Summary Statement Novel Agents in the Treatment of Lung Cancer: Fifth Cambridge Conference Assessing Opportunities for Combination Therapy

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The promise of effective targeted therapy for lung cancer requires rigorous identification of potential targets combined with intensive discovery and development efforts aimed at developing effective "drugs" for these targets. We now recognize that getting the right drug to the right target in the right patient is more complicated than one could have imagined a decade ago. As knowledge of targets and development of agents have proliferated and advanced, so too have data demonstrating the biologic heterogeneity of tumors. The finding that lung cancers are genetically diverse and can exhibit several pathways of resistance in response to targeted agents makes the prospect for curative therapy more daunting. It is becoming increasingly clear that single-agent treatment will be the exception rather than the rule. This information raises important new questions about the development and assessment of novel agents in lung cancer treatment: (1) How do we identify the most important drug targets for tumor initiation and maintenance? (2) What is the best way to assess drug candidates that may only be relevant in a small fraction of patients? (3) What models do we use to predict clinical response and identify effective combinations? And (4) how do we bring combination regimens to the clinic, particularly when the agents are not yet approved individually and may be under development from different companies? The Fifth Cambridge Conference on Novel Agents in the Treatment of Lung Cancer was held in Cambridge, Massachusetts, on October 1–2, 2007, to discuss these questions by reviewing recent progress in the field and advancing recommendations for research and patient care. New information, conclusions, and recommendations considered significant for the field by the program faculty are summarized here and presented at greater length in the individual articles and accompanying discussions that comprise the full conference proceedings. A CME activity based on this summary is also available at www.informedicalcme.com/cme.

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Tumor heterogeneity is a hallmark of lung cancer. Lung tumors that seem to be driven by a single mutant oncogene, the epidermal growth factor receptor (EGFR) gene, are more complex than previously thought, and efforts to cure such patients may require multiple drugs that attack multiple targets. This realization is setting the stage for new ways to think about how to treat lung cancers, putting emphasis on tools to assess the characteristics of individual tumors, the pathway(s) a given tumor is using, and ultimately, the therapies that are likely be most effective in blocking that tumor's growth and progression. As more information emerges, it is likely we will need to reassess how we define lung cancer, how we approach new therapies, and how we define the optimal way to use targeted therapies that may be effective in subsets of patients.

THE VEGF PATHWAY AS TARGET

Angiogenesis is critical to cancer growth and is clearly validated as a target for cancer treatment. Vascular endothe-

lial growth factor (VEGF) is a key proangiogenic factor used by solid tumors. Antiangiogenic therapy, in particular with antibodies that bind VEGF, has been shown to be beneficial (in terms of both response and survival) in many patients with epithelial cancers. Along with VEGF, platelet-derived growth factor (PDGF) also plays a role in non-small cell lung cancer (NSCLC) and may be an important target of antiangiogenic agents.

Bevacizumab (Avastin), a monoclonal antibody directed against VEGF, was first demonstrated to be effective against lung cancer in Eastern Cooperative Oncology Group E4599, a phase 3 trial that randomized patients with newly diagnosed, nonsquamous NSCLC to receive carboplatin/paclitaxel with or without bevacizumab. The E4599 study demonstrated significant improvements in response rate and survival with the addition of bevacizumab, although notable toxic effects occurred. The most concerning toxicity was hemoptysis, a side effect that is relatively unique to lung cancer patients. Severe life-threatening hemoptysis limits the use of this agent to nonsquamous lung cancer and to patients without brain metastases, need for anticoagulation, or recent cardiac issues. The role of bevacizumab in these currently contraindicated populations is being studied in several ongoing trials. Physicians need to exercise caution when prescribing bevacizumab to elderly patients because toxic effects seem to be more common in this patient population.

Another agent that shows promise in the treatment of lung cancer is sunitinib (Sutent), which inhibits the VEGF and PDGF pathways and is currently approved in the United States for the treatment of advanced renal cell carcinoma and imatinib (Gleevec)-refractory gastrointestinal stromal tumors. The initial studies of sunitinib incorporated rest periods during the drug therapy because of adverse effects such as fatigue, diarrhea, nausea, mucositis, hypertension, myelosuppression, and skin abnormalities. However, some investigators believe that the 2-week break may allow tumor growth during these rest periods, so continuous dose schedules are under review. Currently, both intermittent and continuous dosing strategies are being evaluated in ongoing clinical trials. Ongoing trials are integrating sunitinib with standard chemotherapeutic regimens in advanced NSCLC and small cell lung cancer. Conference participants felt that exploring whether sunitinib has activity in patients previously treated with bevacizumab was a valid approach.

Another novel agent being investigated for lung cancer treatment is sorafenib (Nexavar). Sorafenib, a multikinase inhibitor of VEGF receptor (VEGFR), PDGF, KIT, FLT-3, and RET, has also been approved in the United States for the treatment of advanced renal cell carcinoma. Currently, at least two phase 3 studies of sorafenib for the treatment of lung cancer are underway, with one coming to maturity in the near future. These studies are evaluating sorafenib as a single agent and in combination with chemotherapy or gefitinib (Iressa) for the treatment of refractory NSCLC. Many in the group felt that sorafenib derived much of its clinical activity from its anti-VEGF properties. Active Raf kinase inhibitors are under development for *RAF*-mutated and *RAS*-mutated lung cancer.

Vandetanib (Zactima, ZD6474) is an inhibitor of both VEGFR and EGFR. The relative potency of this drug is greater for VEGF but it may derive some of this unique activity from its anti-EGFR action. This drug has been shown to prolong disease-free survival in randomized phase 2 studies both as single agent and in combination with docetaxel in previously-treated patients with NSCLC. In addition, vandetanib was evaluated alone and in combination with carboplatin/paclitaxel in previously untreated lung cancer patients. In the first-line trials, no significant survival differences were found in the chemotherapy alone and the chemotherapy-vandetanib arms (the vandetanib-alone arm was terminated prematurely because of a low progression-free survival rate). Maintenance vandetanib in responding patients with small cell lung did not result in prolonged survival compared with treatment with placebo. This agent is of great interest and conference participants felt that this was an example of an agent whose development was more rational than many agents. It is now in phase 3 development in previously-treated patients based on positive progression-free survival data from randomized phase 2 trials.

Cediranib (Recentin, AZD2171) is an oral, selective VEGF signaling inhibitor. Cediranib is currently being investigated in a Canadian phase 2/3 trial, which randomizes patients to carboplatin/paclitaxel with or without cediranib. Results of these trials are not expected for another 2 to 3 years. The discussion of cediranib and vandetanib touched on the concept of whether it will be more effective to combine two singly targeted agents such as erlotinib (Tarceva) and bevacizumab or use one drug with dual targets such as vandetanib. Many of the participants considered both the ability to modify toxicity and to validate individual targets to favor use of multiple agents, but this remains an open question.

ANTIANGIOGENESIS IMAGING

Traditional tumor imaging uses intravenous contrast agents as tracers: the degree of tracer accumulation observed in the tumor is used to both detect lesions and characterize them. Because antiangiogenic agents are postulated to affect blood vessel permeability, their use can confound the traditional metrics used to identify a tumor and to characterize tumor changes. This has led to a broad interest in the development of other methods to visualize and characterize antiangiogenic effects in cancer patients. One new technique that seems promising is a magnetic resonance imaging-based method that allows estimation of microvessel caliber (diameter) and may be able to visualize changes over the course of therapy. Positron emission tomography can also be used to measure antitumor effects such as decreases in glucose use or decreases in proliferation, though the degree to which these methods may be influenced by permeability changes is not yet well understood. Magnetic resonance spectroscopy also is another tool under development that may be useful in identifying tumor characteristics and changes in response to therapy. These more advanced imaging techniques do not directly interrogate angiogenesis or changes in angiogenesis after therapy but can provide important information about

whether the antivascular effect is associated with direct or indirect antitumor effects.

Further development of new modalities to monitor the direct effects of antiangiogenesis, such as distributions of microvessel diameters, and the downstream impact of these antiangiogenic therapeutic agents, will be valuable as efforts continue to identify optimal treatment approaches.

THE EGFR PATHWAY AS TARGET

EGFR-targeted treatments have become more important to the therapeutic armamentarium of NSCLC. The EGFR TKIs gefitinib and erlotinib are associated with increased radiographic response rates and prolonged survival. Patients benefit when treated in the second- and third-line settings and patients with EGFR mutations likely benefit from such therapies in the first-line setting. In contrast to the studies of EGFR TKI therapy in combination with chemotherapy, several phase I and II trials have now shown that the monoclonal antibody cetuximab (Erbitux) may improve response and prolong survival when added to first-line platinum-based chemotherapy.

Identifying which patients benefit the most from EGFR-based therapy has been a major endeavor in the lung cancer research community for the past 5 years. Retrospective data have indicated that increased *EGFR* gene copy number detected by fluorescent in situ hybridization (FISH) is a good predictive marker, especially in trials where TKIs are compared with best supportive care. It seems that *EGFR* copy number may also predict benefit from cetuximab therapy in lung and colon cancers. However, the group also considered data demonstrating that FISH does not identify patients who benefit from gefitinib over docetaxel (Taxotere) in a subset analysis of the recently presented INTEREST study. Clearly, more work is needed to elucidate the role of *EGFR* FISH as a biomarker for selecting patients most appropriate for EGFR TKI therapy. The FISH assay is now being validated in prospective clinical studies. Through the Intergroup mechanism an NCI/CPATH initiated prospective study is planned to prospectively validate primarily *EGFR* gene copy number by FISH as a predictive marker for EGFR TKI therapy.

Somatic mutations in *EGFR* have been documented to lead to activation of EGFR and are thought to be associated with a dependency on EGFR signaling. These mutations are associated with a several-fold increase in response rates to EGFR TKIs and possibly increased survival after treatment. The discovery of these mutations has led to exploration of genotype-directed therapy, which aims to create a more specific treatment algorithm based on the tumor biology of individual patients. Internationally, several groups have conducted first-line trials wherein patients with NSCLC are selected for gefitinib or erlotinib therapy based on *EGFR* mutation status. The results of these trials are promising with response rates ranging from 55% to 80% and median progression free survivals in excess of 9 months. Conference participants were enthusiastic about these initial studies but agreed that randomized trials comparing first-line EGFR TKI treatment with first-line chemotherapy were needed in this unique population of patients, because *EGFR* mutations may also be associated with a better prognosis independent of therapy.

Most NSCLC patients with EGFR-dependent tumors, as evidenced by mutations in *EGFR*, experience an initial response to treatment with erlotinib or gefitinib. However, a few patients with *EGFR* mutations are noted to have primary resistance to these TKIs, and essentially all of the *EGFR* mutation-positive patients who initially respond to TKI treatment eventually acquire resistance. The T790M mutation in *EGFR* has been identified in nearly half of resistant patients. Recently, a second resistance mechanism, amplification of *C-MET* has been shown to account for an additional significant proportion of resistant patients. Several second-generation EGFR TKIs that have activity against cells harboring the T790M mutation are currently being studied: HKI-272, a second-generation irreversible EGFR TKI that also inhibits HER2; XL647, a reversible inhibitor of EGFR, HER2, and VEGFR; and BIBW2992, an irreversible EGFR TKI that also inhibits HER2 and VEGFRs. These agents have the potential to prevent or delay the development of acquired resistance or overcome acquired resistance in patients previously treated with gefitinib or erlotinib, and are worthy of study both in patients who have not received prior erlotinib or gefitinib and in patients with acquired resistance. C-MET inhibitors given in conjunction with EGFR inhibition are also under study as a means to overcome resistance.

Because mutant EGFR has been demonstrated to be a client protein for the heat shock protein 90 (Hsp90) chaperone, inhibitors of HSP90 are currently being evaluated. *EGFR* series harboring exon 20 insertions that are not inhibited by erlotinib, as well as those with secondary T790M mutation conferring erlotinib resistance remain dependent on Hsp90 for conformational stability. c-Met is also an Hsp90 client. Therefore, Hsp90 inhibitors may be useful against EGFR mutant lung cancers with primary or acquired TKI resistance. Additionally, lung cancers expressing wild-type EGFR may depend on other kinases that are Hsp90 clients, so that the strategy of Hsp90 inhibition may be useful for multiple lung cancer subsets. The geldanamycin family of compounds has been most well-studied, including 17-AAG, 17-DMAG, and IPI-504, which have high binding affinity to human Hsp90 and have entered phase 1 and 2 trials. However, because of the limitations of these geldanamycin derivatives, including off-target toxicity and formulation challenges, other Hsp90 inhibitors are also being explored, including purine scaffold inhibitors such as CNF-2024 and diarylpyrazole compounds such as the 3,4-diarylisoxazole NVP-AUY922/VER-52296. These and other Hsp90 inhibitors are in early phase 1 development.

The conundrum of how to treat KRAS mutant lung cancer was discussed at length at the meeting. This is a particularly attractive area of investigation because tumors that harbor mutant KRAS seem to be refractory to most available systemic chemotherapies and also do not respond to EGFR-TKIs. Currently, no selective, specific inhibitor of the KRAS pathway has been successfully developed for clinical use. Although some treatment strategies targeting KRAS have resulted in antitumor activity, it is still unclear whether KRAS inhibition will be able to be realized as a therapeutic

option. However, this group remains an important subset of lung cancers that need to be addressed in future studies of novel agents that target the pathway, such as inhibitors of MEK and BRAF. Thus, aside from serving as a negative predictive factor for EGFR-TKI therapy, sequencing patients' specimens for *KRAS* mutations may have value in identifying patients who should be treated with novel agents.

OTHER TARGETS

Another novel approach to the treatment of lung cancer is immunotherapeutic vaccines. Several vaccines are currently being investigated in randomized trials, including L-BLP25 (Stimuvax), BEC-2 (Mitumomab), 1E10, PF-3512676 (Promune), melanoma-associated antigen A3 (MAGE-A3) immunotherapeutic, granulocyte-macrophage colony-stimulating factor-transduced allogeneic cancer cellular immunotherapy (GVAX), and belagenpumatucel-L (Lucanix). Many of these vaccines have intriguing early data such as prolonged disease-free survival compared with historical controls. Large phase 3 trials are underway examining the role of therapeutic vaccines in patients with lung cancer. Conference participants considered that, as with other targeted agents, it is probable that vaccines may be beneficial for certain subgroups of patients, and so the advancement and incorporation of correlative studies within vaccine trials will be crucial to avoid discarding a vaccine that may have potential benefit for some patients.

As noted earlier, the future of lung cancer treatment will likely require combination therapy. Some of these combinations will include a new, targeted drug given with chemotherapy whereas others will be combinations of targeted drugs without any traditional chemotherapeutic agents. To optimize treatment, it will be essential that the most active chemotherapeutic agents are identified. Currently, platinum-containing doublet therapy is the standard first-line treatment of advanced NSCLC. The combinations of cisplatin and paclitaxel (Taxol), cisplatin and gemcitabine (Gemzar), cisplatin and docetaxel, and carboplatin and paclitaxel have produced similar response rates and survival advantages.

Some toxicity differences may help to guide investigators in optimal strategies for adding targeted agents to established doublets, but the relative efficacy of platinum-based double regimens is very similar. Several newer cytotoxic agents are in development for lung cancer. These agents include drugs that are modifications of existing agents, such as albumin-bound paclitaxel, and oral topotecan. Others, such as pemetrexed (Alimta), vinflunine (Javlor), or ixabepilone (BMS-247550), are newer-generation agents derived from previously identified drug classes. Of these agents, pemetrexed, in combination with either cisplatin or carboplatin, has shown similar activity to established platinum-based doublets and will likely become a clinically widely used and often studied base for combination with novel drugs. Likewise, albumin-bound paclitaxel (Abraxane) may provide certain advantages over existing taxanes and its evaluation as a cytotoxic to pair with standard chemotherapy is under way.

IMPORTANCE OF MOLECULAR PROFILING, PRECLINICAL MODELS, AND TISSUE BIOPSIES

As has been the case in prior years of this program, participants emphasized the need for increased focus on developing and using preclinical models in the development of targeted agents. Murine models, including both xenografts and genetically engineered mice, were thought by the participants to be useful tools in assessing drug efficacy. Broad cell line screening was also felt to be vital. The program faculty stressed the need to use all three techniques to most effectively develop drugs. There was no single technique that provided guidance in optimizing leads in all situations. It was emphasized that flexibility in methods to assess new candidate targets and newly developed drug compounds was central to potential success.

The importance of using preclinical modeling to understand the biology of drugs and targets is driven by the need for sufficient data to support rational trial design, including decision making for safety, dose, and endpoints. Participants felt strongly that a dynamic assessment of genetics and "target biology" is essential to inform the trial process. To move toward the goal of individualizing or personalizing the approach to lung cancer treatment, molecular profiling of treatment-sensitive and treatment-resistant tumor molecular subtypes at the time of diagnosis, during treatment and at relapse, will be essential. There was agreement that clinical trials need to mandate collection of tumor specimens at baseline and at relapse whenever feasible. With better correlative studies, even negative clinical trials can provide insights to advance our understanding of the disease. Conference participants emphasized the need for regular and iterative communication between clinicians and basic scientists. This will ensure that preclinical studies are focused on relevant clinical needs and that preclinical data appropriately inform patient selection and other aspects of trial design. Keeping basic scientists appraised of clinical information to expedite efforts in biomarker and assay development was also considered to be essential.

Conference participants noted that core biopsies will play an increasingly important role in lung cancer diagnosis as they do now for lymphoma. Needle aspirations do not yield sufficient tumor material for both standard pathologic evaluation and molecular diagnostics. Broad sequencing of suspected lung oncogenes will have a critical role in clinical decision making in the future. Alternative technologies, such as assessment of circulating tumor cells and circulating serum DNA, will be essential to increase our access to sufficient and longitudinal tumor tissue samples.

INDIVIDUALIZING THERAPY—PATIENT SELECTION

Recent studies have demonstrated that patients with specific mutations in the EGFR gene or increased numbers of gene copies had a significantly higher likelihood of responding to the EGFR TKIs gefitinib and erlotinib. These findings have sparked widespread efforts to find ways to better match patients with effective therapies. These efforts have included evaluating gene mutation status, gene copy number, and

surface protein expression and have led to the identification of smaller groups of patients who might experience larger degrees of benefit. Interest in this topic remains very strong as more agents move forward that show signs of being highly efficacious in a small percentage of patients.

Conference participants noted that although the biomarkers used now are not yet mature or validated for patient selection, it will be increasingly important to think about not only who to select for treatment but also who not to select for treatment in trial designs for new agents. For example, it has recently been shown that patients with an *RAS* mutation have almost no chance of responding to EFGR-TKI therapy. Knowing this in advance of EGFR-TKI therapy is just as important as knowing which patients have *EGFR* mutations or high copy number and might respond dramatically. Many of the faculty commented that biomarkers are likely to be just as useful in negative patient selection (helping to decide when an agent will be of no benefit) as in positive patient selection (given only to those in whom benefit has been demonstrated). Trying to find a biomarker that will predict a positive outcome when the outcome is on a continuum, from a small improvement in survival to a dramatic improvement in survival, is challenging but important.

CLINICAL TRIAL DESIGN—MEETING THE CHALLENGES OF COMBINATION THERAPIES

Conference participants were uniform in their assessment that a disease as complicated as NSCLC will likely not be cured, or even effectively controlled, with monotherapy. Combinations of targeted agents and of targeted agents with chemotherapy are essential. Conference faculty noted that experience in combination trials over the past decade has been very disappointing. With the notable exception of trials combining chemotherapy with cetuximab and chemotherapy with bevacizumab, most studies have failed to demonstrate that adding a targeted drug to standard combination chemotherapy is able to improve outcome. The results of combinations of targeted agents are even more rudimentary at this point.

Several participants noted that contributing factors to the low level of success in combination trials include a lack of preclinical models that faithfully represent human disease and the economic climate of drug development, which forces phase 3 trial design before adequate phase 2 work has been completed. Most of the failed studies were preceded by a single-arm phase 2 study or only phase 1 study. For future studies of novel agents and combination studies including novel agents, conference participants strongly recommended that the process should start with a thorough and critical assessment of preclinical data followed by adequate phase 2 studies, preferably in molecularly defined populations selected on the basis of a demonstrated mechanism of action. Of course, it was recognized that this is unlikely until we better understand tumor and patient heterogeneity. Participants strongly recommended that investigators should make every effort to mandate tissue and serum studies as part of every new trial of a targeted agent. Performing correlative studies at all phases of clinical development may provide valuable insights into the mechanisms of sensitivity and resistance.

It was strongly recommended that positive, randomized phase 2 studies be completed and assessed as positive before proceeding to phase 3 trials. If the earlier studies are negative or questionable, this is the time to rethink the hypothesis or perform the study in a different way. This is a challenge to both the academic community and industry to step back and do things more prudently. Looking forward to the large number of new agents in development, the need to establish both a rational procedure for selecting combinations for further study and appropriate approaches to patient selection is clear.

COOPERATIVE GROUP STUDIES

A discussion of cooperative group trials in developing targeted agents for lung cancer highlighted strong feelings that the system is important but also is facing issues in administration, delays, funding, and accessibility. There was broad agreement among the conference faculty that the cooperative group system has made significant contributions and in most cases led the effort for most of the advances in lung cancer therapy for the past decade. It was agreed that the cooperative groups provide a unique opportunity to conduct important trials that do not have an obvious commercial angle. Most felt that cooperative group trials allow broader access to trial design and implementation than industry-supported trials. They also allow data pooling across studies and provide valuable opportunities for young investigators to access training, mentoring, and data. However, concern was expressed that almost all of the "significant" recent cooperative group studies are phase 3 studies and that the system generally adds 1 to 3 years to study implementation. Today it is widely considered to be extremely time consuming and inefficient to put a phase 2 study through the cooperative group system. If trends that require more comprehensive data acquisition for drug approval studies continue, many questioned the fiscal viability of the cooperative groups. The limited payments for patients in the studies are raising financial issues for academic centers. If these issues are not addressed, fewer innovative studies will be able to use this framework. Conference participants were united in their belief that the cooperative group system needs to be saved but were unsure how best to do this.

CONCLUSION

The 2007 Cambridge Conference concluded with participants expressing hope that continued work in understanding lung cancer biology will drive new therapeutic developments. Participants were unanimous in stressing that investigators need to be committed to trials that gather tissue to determine if target pathways are being affected by a given therapy. This collection of tissue is important in determining the potential impact of treatments in overcoming resistance.

Despite the hurdles experienced over the past 5 years in targeted drug development, participants felt that major accomplishments have been made. The discovery of EGFR mutations and their potential role in the biology of EGFR-

driven cancers is one notable achievement, as is the discovery that the targeted agent bevacizumab is able to improve survival when added to standard chemotherapy. Over the next 5 years we hope to identify agents that have activity in the treatment of tumors that are resistant to first-generation EGFR inhibitors and develop oral VEGF inhibitors that have activity in lung cancer. In the meantime, we should also recognize that this field has made rapid progress over the past decade. Our understanding of the underlying biology of disease has expanded tremendously, as has recognition of its complexity; a variety of important lung cancer targets have been identified and characterized; and several important new, targeted therapies are now part of our treatment armamentarium. This new information and these new tools are radically changing how we think about lung cancer, how we treat patients, and how we need to approach future drug development.

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