

Novel Agents in the Treatment of Lung Cancer: Fourth Cambridge Conference

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Abstract The Fourth Cambridge Conference on Novel Agents in the Treatment of Lung Cancer was held in Cambridge, Massachusetts on September 29 to 30, 2006, to discuss ongoing clinical research of novel targeted agents for the treatment of non-small cell lung cancer, along with supportive basic and translational research into the molecular pathways implicated in cancer growth and resistance. New information, conclusions, and recommendations considered significant for the field by the program faculty are summarized below and presented at greater length in the individual articles and accompanying discussions that comprise the full conference proceedings.

With the important exception of the E4599 trial of bevacizumab in conjunction with combination chemotherapy, recent clinical trials in non-small cell lung cancer (NSCLC) that combined novel agents with standard chemotherapy have produced disappointing or equivocal results. Many agents identified as promising at the First Cambridge Conference in 2003 have subsequently failed to show statistically and clinically meaningful effects in phase II/III trials. As a consequence, much of the conference discussion focused on critiques of the preclinical and phase I/II evidence used as the rationale to bring these agents forward into large-scale clinical testing.

Conference participants nonetheless noted that the field of lung cancer research and treatment has witnessed major advances over the past 5 years. The role of platinum-based chemotherapy as an adjuvant therapy for early stage NSCLC has been unequivocally established. Two well-studied pathways are now known to be of importance in the mechanisms of cancer growth: the epidermal growth factor receptor (EGFR) and the

vascular endothelial growth factor (VEGF) pathways. Two agents targeting these pathways, erlotinib and bevacizumab, have shown prolongation in overall survival in patients with NSCLC. Although we continue to make progress in defining the subsets of patients with tumors most likely to respond to EGFR inhibitors, we have yet to define such a subset for VEGF-targeted therapy.

Both successes and failures speak to the complexity of lung cancer and of its many mechanisms of resistance to currently available therapeutics. We develop and test drugs targeting the cancer growth pathways that we understand, yet we still lack validated and clinically feasible tools to determine the molecular profile for the individual patient's tumor and to select the optimal therapy regimen on that basis. If we are to make progress, we will need to develop better techniques for assessing the benefits of targeted drugs (particularly combinations) and more complete methods for molecularly profiling patients' cancers.

Lung Cancer Biology as a Guide to Novel Agents

As in the previous meetings, there was considerable discussion of the need for better preclinical studies of new agents in biologically relevant models. Too often, agents have moved forward to clinical trials without the preclinical work necessary to show on-target effects in specific, well-characterized tumor subtypes. In addition, more information needs to go back to the laboratory from the clinical trials via well-designed correlative studies. In order to move toward a goal of individualized medicine with rationally targeted therapies, it is imperative to do more molecular profiling of treatment-sensitive and treatment-resistant tumors, to better understand the underlying biology of specific molecular subtypes. Wherever feasible, clinical trials should mandate the collection of tumor specimens both at baseline and at relapse. With better correlative studies, even negative clinical trials can yield important insights to advance the field. Conference participants

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noted a fundamental need for improved two-way communication between clinicians and basic scientists, in order to focus preclinical studies towards relevant clinical needs and to improve the awareness of subtle flaws in preclinical studies being used as the rationale for bringing a drug forward for clinical study.

Targets for novel therapeutics. Conference participants noted two problematic concerns with the translational science that has been done to date on novel targets and targeted agents. One is that many compounds have been brought into clinical trials without the evidence to show that they hit their putative target effectively at clinically achievable doses. More fundamentally, in some instances, the preclinical research has been insufficient to show that the target is truly critical to the growth and survival of malignant cells. Genetic instability is characteristic of all cancer, but only a small proportion of the genomic and somatic mutations present in tumors prove to be important in terms of mediating tumor growth or resistance to apoptosis. In the laboratory, it is often possible to arrest cell growth or induce apoptosis by inhibiting a single pathway, but this may have little relevance to the complex escape mechanisms possessed by malignant cells *in vivo*. Many targets are already known, and more will be discovered through genomic and proteomic research, but studies to show their importance are needed prior to drug development efforts.

Towards individualized therapy. In designing and analyzing clinical trial results, the focus has traditionally been on achieving incremental improvements in the median overall survival. Several conference participants commented that investigators should be acquiring more data on the patients at the tail of the survival curve, the ones who have dramatically prolonged survival times. Some trials have censored survival data beyond 1.5 years, despite the potential value of studying tumor biology in those few patients who achieve a 2-year survival or greater. Among the many recent trials of targeted agents that have been negative in terms of median and overall survival, investigators can often describe a few patients with dramatic and sustained responses to an otherwise relatively inactive agent. Rather than undertaking unplanned subset analyses to make a negative trial appear positive, efforts should be made to characterize these individual tumors and thereby further our understanding of tumor biology. The traditional clinical trial approach has not been adequately cognizant of the growing awareness that NSCLC is not one, two, or three histologically defined conditions, but possibly one, two, or three hundred molecularly distinct disease processes.

As Dr. Bruce Johnson observed during the conference discussions, both clinicians and investigators generally devote their efforts to making 100% of patients 20% better, instead of identifying the subset—whether 20% or 2%—who can be made 100% better with appropriately targeted treatment. However, pharmaceutical companies have been reluctant to pursue appropriate studies in small subsets because their research and development efforts are still focused on developing “blockbuster drugs” that will gain approval for broadly defined populations. The role of the academic investigator may be to better characterize these dramatic responders.

Preclinical studies. Basic scientists attending the conference commented that much of the preclinical data that have been used to support clinical development are not derived from optimal studies. A rigorous program of preclinical study would

require demonstrating that (a) the target molecule is not only overexpressed but is crucial to the tumor cell's survival and growth, (b) the investigational agent has on-target effects that can be differentiated in models with wild-type and mutated targets, and (c) the concentrations and dosing regimens used in the cell lines are achievable *in vivo*. Virtually any agent can be shown to be active in one or more cell lines that may have little relevance to human disease. Too often, drugs move forward based on growth arrest in preclinical models that have not been selected to mimic the human tumor. There is no requirement to report how many cell lines were tried or how they were selected. More rigorous and objective preclinical studies of putative targets have great potential for advancing our knowledge of tumor biology.

Clinical Trial Design

For new agents with properly done preclinical investigations, conference participants agreed that the first step should be a phase I/II single-agent study with molecular profiles in a population selected on the basis of a demonstrated mechanism of action. Participants felt that, going forward, trials should make every effort to mandate tissue and serum studies. Performing correlative studies at all phases of clinical development may provide valuable insights into the mechanisms of sensitivity and resistance.

Conference participants differed in their views regarding the optimal use of the clinical trial process for novel targeted agents. A minority felt that new agents should show single-agent activity in phase I/II before any studies of combination therapy are undertaken. Others argued that phase II investigations of rationally selected combinations would be appropriate before further development is abandoned. There was no consensus as to whether a randomized phase II trial of chemotherapy plus or minus the investigational agent should be routinely undertaken. Several participants commented that combinations with chemotherapy should be based on good preclinical data demonstrating synergy rather than merely additive effects. Similar issues arise with combinations of targeted agents, with conference participants expressing concern that some may be antagonistic in combination. Given the number of new agents in development, there is a clear need to establish a rational procedure for selecting combinations for further study, particularly to explore combinations of agents developed by different pharmaceutical companies.

There was general agreement that too many drugs have been taken to large randomized trials based on unplanned or underpowered subset analyses or on modest improvements in overall survival that may have been influenced by subsequent therapeutic manipulations. Conference participants felt that a randomized phase II trial should provide confirmation of activity in terms of significant improvement in time to progression before phase III studies are undertaken. Time to progression was universally endorsed as the most important end point in clinical phase II studies. Bevacizumab was viewed as an example of a rational development process because there were positive data from a randomized phase II trial to support a phase III study.

In discussing the data for agents with relatively modest results to date, conference participants disagreed as to whether agents with negative single-agent phase II trials should be

dropped from further development. Some felt that a randomized phase II trial in combination with chemotherapy was a rational choice, to avoid discarding an agent that is potentially effective in combination regimens. Others thought that the current number of investigational drugs is too large to permit further testing when preclinical studies have not been done to show either true synergy in combination or efficacy in a well-defined subset with a known mechanism of action. Conference participants concurred that randomized phase II trials should be done before taking an agent with equivocal data forward into phase III testing. Hypotheses regarding potential efficacy in subgroups or in combination with chemotherapy should be validated in phase II before phase III studies are launched.

Studying subsets. In addition to the VEGF, EGFR, and phosphoinositide-3-kinase (PI3K)/Akt pathways, there are three additional targets that have been validated as present in subsets of patients. Between 2% and 5% of lung cancer patients have the same degree of HER amplification as found in breast cancer, providing a compelling rationale to study trastuzumab in patients positive for HER2 by immunohistochemistry or fluorescence *in situ* hybridization. Another 2% to 3% have B-Ras/Raf mutations and are potentially sensitive to the Mek inhibitors currently being studied in melanoma. HER2 mutations are present in 2% to 3%, and preclinical data indicate that HKI-272 is potentially effective in that group of patients. Smaller studies that isolate these subgroups may provide more benefit to patients and more progress to the field than large phase III studies in unselected populations. Finally, more in-depth research needs to be done to differentiate the effects of specific EGFR mutations and to develop strategies to delay the onset of resistance in tumors of patients who initially respond to EGFR tyrosine kinase inhibition.

Trial end points. In an era when many patients with lung cancer are receiving third- and fourth-line therapies, progression-free survival may now be a more appropriate end point for clinical trials than overall survival. Subsequent therapies will inevitably have a confounding effect on survival. The data from the single-agent cetuximab trial were noted as an illustration of this effect; given that the response rate was only 5%, the 8.9-month median survival time was most likely due to the effects of choosing good functional status patients who might have benefited from receiving further therapy subsequent to completing cetuximab.

The EGFR Pathway as Target

EGFR inhibitors have revolutionized the care of patients with lung cancer but ultimately will be best used in selected populations. Potential selection criteria include EGFR somatic mutation status, gene copy number, proteomic profiles, and clinical criteria. Interestingly, response to EGFR inhibition is independent of performance status; however, it is clear that for performance status 2 patients who are "unselected," chemotherapy remains a preferred approach.

A major goal in improving outcome in lung cancer is moving the targeted agents into front-line treatment of metastatic disease. First-line use of erlotinib will likely be based on clinical and/or molecular predictors of response. If first-line treatment will be based on molecular predictors, it is important to develop well-validated standardized molecular assays that provide timely and cost-effective information to

guide treatment selection. Because most patients are diagnosed with advanced disease requiring early institution of therapy, it is impractical to delay a treatment decision for more than 2 weeks to await assay results. A major theme running throughout the conference discussions was the pressing need, in both the research and the clinic settings, to use and to study targeted drugs in a targeted fashion—that is, in the patient subset shown to have tumors dependent on the targeted pathway.

Small-Molecule Tyrosine Kinase Inhibitors

Erlotinib and patient selection. Ongoing research continues to define and refine the genetic and clinical characteristics that predict response to an EGFR tyrosine kinase inhibitor. EGFR mutations (particularly in exon 19) are associated with a high response rate, and high EGFR gene copy number (as determined by fluorescence *in situ* hybridization) is associated with prolonged survival. It now seems that patients with KRAS mutations do not benefit from treatment with EGFR inhibitors; KRAS mutation analysis is commercially available and may be considered for use by physicians to identify patients who are unlikely to benefit from treatment with erlotinib. As with EGFR mutation and copy number testing, the current delays in turnaround for KRAS mutation assays limit their clinical application.

Where molecular testing is not yet time- and cost-effective, clinical characteristics may provide a basis for patient selection. Features such as female sex, never-smoking status, East Asian ethnicity, and adenocarcinoma histology are favorable baseline characteristics associated with response to erlotinib, and the development of a rash with treatment predicts improved survival. It is likely that some combination of clinical and genetic variables will ultimately be validated as a patient selection algorithm. As trials of erlotinib in combination with other targeted agents proceed, it will be of interest to determine if molecular profiles can be used to select patients for these combination therapies.

Key ongoing trials that may provide new data to guide patient selection include the SATURN study of erlotinib versus placebo as first-line maintenance therapy and the TITAN trial of erlotinib versus docetaxel as second-line therapy. In both trials, EGFR status will be determined prior to randomization. The Cancer and Leukemia Group B 30406 study is a randomized phase II trial of erlotinib with or without carboplatin/paclitaxel as first-line therapy in never-smokers or former light smokers with adenocarcinoma histology. The RADIANT phase III trial will examine the efficacy of erlotinib as adjuvant therapy in patients with stage IB-IIIa NSCLC whose tumor tissues are EGFR-positive according to immunohistochemistry or fluorescence *in situ* hybridization.

HKI-272. There are several new compounds that are dual kinase inhibitors in that they inhibit EGFR (HER1) and HER2. In addition, many of these are irreversible inhibitors of EGFR, suggesting that there may be some circumstances in which cells that are resistant to erlotinib might respond to a "second generation" tyrosine kinase inhibitor. HKI-272 is one such agent, an irreversible EGFR/HER2/ErbB inhibitor. Laboratory studies have indicated that HKI-272 can inhibit the growth of T790M mutant lung cancer cells, suggesting a potential benefit for patients with this mechanism of acquired resistance to

erlotinib. A phase I HKI-272 monotherapy trial in patients with solid tumors has been completed. Preliminary analyses of the trial showed stable disease in five patients with NSCLC that progressed following treatment with gefitinib or erlotinib. A phase II trial of HKI-272 in NSCLC patients has been initiated. The trial design includes tumor sequencing of EGFR exons 18 to 24 for all patients, as well as biopsy and mutation testing for patients who respond and then relapse.

Monoclonal Antibodies against EGFR

Cetuximab. Cetuximab is a chimeric human-murine monoclonal antibody against the extracellular domain of EGFR. In phase I/II trials in advanced NSCLC, cetuximab has shown only modest single-agent antitumor activity. Trials combining cetuximab with chemotherapy have shown a trend to increased response rate and prolonged progression-free survival. Two large randomized studies of chemotherapy with or without cetuximab are under way and will be reported within 1 to 2 years. At this point, pending trial results, the use of cetuximab in combination with chemotherapy in patients with previously untreated advanced NSCLC cannot be recommended outside of a study.

Cetuximab may yet show benefits for NSCLC in other treatment protocols. In particular, *in vitro* observations of synergy between the EGFR inhibitor cetuximab and radiation therapy have been confirmed in the clinical setting of head and neck cancer. This combination is currently being investigated in NSCLC in three cooperative group trials. The Radiation Therapy Oncology Group 0324 trial is evaluating the role of cetuximab in combination with chemotherapy and chest radiation in patients with unresectable stage III NSCLC. The Cancer and Leukemia Group B study has a phase II trial (CALGB 30407) of concurrent carboplatin, pemetrexed, and chest radiation with or without cetuximab for the same patient population. The Southwest Oncology Group has a phase II trial in poor-risk patients with unresectable stage III NSCLC with docetaxel, cetuximab, and thoracic radiation.

A major frustration with cetuximab is that, unlike the small-molecule EGFR tyrosine kinase inhibitors, no molecular or clinical predictors of treatment success in NSCLC have as yet been identified for cetuximab or the other investigational anti-EGFR monoclonal antibodies. Studies in patients with colorectal cancer treated with cetuximab may shed light on markers of benefit that may be applicable to patients with NSCLC.

Matuzumab and panitumumab. Matuzumab is a humanized and panitumumab is a fully humanized monoclonal antibody targeting EGFR/HER1. Panitumumab has been approved for the treatment of colorectal cancer. An ongoing randomized phase II study in the second-line setting is examining the combination of matuzumab and pemetrexed. Single-agent responses to matuzumab have been documented in other tumor types (esophageal squamous cell and colorectal carcinoma), although not in lung cancer. In a randomized phase II trial in patients with untreated advanced NSCLC, the addition of panitumumab to paclitaxel/carboplatin did not result in improved time to progression. The population for this study ($n = 166$ patients) was unselected; however, EGFR and KRAS gene mutations were not correlated with response or lack of response. Further analyses of patient samples to identify

predictive biomarkers for panitumumab therapy have been undertaken.

The VEGF Pathway as Target

In addition to the recently approved bevacizumab, several small-molecule VEGF inhibitors as well as other anti-VEGF monoclonal antibodies are in various stages of clinical testing for patients with NSCLC, some with promising early results. Bevacizumab in combination with chemotherapy is the standard for comparison at this point. The hope is that agents will be developed that have either improved efficacy or fewer adverse effects than bevacizumab. Also, in lung cancer, there is a great urgency to expand the patient population that can benefit from these drugs. Ongoing research will investigate VEGF inhibitors both in the first-line chemotherapy setting and in second-line therapy in combination with other targeted agents, such as erlotinib.

Small-molecule inhibitors of VEGF receptor tyrosine kinase activity include sorafenib (approved for advanced renal cell carcinoma and currently in phase III trials in NSCLC in combination with chemotherapy), sunitinib (approved for gastrointestinal stromal tumor and renal cell carcinoma, with an encouraging phase II trial in lung cancer), vandetanib (with an intriguing phase II trial in combination with docetaxel in second-line NSCLC), and AZD2171 (in phase II/III testing in NSCLC in conjunction with chemotherapy). If approved, the oral small-molecule VEGF inhibitors would offer obvious advantages as potential maintenance therapy, compared with bevacizumab. Unlike the monoclonal antibodies, many have multiple targets, which is potentially advantageous for delaying the onset of resistance.

A major concern with this class of agents is toxicity. Even with the exclusion of patients with squamous cell carcinoma and brain metastases, pulmonary hemorrhage, some of them fatal, occurred in the Eastern Cooperative Oncology Group 4599 study of bevacizumab, as well as in the trials of sorafenib and sunitinib. Brain metastases are common in patients with NSCLC, so it is obviously important to develop and test VEGF-targeted agents in this population.

It is as yet unclear whether predictive markers will be identified to select patients for therapy with bevacizumab or other VEGF-targeted agents. In the E4599 trial, response did not correlate with plasma VEGF levels.

Bevacizumab. Following the report of the E4599 phase III trial, bevacizumab was approved by the U.S. Food and Drug Administration for first-line treatment of locally advanced, recurrent, or metastatic, nonsquamous NSCLC in combination with carboplatin and paclitaxel. Ongoing research directions include the evaluation of bevacizumab in small cell lung cancer, early stage NSCLC, patients at higher risk for bleeding complications (i.e., those with squamous histology or brain metastases), locally advanced NSCLC with radiation therapy, and in combination with other targeted agents. The Eastern Cooperative Oncology Group 1505 trial will study the potential benefit of bevacizumab in conjunction with cisplatin-based adjuvant chemotherapy in resected stage IB-IIIa NSCLC. The BETA lung study is a phase III trial of erlotinib with and without bevacizumab in the second-line setting that includes evaluations of putative predictors of response to erlotinib. ATLAS is a phase III trial of bevacizumab with

chemotherapy followed by erlotinib after chemotherapy is completed that will enroll patients with nonsquamous or squamous cell histology. Unanswered questions regarding the role of bevacizumab in the treatment of lung cancer include the optimal duration of therapy and the safety and efficacy of bevacizumab in combination with other standard chemotherapy regimens.

VEGF Trap. VEGF Trap is a fusion protein consisting of key domains from human VEGF receptors 1 and 2 with human IgG₁ Fc. It binds VEGF with high affinity and blocks all VEGF-A isoforms as well as placental growth factor. Phase I studies showed tolerability and signals of efficacy (i.e., stable disease), and a phase II trial of single-agent VEGF Trap is under way in patients with NSCLC. The primary end point of this trial is response rate using a modified version of Response Evaluation Criteria in Solid Tumors that allows recognition of tumor cavitation as a response.

Vandetanib (ZD6474) and AZD2171. These agents were discussed as promising representatives of the class of oral VEGF tyrosine kinase inhibitors. Although vandetanib inhibits both the VEGFR2 and the EGFR pathway, its affinity for VEGFR2 is substantially greater than for EGFR. This ability to target both pathways might be advantageous in treating NSCLC. In a randomized, blinded crossover trial of vandetanib versus gefitinib, vandetanib showed a response rate of 8% and a median progression-free survival of 11 weeks. In a phase II study as second-line therapy for NSCLC, vandetanib plus docetaxel prolonged progression-free survival by 57% compared with docetaxel alone (18.7 weeks for docetaxel plus 100 mg vandetanib versus 12 weeks for docetaxel alone); a phase III trial of docetaxel plus or minus vandetanib has opened. AZD2171 shows even greater preclinical affinity for VEGFR2 without inhibiting EGFR. The Clinical Trials Group of the National Cancer Institute of Canada is conducting a phase II/III trial of carboplatin/paclitaxel in combination with AZD2171 as first-line treatment for stage IIIB-IV NSCLC. In both this and the vandetanib trials, all NSCLC histologic subtypes as well as patients with treated brain metastases are allowed.

The PI3K/Akt Pathway as Target

The PI3K/Akt pathway is activated by VEGFR1, VEGFR2 and VEGFR3, EGFR, and platelet-derived growth factor receptor, among other growth-promoting signals. Activation of the PI3K/Akt pathway induces cellular proliferation, suppresses apoptosis, promotes cell motility, and induces the expression of growth and angiogenic factors. PI3K is overexpressed and PI3K signaling is elevated in NSCLC. Somatic mutations of different receptors and signaling molecules directly amplifying the PI3K/Akt signaling pathway are among the most common in cancer. Down-regulation of PI3K signaling is necessary for the induction of apoptosis by all of the targeted therapies. Agents directly targeting PI3K are in preclinical development. Class IA PI3K is the one most commonly associated with cancer. Because of the existence of multiple isoforms, the efficacy and tolerability of a putative PI3K inhibitor will depend on how specific it is for the targeted isoform. PI3K inhibition has tremendous potential as a combination approach with other cytotoxic agents and targeted therapies.

Other Targets

Bortezomib (Velcade). Bortezomib, a small-molecule proteasome inhibitor, has shown limited single-agent activity in NSCLC. It is currently being studied in the subgroup of bronchioloalveolar carcinoma where it seems to have some efficacy in terms of clinical responses. It is also being investigated in conjunction with chemotherapy in randomized phase II trials. Several conference participants expressed the view that the preclinical work to support additive effects with chemotherapy used clinically unachievable plasma levels of bortezomib. Based on the preclinical work, conference participants felt that there are issues with scheduling and dosing for this agent that are not easily resolved, and thus, it may be unlikely to play a prominent role in the treatment of patients with NSCLC.

Paclitaxel poliglumex (Xyotax). Paclitaxel poliglumex is a drug conjugate linking paclitaxel to a biodegradable polymer. The complex has enhanced vascular permeability, achieving greater paclitaxel distribution to tumor tissue than unconjugated paclitaxel. Subgroup analyses of two phase III trials found a nonsignificant trend to improved response over standard paclitaxel chemotherapy in women but not in men, with a significant survival advantage in the subgroup of women under age 55. Preclinical studies suggest that estrogen may exert effects on both tumor biology and the mechanisms of action of paclitaxel poliglumex. A phase III trial currently being planned (PIONEER follow-on study PGT306) will enroll women with advanced NSCLC who are either premenopausal or receiving hormone replacement therapy.

TLK286 (Telcyta). Glutathione S-transferases are intracellular enzymes that protect cells by facilitating the conjugation of toxic compounds with the antioxidant glutathione. They play a critical role in mediating cellular resistance to several classes of anticancer drugs. In particular, glutathione S-transferase P1-1 is frequently overexpressed in NSCLC, and its overexpression is associated with poor prognosis and resistance to cytotoxic chemotherapy. TLK286 was designed as a pro-drug that is activated by its target, glutathione S-transferase P1-1. Early clinical studies have indicated that TLK286 is well tolerated and there are several phase II and phase III studies under way to evaluate this agent in NSCLC and other solid tumors.

RAD001 (Everolimus). RAD001 is a derivative of rapamycin formulated for oral administration that is being developed as an antiproliferative drug with applications as an anticancer agent. RAD001 acts by selectively inhibiting the mammalian target of rapamycin (mTOR) pathway. mTOR functions as a downstream component of the PI3K/Akt pathway. RAD001 has entered the clinic in combination with erlotinib for patients with relapsed NSCLC. Phase I trials are examining RAD001 given in conjunction with erlotinib and with etoposide/cisplatin.

L-BLP-25 vaccine (StimuVax). L-BLP-25 is a peptide vaccine that targets MUC1, a mucinous glycoprotein present on normal epithelial cells but overexpressed in most cancers. Approximately 60% of NSCLC tumors are MUC1-positive. MUC1 integrates signals from growth factor receptors such as EGFR and influences the invasion and metastasis of tumor cells. It may confer a survival advantage under conditions of oxidative stress, and it may also enhance resistance to chemotherapy.

Preclinical studies in a MUC1-positive tumor model found that an additive antitumor effect was achieved when given in combination with carboplatin. A randomized phase II trial of maintenance vaccine versus best supportive care in stage IIIB/IV NSCLC has reported a trend to longer survival for the vaccine in patients with stage IIIB disease (30.6 versus 13.3 months). A phase III placebo-controlled study has been initiated to investigate L-BLP-25 in this population.

Imatinib (Gleevec). Imatinib inhibits KIT kinase activity and has been investigated in small cell lung cancer, in which KIT overexpression frequently occurs. In contrast to gastrointestinal stromal tumors, where KIT is activated by mutation, there is no consistent evidence that KIT is activated by somatic mutations or is important to the growth of small cell lung cancer. No significant antitumor activity was found in phase II testing in small cell lung cancers. However, imatinib is also a potent inhibitor of platelet-derived growth factor, a regulator of interstitial fluid pressure with a resulting influence on trans-capillary transport of chemotherapy. It is not entirely clear that such a targeted agent will work in an off-target setting such as NSCLC in which neither c-kit nor bcr-abl has been implicated as important in the pathogenesis of the tumor. However, if the interstitial fluid homeostasis mechanism is shown to be important, this will be an interesting use in this setting.

Enzastaurin. Enzastaurin is an inhibitor of protein kinase C that also targets the PI3K/Akt pathway. Protein kinase C is implicated in processes that control angiogenesis, cell growth, motility, and apoptosis. Phase II trials of enzastaurin in other tumor types, including lymphoma, have documented objective responses. Phase II combination therapy trials in NSCLC are in progress.

Conclusion

With the novel targeted therapies, incremental progress is being made, with modest but clinically meaningful median survival gains of 2 months with erlotinib as a single agent and bevacizumab in combination with chemotherapy. Future drug development and testing should be based on more rigorous target validation and should include molecular profiling of individual patients with sensitive and resistant tumors. We believe we are past the era when so few treatments were available for patients with advanced lung cancer that it was acceptable to take agents without any preclinical evidence of benefit into clinical trials. As more novel agents and combinations are developed, this is no longer a legitimate approach for using limited resources. More thorough preclinical studies need to be done and objectively analyzed, particularly given the potential for targeted agents to be antagonistic rather than synergistic in combination therapies. Although the overall gains thus far have been modest, the novel targeted therapies offer the potential for individual patients to experience prolonged progression-free survival that is measured in years rather than months. To achieve that goal, basic scientists and clinicians must work together more effectively to advance our knowledge of tumor biology and our ability to offer individualized therapy based on tumor molecular profiles.

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