 trial didn't even meet the criterion of that particular protocol for what they needed to be able to establish.

More so than the statistics of how low the lower bound is, one has to be concerned about not just the relatively low response rate, but the relatively

unimpressive nature of those responses, and more so, the fact that we don't know in which group of patients we would anticipate having likely response.

We have to treat at least a tenfold number of patients to achieve a targeted subgroup that would potentially receive a benefit of unknown magnitude, and the cost of that potential benefit is potential toxicity, the financial cost, and inconvenience of administration.

SCHILSKY: The drug has minimal activity in a small and atypical subset of lung cancer patients. In view of the negative phase III trials, I think we have no idea at present whether the drug has benefit and, if so, who is most likely to benefit from it.

As to whether it should have been approved, I think it all hinges on whether one can accept a 10 % response rate as being predictive of clinical benefit, particularly in light of information that the drug does NOT confer benefit in earlier stage patients when combined with chemo. I could accept approval with a very narrow label.

BUNN: I believe it is useful for lung cancer patients who have failed chemotherapy. I think the accelerated approval was correct.

JOHNSON: I think the answer is Yes. This is a drug that shows some activity in these obviously preliminary studies. But I think the results of the IDEAL trials were sufficiently compelling that the drug warranted accelerated approval. There is a small subset of patients that benefit enormously from this drug. I don't know that we necessarily know how to select those patients, but people talk about that like it's something unique to Iressa. Frankly, we don't know how to select patients that respond to cisplatinum, either.

RUCKDESCHEL: It should be approved. It works dramatically about 10% of the time in third-line, and is a useful drug. No idea yet whether it should be moved up, because the studies haven't been done, but many are under way.

BELANI: The efficacy is real. There is QOL and symptomatic benefit as well. There are currently no other approved treatment options for patients with NSCLC who have failed therapy with first-and second-line agents. This novel treatment will fill an important need for patients with advanced NSCLC beyond second-line therapy. Yes, I think that the approval will help patients with NSCLC .

ROTHENBERG: From what I can glean from the available data, Iressa has a dramatic effect on some people. The tumor shrinkage and symptomatic improvement can be quite impressive.

I believe the data supported accelerated approval. My opinion is based on a reasonable objective response rate (10%), the beneficial impact of Iressa on tumor-related symptoms and disability, and a reasonably good correlation between the two. The fact that two large phase III trials failed to show a beneficial impact of Iressa in the front-line setting was quite discomfiting and really threw everyone for a loop. However, as we learn more about therapies like Iressa, we are beginning to gain important insights into why this may have happened.

CL: What about other accelerated approvals? Did the sponsors of Irinotecan, Eloxatin, Gemcitabine provide better data to back their accelerated approval applications?

PAZDUR: The FDA had no problem with the data quality and the design of these clinical trials. I have to credit AstraZeneca for a well-designed and comprehensive clinical development program. We believe the approval of Iressa is consistent with the risk/benefit relationship that has been observed in other accelerated approvals. Looking at response rates in single-arm trials, Irinotecan, approved in June 1996, had a 15 % (95% CI 10-20 %) response and considerably more toxicity, with approximately 25 % of the patients having hospitalizations for drug-related toxicities, and about 1.6 % of patients deaths potentially related to drug.

FLEMING: I'll skip that.

SCHILSKY: Irinotecan was marginally better than Iressa (13%) response rate. What is encouraging is that, even with such a low RR, four subsequent randomized trials showed a survival advantage for including Irinotecan. Hopefully the same will eventually be true with Iressa but AstraZeneca already has two negative trials! Eloxatin had a similarly low RR (9%) but at least that was an interim analysis of a randomized trial and not a single arm trial, so there was a concurrent control arm that was clearly worse. And, we already know from the NCCTG 9741 study that FOLFOX has a survival advantage over Saltz.

BUNN: I don't have the details of those submissions.

JOHNSON: I think everybody worries a little bit about accelerated approval. In a perfect world, would I want perfect data?

We are dealing with human beings here, and human clinical trials, where perfect data simply do not exist. The data clearly met the spirit as well as

the letter of the law. They were looking at an unmet need. They measured traditional endpoints, like response rates, times to progression, survival. They measured patient benefit in terms of symptom improvement. And there was correlation of those findings in a manner that would make one believe that this was a drug with activity in this very difficult subset of patients.

RUCKDESCHEL: The rigidity of the statistician-dominated FDA process has led to a dance where the comparison of "X" plus cisplatin against cisplatin alone for lung cancer is accepted as a randomized survival study warranting approval.

No one, even the most cynical, would ever use cisplatin alone as a treatment for lung cancer. Therefore, the studies were, to my mind, immoral and unethical, in that those physicians randomizing did not have a reasonable expectation to present to the patient that there was a standard therapy they were comparing to.

BELANI: In the above cases, mature phase III survival data were submitted leading to approval. However, there are examples where approval has been granted by the agency on just phase II studies—IL-2 , capecitabine, and Gleevec .

ROTHENBERG: Subsequent phase III trials of Irinotecan demonstrated improved outcome, including survival, in patients with advanced colorectal cancer who received single agent Irinotecan as 2nd-line therapy and, subsequently, as part of combination chemotherapy in the front-line setting. You may want to check your records, but I believe that gemcitabine received full, not accelerated approval in 1996. Approval was based on survival and clinical benefit response advantages of gem over 5-FU in one phase III trial and supportive data from a single arm trial performed in patients with relapsed disease. As for oxaliplatin, the jury is still out: it currently has accelerated approval and several important trials—including mature results from three phase III trials—will be presented at ASCO. We will see if any of these are compelling enough to convert this to full approval.

CL: Accelerated approval standards amount to an invitation to take a guess. Are these standards, as they are interpreted by FDA oncology division, rational and appropriate for a science-based agency?

PAZDUR: By definition, the accelerated approval regulations provide for the surrogate endpoint to be reasonably likely to predict clinical benefit.

There is a degree of clinical judgment involved with the link of the surrogate endpoint to the ultimate clinical benefit. Can a 10 % response rate translate into a survival advantage? We have observed this with other drugs. For example, Irinotecan had a 15 % response rate, and went on to demonstrate a survival advantage in the 5-FU refractory population, as well as in a first-line setting.

In a docetaxel trial in a second-line setting for lung cancer, a 5 % response rate was observed and associated with a survival advantage. A similar response rate associated with an improvement in TTP supported accelerated approval of oxaliplatin for refractory colon cancer. Reports have indicated a survival advantage for this drug in combination with 5-FU/LV in the first-line setting of colorectal cancer. These single-arm trials looking at response rate do not allow us to adequately assess TTP.

We encourage sponsors to investigate their drugs fully, during their development. We want them to test drugs in different settings, in different diseases. Unfortunately, the randomized first-line trials failed to demonstrate improvement in survival, TTP, or response rate by the addition of Iressa to two doublet combinations.

The drug studied in the context of these trials failed to demonstrate activity. At the ODAC meeting, several reasons were presented by the sponsor to potentially explain this lack of activity.

The results of the first-line studies do not test response as a surrogate for survival, because the addition of Iressa to chemotherapy in the first-line setting did *not* significantly affect the surrogate outcome (response rate). The purpose of a confirmatory trial in accelerated approval is to test the surrogate's relationship to clinical benefit.

We should be reminded that the sponsor is seeking a third-line indication—not a first-line indication. As stated previously, the FDA wants to encourage robust data packages and exploration of drugs in different indications and settings. We do not want to penalize sponsors for providing additional information.

We can learn things from "negative" trials. In this case, the drug is clearly labeled as a monotherapy, and physicians are instructed on the negative phase III trials.

FLEMING: The motivation behind accelerated approval is to provide earlier access to interventions that potentially could provide benefit to patients who

are in a life-threatening disease setting.

The basis for this assessment is to be, in general, use of a surrogate endpoint that is reasonably likely to predict a clinical benefit. The positive aspect of accelerated approval is the potential for providing earlier access to such patients. The unfortunate aspect is that these agents, which have only been established to be biologically active, may not be clinically effective.

Patients may be receiving interventions that are more toxic than effective.

It has been long recognized that one of the negative consequences of accelerated approval is the subsequent trials that are, in theory to be conducted in a timely way to validate whether the agent provides true clinical benefit may be much more difficult to complete in a reliable and timely manner.

This is due in part to the increased ability that patients on the control arm, receiving standard of care may cross into the intervention, thereby diluting our ability to assess longer-term benefits on important endpoints, such as survival, and to the risk that there would be decreased rates of enrollment to these trials.

I think these risks were very apparent in the ODAC meeting March 12-13, where eight agents were assessed by ODAC that had previously been granted accelerated approvals.

For illustration, one of these, Ontak in T-cell lymphoma, is in process for obtaining confirmatory data, where the current plan indicates an expected 12-year interval between the time that Ontak first received accelerated approval and when the relevant data from the confirmatory trial are expected to be available.

In the last three years, this pivotal study of Ontak has had enrollments of 7 to 9 patients. It is a striking example of the inadequacy of the timeliness of enrollment, and inappropriateness of the length of time taken to ultimately validate benefit.

Of those eight agents, the average time between the accelerated approval and the projected completion date of the ongoing confirmatory trial is at least ten years. There is, as a result, clearly, a reduced sense of urgency that exists in the completion of these confirmatory trials, relative to the sense of urgency that the sponsors and investigators have prior to marketing approval.

There is also a substantial concern with the approach taken at this point within the FDA oncology division, when the confirmatory studies do not yield clearly positive results. These concerns are illustrated by several of the applications reviewed at that ODAC meeting: Doxil in Kaposi's; Doxil in metastatic ovarian cancer. The confirmatory trials have been completed, and failed to show clear evidence of benefit.

Ethyol injection in renal toxicity has had completion of its pivotal study, where the control patients had one-third longer duration of response, 10 % longer time to progression, 20 % longer survival.

Yet, in each of these three instances, there hasn't been a withdrawal of these agents. There isn't a clear future plan.

If, in fact, accelerated approval is managed by providing a weaker scientific rigor for the agent's initial approval, requiring only effects on surrogates *likely* to predict clinical benefit, and if upon completion of the confirmatory trials there is not a commitment to provide a timely withdrawal of the agent, then accelerated approval is tantamount to full approval.

And if it is, in fact, tantamount to full approval, then how can we continue to implement accelerated approval with weaker criteria for approval than you would have for a full approval?

SCHILSKY: I think these standards are reasonable and probably the best we can do right now. Of the four drugs that got AA that have now completed post-marketing studies, every one has been converted to full approval based on clinical benefit. That suggests to me that RR is 'reasonably likely to predict clinical benefit' and that an educated guess may well pay off.

BUNN: I don't believe your assertion is correct. AA is used when there is a surrogate endpoint that is likely to mean clinical benefit, but has not bee proven to equate with clinical benefit. I think the standards are OK.

JOHNSON: I must say that in my time at ODAC, all of us have felt some unease when a company came in for accelerated approval. I think this unease may be lessened if at some point along the way, if follow-up studies on a drug prove negative, and FDA rescinds the approval. If that were to happen, it shows that there's teeth in this. I do worry that that may be a politically challenging thing for FDA to do.

RUCKDESCHEL: I think the "educated guess" approach is a much better way of approving drugs for life-threatening diseases than a trumped-up phase III study.

BELANI: Decision has been based on expertise and data—the efficacy is real and a certain

number of patients do benefit. I think that the interpretations were appropriate and rational.

ROTHENBERG: Once again, I think that this exposes our naiveté about cancer. We don't know as much as we think we know. However, that has never stopped us from developing drugs in the past, nor should it deter us from developing better drugs in the future. The key thing to keep in mind is that these drugs work in ways that are very distinct from other available drugs and, as we learn more about their mechanisms of action, will allow us to integrate them in a more directed and effective manner.

CL: With Iressa, you see a drug that the sponsor describes as "targeted," but we don't know whether the agent interrupts the molecular target, and we don't know how to prescreen patients who might benefit. Is this what you expected from 21st Century medicine?

PAZDUR: From a clinical perspective, a targeted therapy that does not have a measurable target is not a targeted therapy. The FDA would hope sponsors would develop prospective target in conjunction with a comprehensive drug development plan. The clues of greater activity in subsets of patients (women, nonsmokers, adenocarcinomas) suggest some selectivity. This needs to be confirmed prospectively in randomized trials.

The division had considerable negotiations with the sponsor on the wording of the mechanism of action. We believe the drug, as stated in the package insert, inhibits numerous tyrosine kinases, including those associated with EGFR. In other words, the specificity is questioned.

FLEMING: If a drug providing the clinical burden of toxicities, cost and inconvenience of administration has at best clinical benefit in a small subset of patients, then how does one effectively and responsibly use that agent, if you cannot predict in advance who the patients are, who would be likely to benefit?

A positive example of an effective targeted intervention is Herceptin, where by assessing the levels of Her-2 overexpression, one is in a position to predict those patients likely to benefit.

A poor example is Iressa. Who are those patients? If, in fact, there is a subgroup of 10 % of patients who may be provided some clinical benefit, who are they?

SCHILSKY: We clearly don't know how to use this drug. At least 90% of patients who might get it are not likely to benefit from it and we don't know how to pick out the 10% who will benefit from it. So, it is no different from most any other chemotherapy drugs in that respect. Indeed, we can do better with 5-FU (a targeted drug). If patients are carefully selected based on tumor thymidylate synthase and dihydropyrimidine dehydrogenase expression, we can increase the 5-FU response rate from 15% to 50% without changing a single thing about the treatment. So our "21st Century medicine," with respect to Iressa, is no better than what we can accomplish with a drug from a half-century ago!

BUNN: No and obviously this is the critical question. That being said, all the companies know that this is the cornerstone to being the most successful and are trying to find the answers. The answers are not easy or obvious.

JOHNSON: I think it is 21st Century medicine at the moment, but it isn't what I expect. I expect there to be changes in the near future in our ability to be more precise in "targeting" therapy.

I wish the term "targeted therapy" had never been coined, at least in conjunction with drugs like Iressa. Remember, chemotherapy is, technically, targeted therapy. 5-FU hits thymidylate synthase. That's about as targeted a therapy as you can get.

We know a lot more now that we did 10 years ago. We thought we knew how they worked 20 and 30 years ago, but the term apoptosis was just not in anybody's lexicon. And now we say, these drugs induce apoptosis… Well, duh!

The issue with Iressa was that we were quite confident that EGFR expression was going to be somehow like HER-2 expression, a useful measurement. In fact, it's not. And in fact, these data were known in preclinical studies.

We actually alluded to that when we designed the phase III trials, the INTACT trials. This is one of the reasons we chose not to measure EGFR. It made no sense to do so. It's not the primary factor that determines a patient's responsiveness to Iressa. We are developing some clues about how and why and in what groups of patients these drugs actually work.

As a clinician, I still believe that clinicians are not irrelevant. It was clinicians who observed that bronchioloalveolar carcinoma was, in fact, the histology that seems more responsive to these drugs. When AstraZeneca first was contemplating doing trials, they expressly wished to exclude BAC patients, because, historically, they don't respond well allegedly to chemotherapy and other treatments, and some of us argued rather vociferously that why would you

exclude something when you don't even know what the response rate may be.

Looking at this from a purely scientific perspective, an approval allows a little more freedom amongst clinical investigators to begin to explore some of the very questions that you are asking, that a company, for understandable reasons, is less inclined to want to do at the front end, when they have limited funds and a limited supply of drugs.

RUCKDESCHEL: There seemed to be a race to market for the targeted therapies. I think the company failed to do the proper subset analyses to validate the targets. This is in stark contrast to Herceptin, where before the drug was generally released, we knew what subsets it worked in, and we knew how to test for them.

BELANI: It is the first 'targeted' therapy for lung cancer—but I agree that we do not know the true effect on the target, i.e., EGF receptor.

The future will depend on proper patient selection and to identify those who will benefit before they receive the treatment—this is being addressed in various ongoing and proposed studies.

If we are successful, the efficacy rates will be very high—similar to what has been seen with Gleevec for gastrointestinal stromal tumor and Herceptin for breast cancer. Though one would hope that a 21st Century medicine would cure cancer, but that is far from reality. Proper patient selection will be the key not only for Iressa, but for all targeted agents.

ROTHENBERG: I think accelerated approval is a very appropriate mechanism to speed the approval of drugs for patients for whom no effective therapy exists. I believe that this mechanism represents an appropriate and important response by the FDA to the needs of desperately ill patients who, in most cases, might be willing to accept a higher degree of risk and uncertainty in order to have access to beneficial therapies. Remember, accelerated approval is not a "free pass." There must be clear demonstration of clinical benefit that is meaningful to the patient.

CL: What about off-label use? If the patients flee chemo in favor of this agent, would this be a benefit or a decline in the standard of care for lung cancer?

PAZDUR: We would encourage the sponsor to do further studies to determine the indications where the drug may be commonly used. Since we recognized that the drug is likely to be used off-label, in the second-line setting, the company must study this drug in a randomized study comparing Iressa to Taxotere in patients who have progressed after first-line treatment. This was a mandated Subpart H trial.

FLEMING: It would be very unfortunate for patients to use an agent that may well fail to provide benefit in lieu of chemo regimens proven to provide survival benefit. How can we argue that there is a compelling need to provide earlier access to therapies with unproven benefit, and yet not recognize the compelling need to maximize implementation of agents proven to provide benefit?

SCHILSKY: Fleeing chemo in favor of Iressa would clearly be a mistake, since we have data to show that chemo improves survival and no such data for Iressa. It should be used only within the narrow label.

BUNN: Off-label use will be justified when there are two or more publications justifying the use, and/or when the physician has good reason to believe its use is justified—just like any other off-label use.

JOHNSON: I am very concerned about that. Obviously, we have no data—at least published data—and limited data on first-line use of single-agent Iressa. I think that's important data to have. And we are doing studies in highly experimental settings to try and make that determination.

Obviously, in the INTACT trials, there was no benefit in adding Iressa upfront with chemotherapy. I have already seen patients through the expanded access program who were getting Iressa as their first, initial therapy.

There is no way to police such a situation. I've had patients come to me for second opinions, who I thought were pristine, treatment-naïve patients, and I would say, "I think you might be a good candidate for a study with one of these TKIs." And they say, "Oh, yes, I am taking that now. I got it though my doc in East Elsewhere, through the expanded access program." That means that somebody was not being totally forthcoming and truthful. Patients did that with Herceptin, when Herceptin was available through expanded access.

RUCKDESCHEL: If it is used off-label, and it will be, I don't think there will be any appreciable change in outcomes.

BELANI: Off -label use is likely to occur—there will always be patients who will refuse chemotherapy.

Chemotherapy is still the standard of care in the first line setting and until convincing evidence is seen

in select subgroups, I hope it is not used instead of chemotherapy.

The approval allows the treatment to advance to the next level and I see no 'decline' in lung cancer care overall with the approval of Iressa.

ROTHENBERG: I don't think that we'll see much of that. Over the past several years, we have come to the realization that this new generation of drugs will supplement rather than supplant existing therapies.

CL: Iressa is an oral drug. That means no Medicare reimbursement. Will oncologists prescribe Iressa, in view of its less than overwhelming efficacy, combined with the fact that they would not get paid for administering it?

PAZDUR: The FDA approved this drug because of its safety and efficacy. This overall risk-benefit ratio was consistent with other approvals under Subpart H. FDA is not involved in drug reimbursement nor drug pricing.

FLEMING: I'll leave that to my oncology colleagues.

SCHILSKY: I suspect that there will be intense pressure from lung cancer patients to get the drug and the docs will prescribe it early and often.

BUNN: I don't think reimbursement will be a big issue, just like it has not been a big issue for tamoxifen, Gleevec or capecitabine. Getting CMS to reimburse patient costs is a huge issue.

JOHNSON: We give drugs all the time that we don't get paid for administering. We give Zofran. We give tamoxifen. We give Xeloda. ASCO has long held a position that oncologists would prefer not to have to sell chemotherapy drugs in order to make money to run their practices.

Will docs use this drug? The answer to that is Yes. Now, why will individual doctors use it may change. Some doctors may use it because they think it's the right thing. Some may use it because their patients demand it.

If they don't use it, the patient may say, "Screw you, Jack, I am going down the street to Dr. X, because it's now commercially available," and then you lose the revenue of not taking care of a patient who wants a particular drug.

The other reason is that lung cancer is a horrible disease, and no doc wants to see his or her patients suffer, and if they think that even if there is only a 10-% chance of this drug helping, the toxicity profile is so modest that it's worth a try.

And if the data from IDEAL are, in fact, correct, that this is a drug where people feel well quickly, then one would know in a matter of six to eight weeks, and one could stop the drug if there is no benefit.

RUCKDESCHEL: Oncologists will prescribe it, because patients will demand it. Medicare does not competently reimburse for the care of cancer patients. They under-pay for "administration" costs and wink and tell the docs to make it up on the drug reimbursement side. Oh, the shock when someone in congress gets on their case because of the mark-up on cancer drugs. It makes as much sense as airline ticket pricing.

BELANI: In my view, decisions like this should not be made on financial benefits to individuals. You bring up an issue: Should development of all oral agents be stopped?

I think not, and I hope not. I hope oncologists will appropriately prescribe the agent and Medicare will eventually change their policy—it is only in their own benefit. If cancer could only be converted from an acute illness to a chronic disease by an oral drug (especially if it does not cause significant toxicity), we should continue to look for it, and I hope that day is near.

ROTHENBERG: I believe that oncologists will prescribe Iressa appropriately, at least at first. I think that they will have no choice since third-party payers are likely to be very restrictive about reimbursement for what is likely going to be an expensive drug. However, there is already a very extensive clinical trial program underway to identify other tumors in which Iressa may have activity. I think that off-label use is likely to grow over time as promising data emerge from those other trials.

CL: If oncologists don't prescribe it, will cancer patients go away to internists or Canadian pharmacies, after Canadian approval?

PAZDUR: This is not an FDA issue. I defer to physicians who treat lung cancer.

FLEMING: Ask my oncology colleagues who have more direct evidence.

SCHILSKY: Maybe they'll just be able to order it from Amazon.com.

BUNN: A theoretical question that I don't think will be realized.

JOHNSON: Internists, by and large, don't prescribe drugs like tamoxifen, nor do I believe they should. I don't prescribe certain antibiotics, even though I am by license capable of doing so.

Bluntly, I think most internists have enough on

their hands, trying to deal with day-to-day illnesses of most adults that they are not about to learn how to deal with lung cancer and Iressa.

RUCKDESCHEL: The real worry is that non-oncologists will be able to prescribe it. Witness the demise of pure hematology, as anyone could test for and prescribe B12, folate, B6 or iron. The absence of reimbursement is another bit of Medicare stupidity. They will eventually pay, but first, they will put patients, families and institutions through the wringer for months or years.

BELANI: I really do not think that this is going to happen.

ROTHENBERG: It is unlikely, especially if Iressa is aggressively priced. We'll have to wait and see.

CL: Would it be ethical or even possible for Zeneca to conduct post-approval trials of this agent?

PAZDUR: The FDA would not have approved the drug if we did not believe that post-marketing trials could and would be undertaken with "due diligence." There are already two trials accruing patients that have the potential to demonstrate clinical benefit. Those trials include an adjuvant trial in resected lung cancer patients and a trial examining Iressa's role after radiation therapy and chemotherapy. In requested trials with the potential of demonstrating clinical benefit in the approved third-line setting, the sponsor has made a commitment to have significant accrual in geographic areas outside the U.S. where the drug is not approved. The agency was fully aware of this potential accrual problem in negotiating phase IV commitments.

FLEMING: We don't know whether Iressa provides a clinical benefit, and if it does, to whom. It is ethically and scientifically imperative to determine whether it has a favorable benefit-to-risk profile in the labeled population, and if such trials do not provide timely evidence establishing benefit, Iressa should be promptly withdrawn from the market.

SCHILSKY: It would be unethical NOT to conduct such studies. This drug is not without toxicity and it is likely to be expensive. We desperately need to learn how best to use it and we can only do that with well designed trials.

Unfortunately, the NCI has put up a major roadblock to studying the drug further by taking the position that they will not support phase III trials in lung cancer with Iressa until its biology is better understood.

The only way we may ever really learn how to use it is to do well-conducted, large-scale trials with correlative science endpoints and sufficient sample size to sort out which groups are most likely to benefit. As to whether it will be possible, I believe it will, so long as the drug is provided for free in the trials.

BUNN: Yes, they are planned, ethical, and I believe that they will be done. This is actually the biggest issue for accelerated approval, in my opinion.

JOHNSON: I think it's going to be unethical not to do the trials. This approval may make getting the kinds of studies done that all of us feel would be ideal, no pun intended, may be more challenging with the drug out there.

RUCKDESCHEL: Its ethical to do them, but what is the incentive? AstraZeneca was concerned near the end of the process when this unusual pulmonary toxicity was reported from Japan. Therefore, the company was cautious about authorizing studies. Now that it's available, we will be able to test it in a wide range of studies and against a wide range of targets. The investigators will study this drug extensively, and we will learn quite quickly what this drug really does and whether it has any unusual toxicities.

BELANI: It is perfectly ethical to conduct post-approval trials. Controlled clinical trials have in fact been designed by AstraZeneca as I understand from reading the news and comments by the FDA. Crossover to the treatment arm should be permitted if early benefit is not seen—window of opportunity' studies as one would describe them.

ROTHENBERG: It is not only ethical, but imperative for AstraZeneca to do so. Only in this way will we have any chance of learning which patients are most likely to respond to this therapy. I think that without these kinds of trials, we would end up in the ironic position of using a "targeted" therapy in a very "untargeted" manner.

CL: There was a major patient presence at ODAC, and, clearly, it had an impact on the committee. Are you concerned that decisions to approve or not approve are becoming less scientific and more political?

PAZDUR: ODAC members should formulate their opinions on all available evidence, including patient testimony.

FLEMING: Approval decisions should be based on science and reason, not on emotion. In turn, approval decisions should be based on reliable scientific evidence, not on testimonials from a biased

selection of treated patients.

SCHILSKY: There is always politics, but the decision on whether drugs are safe and effective for the American public should be based on data.

BUNN: Concerned, yes, but I still think science and physician experience carry the day.

JOHNSON: It looked to me like patients coming forward and saying, "I wouldn't be here if not for this drug," which may be true. But all of us who sit on these panels understand that there is always a case or two that does well.

The people who can't come forward and speak are the ones who are dead. The people who died because of their disease or because of the drug, those are the ones aren't standing there saying, "I am not here today because I am dead." Just by the nature of how it's done, there is a bias interjected.

The public should, and has every right, to participate. I have no doubt that in this instance, patient testimony had an impact on not just ODAC, but FDA, and, quite frankly, a lot of people. How often do you see people with metastatic lung cancer standing in front of you saying, "I am well, I am alive, and I am doing great."

That's just vanishingly small. It had an impact. It may be like the courtroom statement that the judge says, "Ignore that comment. Strike that from the record." You cannot ignore that or strike that from your brain.

RUCKDESCHEL: I think the role of advocates at the meetings is appropriate, but it should not be a Greek chorus.

BELANI: I think that the approval is still scientific and the efficacy is real. We have seen the benefit ourselves. Patient presence substantiates the efficacy.

ROTHENBERG: I think that it is imperative to have patient and lay involvement in the drug approval process. However, I'm not sure that having patient testimonials at ODAC is the best way of involving the public in this process. I think that the FDA should incorporate patients, family members, and interested members of the public in all levels of the drug evaluation process.

It would also be incumbent for these representatives to have a more complete and accurate knowledge of the guidelines by which new drugs are evaluated and approved. The effect of extraneous, "political" forces must be limited as much as possible.

CL: Should CMS or private insurers pay for this drug?

PAZDUR: This is not an FDA issue.

FLEMING: I don't know, but maybe not. Agents approved under accelerated approval do not have established efficacy. If CMS or private insurers did not pay, might we see some level of restoration of a sense of urgency on the part of the sponsors and investigators to complete the subsequent clinical endpoint trials in a timely and reliable manner?

SCHILSKY: If it is FDA-approved, they should pay for it within indication and cover the costs of patient participation in clinical trials designed to study it further.

BUNN: Of course.

JOHNSON: I find it amazing that CMS has the capacity to decide this independent of the FDA. It seems to me that FDA is the agency that determines whether a drug should be approved.

In my mind, until Congress changes its rules and regulations, CMS ought to pay for the drugs. Should they pay for an accelerated approval drug, I have to confess, there I think they should, but I can understand why CMS might say, "We are waiting for confirmatory data, before we go forward with payment."

I can understand that. I didn't say I agreed with that, but I can understand it. It's sort of like saying that a woman shot her husband for dilly-dallying around on her, I don't condone it, but I understand it.

RUCKDESCHEL: Yes.

BELANI: They should. The burden should not fall on the patient. The patient already has overwhelming pressure and distress from the disease.

ROTHENBERG: In the past, Medicare and Medicaid automatically paid for FDA-approved indications of any new anticancer drug. However, that is changing. CMS now performs its own review of new drugs to determine whether the agent represents a true therapeutic advance over existing therapies.

Unlike the FDA, CMS takes cost into account. Lung cancer kills more Americans each year than any other cancer. Given the number of individuals likely to receive Iressa in a given year, CMS must determine whether the cost of the therapy is outweighed by the benefit.

It is quite possible that Iressa might set a precedent by being approved by FDA for one indication, but reimbursed by CMS for a much narrower indication—if at all. I believe that CMS is likely to request that additional studies be performed in order to identify more precisely those patients most likely to benefit from Iressa.

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