Targeted Therapies in Combination with Chemotherapy in Non–Small Cell Lung Cancer

David H. Johnson

Abstract

With rare exceptions, attempts to combine so-called targeted agents with standard cytotoxic chemotherapy in advanced non–small cell lung cancer have yielded disappointing results. The reasons underlying these spectacular failures are not always fully understood, but certainly the lack of careful patient selection is a major contributing factor. In addition, recent preclinical and clinical studies indicate that antagonism may exist between the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and chemotherapy primarily in tumor cells with wild-type EGFR. By contrast, tumor cells harboring somatic mutations in EGFR experience massive apoptosis when exposed to the EGFR tyrosine kinase inhibitors. Therefore, in theory, mutant tumor cells should exhibit enhanced cell kill when treated with concomitant chemotherapy and EGFR tyrosine kinase inhibitors akin to what is observed with chemotherapy and trastuzumab in breast cancer. Clinical data from the recently completed TRIBUTE trial support the latter possibility. Ideally, future studies of EGFR tyrosine kinase inhibitors and other targeted drugs will use careful patient selection criteria based on well-characterized and validated predictive markers. However, in the absence of such biomarkers, clinical judgment, common sense, and innovative clinical trial design are necessary to avoid undue delay in drug development.

One only has to casually peruse the lay or scientific press to appreciate the high level of enthusiasm for the burgeoning field of so-called targeted therapy in the management of various malignancies, including non–small cell lung cancer (NSCLC; refs. 1, 2). However, in spite of some recent notable successes using targeted therapy (3), classic cytotoxic drugs remain the mainstay of treatment for locally advanced and metastatic NSCLC and more recently as an adjunct to surgery for patients with resected early-stage disease (4, 5). Thus, it is not surprising that investigators continue to use standard chemotherapy as the foundation on which newer treatment regimens are developed for NSCLC. Most of the earliest efforts to incorporate targeted agents into the treatment of NSCLC concentrated on patients with advanced, metastatic disease, which may not be the optimal setting in which to test these drugs. However, this approach is based in part on data derived from preclinical studies indicating that some targeted drugs yielded additive or even synergistic cytotoxic activity when combined with chemotherapy (6, 7). Unfortunately, with one notable exception (8), all of these efforts have failed. This review will assess some of the posited reasons for the failure of these early trials and will touch briefly on some promising new molecular targets other than the epidermal growth factor receptor (EGFR; to be discussed elsewhere in these conference proceedings). I will also outline some clinical trial strategies to avoid the spectacular phase III failures of the past.

INTACT, TRIBUTE, and TALENT Trials

By now, the results of the INTACT, TRIBUTE, and TALENT trials are well known (refs. 9–12; summarized in Table 1). Each of these studies was designed based on the knowledge that gefitinib and erlotinib have shown impressive antitumor activity in patients with refractory, advanced NSCLC with only modest toxicity (13, 14) and on the premise that these drugs could enhance the cytotoxic effects of standard chemotherapy agents as shown in preclinical studies (6, 7). Thus, it was widely anticipated that combining EGFR tyrosine kinase inhibitors (TKI) with standard chemotherapy would improve outcome in advanced NSCLC compared with chemotherapy alone, and yet all four trials failed to meet their primary end point of improved survival. Why?

The principal criticism leveled at the INTACT and TRIBUTE trial centers on failure to select a proper study population likely to benefit from this class of targeted agents (15, 16). Of course, this particular criticism assumes that an appropriate predictive factor was already well characterized at the time these studies were undertaken. In fact, before initiating these studies, no such predictive marker was universally accepted, nor was there a clear correlation between expression of EGFR (the putative target) and the growth-inhibitory activity of gefitinib in...
preclinical or clinical studies (17, 18). In addition, these studies were undertaken before the discovery of the recently described somatic EGFR mutation in NSCLC that renders tumors more responsive to gefitinib and erlotinib (19–21). However, even today, the optimal molecular marker of gefitinib and erlotinib activity is a matter of controversy (20–25).

Nonetheless, the likelihood of a positive outcome might have been increased by using specific clinical features to select patients for enrollment (26). Early on, even before the discovery of the activating EGFR mutations, certain clinical and histologic characteristics seemed to predict for a higher likelihood of response to EGFR TKIs (13, 26, 27). The predictive ability of some of these factors, most notably smoking history and histology, has held up in several subsequent reports (19, 27) and two prospective trials (3, 11). Whether such selection criteria would have made a difference in the outcome of these phase III trials is purely conjectural, of course, but in retrospect it seems as if it would have been a useful step, especially if one accepts the premise that an EGFR mutation is a necessary feature for a favorable outcome. This is because these clinical features seem to track fairly closely with the presence of EGFR mutations (28). Parenthetically, based on recent reports, mutational status alone might be insufficient to select all patients potentially benefited by EGFR TKIs (23, 24). In any case, had clinical features been used prospectively to select enrollees, these studies might have yielded very different outcomes. Another valid criticism of these studies, or at least of INTACT-2, is the fact that a contemporarily initiated phase II trial testing the activity of chemotherapy plus gefitinib or erlotinib based on preclinical models (32, 34, 35). However, the results of a recently halted Southwest Oncology Group trial showed that sequential use of gefitinib after combined modality therapy in locally advanced NSCLC yielded a numerically worse survival outcome (36).

It is also now well established that gefitinib and erlotinib have proapoptotic effects as well as antiproliferative effects (32, 37–39). In theory, the proapoptotic effects of gefitinib or erlotinib should enhance the effectiveness of cytotoxic drugs. If true, combining the EGFR TKIs with chemotherapy should be a good strategy akin to combining trastuzumab with chemotherapy in breast cancer. Another look at the TRIBUTE data suggests that this may be the case specifically in patients with an EGFR mutation (ref. 33; Table 2). The TRIBUTE data

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patient no.</th>
<th>Odds ratio (%)</th>
<th>Time to progression (mo)</th>
<th>Mean survival time (mo)</th>
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<td>INTACT-1</td>
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<td>51.2</td>
<td>5.8</td>
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<td>50.3</td>
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<td>INTACT-2</td>
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<tr>
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<td>29.9</td>
<td>5.7</td>
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<td>5.1</td>
<td>10.6</td>
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NOTE: Data from Giaccone et al. (9), Herbst et al. (10, 11), and Gatzemeier et al. (12).
Abbreviations: P, cisplatin; Gem, gemcitabine; G, gefitinib; Cb, carboplatin; Pac, paclitaxel; E, erlotinib; ↓, 250 mg; ↑, 500 mg.

Table 2. Overall response rates in TRIBUTE with or without EGFR mutation

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<tr>
<th></th>
<th>EGFR mutation (%)</th>
<th>Wild-type EGFR (%)</th>
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<tr>
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<tr>
<td>Overall response rate</td>
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<tr>
<td>Stable disease rate</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td>Progressive disease rate</td>
<td>13*</td>
<td>21</td>
</tr>
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</table>

NOTE: Data from Eberhard et al. (33).
Abbreviations: CT, chemotherapy (carboplatin + paclitaxel); E, erlotinib.
*P < 0.01.
suggest that the antiproliferative effects of the EGFR TKIs seem to be the dominant antitumor effect in tumors with wild-type EGFR, whereas tumors harboring one of the identified EGFR mutations experience profound apoptosis when exposed to an EGFR TKI (37, 39). These observations indicate that more studies are needed to determine the optimal scheduling of EGFR TKIs and chemotherapy.

Future Directions

In light of the INTACT, TRIBUTE, and TALENT failures, one might question the wisdom of continued trials that seek to combine standard chemotherapy with a targeted agent, such as gefitinib or erlotinib. This concern has been allayed somewhat by the recent finding that bevacizumab, when administered concomitantly with chemotherapy, imparts a statistically significant survival improvement in advanced lung adenocarcinomas compared with chemotherapy alone (8). Moreover, continued progress in our knowledge of lung cancer biology will doubtless provide many additional opportunities to build on this exciting advance (1, 40).

HER-2/neu. HER-2/neu is a member of the family of receptor tyrosine kinases that includes EGFR (41). The knowledge that HER-2/neu plays a role in the pathogenesis and progression of lung cancer dates back to at least 1990 when Kern et al. described a negative effect of HER-2/neu expression on the survival of patients with lung adenocarcinomas (42). Subsequently, these investigators found that a monoclonal antibody to HER-2 inhibited the growth of HER-2/neu-expressing lung cancer cell lines in a dose-dependent manner (43). This important observation went more or less unexplored until nearly a decade later when several groups initiated phase II trials designed to assess the effect of trastuzumab on the response rate and survival of lung cancer patients (44–48). Support for these trials came from preclinical studies indicating that trastuzumab could inhibit growth of lung cancer cell lines in vitro (49). Moreover, a significant synergistic effect was seen when trastuzumab was combined with cytotoxic agents (i.e., gemcitabine, cisplatin, vinorelbine, and paclitaxel) in HER-2/neu-positive cell lines (49). Unlike the preclinical studies with EGFR, treatment effect was shown to correlate with the level of HER-2/neu expression (49). However, in spite of these encouraging preclinical data, the results of the completed phase II studies were thought to be insufficient to carry forward into larger phase III studies in large part due to the low rate of HER-2/neu overexpression. In fact, using the HercepTest (DAKO, Carpinteria, CA) immunohistochemistry assay, only 6% to 8% of NSCLC tumors have 3+ overexpression (50, 51). Likewise, increased gene copy number as determined by fluorescence in situ hybridization is quite rare (51). Positive HER-2/neu expression is most often seen in adenocarcinomas but rarely in squamous cell carcinomas or large cell carcinomas, further limiting the population from which patients might be drawn for a large-scale study. Thus, to conduct a phase III trastuzumab trial in NSCLC potentially would require the screening of an extremely large number of patients to identify the relatively small percentage of patients with tumors overexpressing HER-2/neu. Many experts feel such a study would be logistically difficult if not impossible.

In spite of the potential logistical problems described above, the recent discovery of somatic mutations in HER-2/neu has rekindled interest in HER-2/neu as a potential target (52, 53). Recently, Stephens et al. identified in-frame and missense mutations in the kinase domain of HER-2/neu in 4% of 120 primary lung tumors (52). This figure is remarkable similar to the aggregate number of 3+ HercepTest patients screened for the published clinical trials (44–48). Similar to the frequency of EGFR mutations, all HER-2/neu mutations were found in adenocarcinomas. Subsequently, Shigematsu et al. sequenced the HER-2/neu tyrosine kinase domain in 671 primary NSCLC tumors and 80 NSCLC cell lines (53). In contrast to the work of Stephens et al., these investigators found HER-2/neu mutations in just 1.6% (11 of 671) of primary tumors and one adenocarcinoma cell line (NCI-H11781). All HER-2/neu mutations were in-frame insertions in exon 20 and target the identical corresponding region as did EGFR insertions. Notably, however, HER-2/neu mutations were significantly more frequent in never smokers (3.2%; \(P = 0.02\)) and adenocarcinoma histology (2.8%; \(P = 0.003\)). Interestingly, among the adenocarcinoma cases, HER-2/neu mutations preferentially targeted Asian ethnicity (3.9%) compared with other ethnicities (0.7%), females (3.6%) compared with males (1.9%), and never smokers (4.1%) compared with smokers (1.4%). Mutations in EGFR, HER-2/neu, and KRAS genes were never present together in individual tumors and cell lines. As noted by these investigators, the remarkable similarities of mutations in EGFR and HER-2 genes involving tumor type and subtype, mutation type, gene location, and specific patient subpopulations targeted are unprecedented and suggest similar etiologic factors (53).

Collectively, these data suggest that inhibitors of HER-2/neu should be considered for retesting in NSCLC albeit in a more defined way. Given preclinical data showing marked synergistic growth inhibition when standard cytotoxic chemotherapy is combined with trastuzumab in HER-2/neu-expressing cell lines (49), it seems reasonable to consider administering trastuzumab concurrently with chemotherapy. However, unlike previous studies, trastuzumab should be tested in the subset of lung adenocarcinomas that overexpress HER-2 protein, have an increased gene copy number, or carry a HER-2/neu mutation (52, 53). In support of such a trial, Gatzemeier et al. reported an overall response rate of 83% and a median progression-free survival of 8.5 months in HER-2/neu 3+ and fluorescence in situ hybridization–positive NSCLC patients, which is considerably better than what is normally achieved with chemotherapy alone (48). Although performing a phase III study in a population selected for a molecular abnormality that occurs in <5% of patients is a daunting challenge, it can be done efficiently under the right circumstances. Simon and Maitournam calculated that a randomized trial in as few as 138 patients could detect a 20% survival improvement over baseline, provided one has a validated molecular target and a means of testing for the presence of the target (54).

Raf. The RAS-RAF-MEK-ERK-MAPK pathway is a potential therapeutic target because it represents a common downstream pathway for several key growth factor tyrosine kinase receptors that are often mutated or overexpressed in human cancers (reviewed in ref. 55). RAF is a serine/threonine kinase and consists of three isoforms, ARAF, BRAF, and CRAF (Raf-1; refs. 55, 56). Although mutations in ARAF and Raf-1 have not been reported in human tumors, BRAF somatic missense mutations were recently noted to occur in two thirds of malignant.
melanomas and at a somewhat lower frequency in other human cancers (57). All BRAF mutations are within the kinase domain, with a single substitution (V599E) accounting for 80% of the reported mutations in melanomas. It has been suggested that BRAF activation is less complex than ARAF or Raf-1 activation, possibly accounting for its greater activation of downstream MEK and also for its preferential targeting for mutational activation in human malignancies (56).

BRAF mutations also occur in NSCLC, albeit infrequently (58, 59). Moreover, the BRAF mutations noted in NSCLC frequently differ from the V599E mutation commonly described in melanoma, suggesting that NSCLC BRAF mutations are qualitatively different (59). These different mutational patterns may portend a differential responsiveness to RAF inhibitors between lung cancer and melanoma. Interestingly, BRAF mutations are rarely found in tumors harboring KRAS mutations, suggesting that these mutations provide an equivalent, or at least a redundant, oncogenic stimulus in cancer pathogenesis (57, 60). This pattern is reminiscent of the mutual exclusivity of somatic EGFR and KRAS mutations found in NSCLC as described above (28). Thus, although uncommon, BRAF mutations in human lung cancers may identify a subset of patients that is distinct from those with other specific somatic mutations, thereby further expanding the pool of patients potentially benefited by targeted treatments.

Sorafenib (BAY 43-9006) is an orally administered selective inhibitor of Raf-1 that possesses significant activity against vascular endothelial growth factor receptor-2, vascular endothelial growth factor receptor-3, platelet-derived growth factor receptor-β, Flt-3, and c-KIT. It has shown broad-spectrum antitumor activity in colon, breast, and NSCLC xenograft models (61–63). In phase I trials, sorafenib is generally well tolerated with no dose-limiting toxicity yet encountered. The most common toxicities include diarrhea, nausea, abdominal cramping, pruritus, rash, and cheilitis (63). Ratain et al. recently reported a prolonged progression-free survival with sorafenib versus placebo (24 versus 6 weeks; \(P = 0.0087\)) in renal cancer patients enrolled in a randomized discontinuation trial (64). These results subsequently lead to a phase III trial in renal cancer in which 700 patients were enrolled (63). Although response rates did not differ between the two groups (as one might expect from a cytostatic agent), median progression-free survival was statistically superior in the sorafenib-treated arm (24 versus 12 weeks; \(P < 0.000001\); ref. 65). Given the single-agent activity of bevacizumab in renal cell cancer (66), it is entirely possible that this beneficial effect is primarily related to the anti–vascular endothelial growth factor activity of sorafenib as opposed to its RAF-inhibitory effects. Even if this supposition is correct, a strong argument can still be made for testing this agent in NSCLC given the results of Eastern Cooperative Oncology Group E4599 trial (8). Nonetheless, these encouraging data have resulted in further studies being initiated in other tumors harboring perturbations in the RAS-RAF-MEK-ERK-MAPK pathway, including studies in NSCLC. For example, the Eastern Cooperative Oncology Group has an ongoing randomized discontinuation trial under way in patients with stable disease following initial chemotherapy, and the manufacturer of sorafenib has recently initiated a phase III trial in previously untreated patients comparing chemotherapy with and without sorafenib.

Given the relatively infrequency of RAF mutations in NSCLC, one might question the wisdom of such a trial design. Interestingly, however, Wan et al. recently reported that sorafenib interacts preferentially with an inactive conformation of BRAF, suggesting that the mutant form of BRAF might be less sensitive to this agent (67). They found that the V599E mutant form of BRAF is 2-fold less sensitive to sorafenib than wild-type BRAF. Therefore, like other targeted drugs (68), our knowledge of the precise mechanism of action of sorafenib may be incomplete, suggesting occasional empiricism still plays a role in study design.

### Optimal Design of Trials for Targeted Agents

The optimal design of studies undertaken to assess the activity of targeted agents has been much discussed in the literature but perhaps nowhere more cogently than by Ratain and Eckhardt in a recent editorial (69). These drug development experts suggest that the biggest challenge in oncology drug development today relates to phase II testing of targeted agents. They note that the RECIST criteria, commonly employed to judge drug “activity,” may not apply in certain circumstances and especially in the development of drugs thought to be cytostatic (e.g., bevacizumab or cetuximab). They suggest that this lack of applicability to targeted agents contributed to the premature move to phase III testing of EGFR TKIs and to the spectacular failures seen with the INTACT, TRIBUTIE, and TALENT in NSCLC and in the studies of matrix metalloproteinase inhibitors (70, 71). Ratain and Eckhardt propose some plausible options to minimize such failures, such as greater use of randomized phase II trials employing readily attainable end points like time to progression (72, 73). Such trials can also use crossover and randomized discontinuation designs, which they suggest will increase the attractiveness of such trials to the participants and physicians involved. Moreover, randomized discontinuation designs can be useful in some settings in the early development of targeted agents where a reliable assay to select patients expressing the target is not available (74). There are other possible benefits with this approach, including the ability to assess biomarkers and pharmacokinetic/pharmacodynamic relationships. On the downside, randomized phase II trials require larger numbers of patients than most traditional phase II studies, thereby potentially slowing drug development somewhat (75). However, Ratain and Eckhardt also point out that it is possible to enroll patents with a variety of malignancies rather than a single cancer, because one is primarily interested in the ability of the drug to affect a specific target of interest (69). In other words, the target of interest (e.g., HER-2 amplification or BRAF mutation) might be important in many different diseases, so why limit the study to one organ site?

As a precautionary comment, it is worth noting that some predictive factors double as prognostic factors. In the TRIBUTIE trial, for example, patients with an EGFR mutation achieved a higher response rate with erlotinib compared with those given a placebo (11). That is, the presence of EGFR mutation predicted for a “good response” but patients harboring an EGFR mutation also had a better survival irrespective of treatment arm. Thus, the activating EGFR mutation found in NSCLC seems to be both a predictive marker for response and
a prognostic marker for survival (76). Consequently, even if patients are “selected” using a molecular marker, an uncontrolled trial could lead to an erroneous conclusion regarding the “effectiveness” of a targeted drug. This is not to say that careful a priori patient selection is not needed in assessing targeted agents. Quite the contrary, when an appropriate molecular target is identified and validated, scientifically well-designed trials can be undertaken with considerable economy in terms of both patient and financial resources (55, 77, 78). In summary, given the plethora of new agents available for testing, it is important to avoid future INTACT-like trials and instead work toward studies that carefully select patients for inclusion to improve the potential for a favorable outcome. Thoughtful investigators are already headed in this direction (55, 69).

Open Discussion

Dr. Alan Sandler: The one comment I would add regards our inability to actually follow the results of the phase II trials. A perfect example is the C225 study with cisplatin and vinblastine: 8.1 versus 7 months median survival time. No difference in response, and still a phase III study is going forward.

Dr. David Johnson: When a company has invested hundreds of millions of dollars in a drug, they look for any possible signal. That is the problem. Somebody alluded to Bruce Johnson’s JNCI paper [J Natl Cancer Inst 2000;92:1601–7] where he talked about signals from phase II trials. We’ve ignored the signals. We the investigators are to blame, because we all fall in love with our own ideas, and if they are negative, we still find a way to pursue them. So I think doing some randomized phase II trials would be useful, to get better signals, so that we don’t spend $8 billion a year unnecessarily. We should spend our research dollars more wisely.

Dr. Bruce Johnson: I want to make a comment about the JNCI paper. The one thing we never quantitated is a measure of how representative the study patients are of the overall patient population. That is not in the model, so you have to make certain assumptions. If you do a phase II trial in any population and get a median survival that hovers around 8%, the chances of that being positive in phase III is 1 in 33 trials. There’s only a single positive one, from the old days at Memorial Sloan Kettering. So if you do a phase II and you come up with that standard, you have about a 0% chance of that being positive in a randomized phase III.

Dr. David Johnson: I would carry that one step further and just remind folks that when you do a single-arm trial, there is a 1 in 20 chance that you will come up with something that looks promising but is totally fallacious. We see this all the time.

Dr. Rogerio Lilenbaum: But the converse is not true, though. Even if you get a 14-month median survival, still some of those trials will not make it into phase III. Isn’t that correct?

Dr. Bruce Johnson: Absolutely. Prior to the ECOG trial [J Clin Oncol 2005;23(16S):28], there were a grand total of 5 out of 33 trials in non–small cell lung cancer that were positive over 20 years. Of those 5, 3 of them were single agent versus two drugs. So it is only two trials that showed a difference between two different regimens. We should do better than that.

Dr. David Johnson: I don’t think any of us can take great pride in that level of accomplishment. Now, incidentally, before you go home feeling sorry for yourselves, if we put up any other field in oncology, they don’t do as well as we do in lung cancer. If you look at the chemotherapy trials in breast cancer, to this day, they still don’t know whether one drug is better than two, or vice versa, in metastatic disease, because they haven’t done the proper trials. In lung cancer, we’ve at least done the definitive trials. We have attempted to answer “simple” questions.

Dr. Alex Adjei: For those of us who do phase I trials, the key issue is what is the drug target. Taking sorafenib as an example, initially it was felt to be a RAF kinase inhibitor. Just by accident, we picked the cell line where you don’t really see an inhibition of RAF kinase, so we could never show that if you added the drug to the cells you block phospho-ERK. What we are finding is that a lot of times in the early phase I/II, we don’t know enough about the target. That is the challenge at this point.

Dr. David Johnson: As Dr. Simon points out in his paper [Clin Cancer Res 2004;10:6759–63], with the randomized phase II design, you don’t have to know the target. It may allow you to identify unknown targets. Again, we don’t always know what we think we know. Let me give you a perfect example. The two MMPI (matrix metalloproteinase inhibitors) trials were completely negative. Those drugs no longer exist. I have a couple of patients who were on the AG3340 drug who are in complete remissions 5, 6, 7 years after the fact. Now, that is not enough to have bumped the overall survival curve, but I have yet to have a patient on chemotherapy who is alive that long out from initiation of treatment. I would submit that studying those two patients’ tumors would have given us far more information than a 3,000-patient trial. Perhaps that is the value of doing “untargeted” studies.

Dr. Glenwood Goss: To continue along Dr. Adjei’s thought, we do these phase I/II studies where we try our very best to identify the target, to look for surrogate markers of response, etc. But there are inherent difficulties in collecting pre- and post-biopsies. Then, even when you’ve collected it, the quality of the biological material when you come to actually use it is not sufficiently standard. The final number of samples that you are dealing with doesn’t give you statistically a strong result. I’m not adverse to this effort to establish better targets, because the more information we have the better. But the idea that we’re going to be able to have good targets is somewhat naïve, I think.

Dr. David Johnson: I think that we will identify appropriate targets over time. Estrogen receptor positivity was known in the 1950s and it took until at least the late 1980s to develop that particular test for assessing how to use the drug tamoxifen. It took decades. So, hopefully, we can compress that timeline along the way. We do need to look in the tumor itself. We know, as lung cancer specialists, how difficult it is to get tissue. We also know the inherent difficulties of doing needle aspiration biopsies because of the heterogeneity of the tumor. I would submit that we need to continue to work on technology that would allow us to use small snippets of tumor to make assessments of these targets. It is far easier to do one or two fine-needle biopsies on a higher percentage of our patients than it is to do single core needle biopsies on patients whose tumor is abutting the chest wall.
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69. Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. J Clin Oncol 2004;22: 1375–81.


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