New Targets and New Mechanisms in Lung Cancer

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This review will describe the well-known use of VEGF antibodies; the current uses of EGFR and ALK tyrosine kinase inhibitors; newer agents being used against MET, FGFR, and other intracellular targets; insights regarding the field of immunotherapy in lung cancer; and finally, newer developments in chemotherapy.

Introduction

Lung cancer is the second most common form of cancer and the most common cause of cancer-related deaths in men and women, yet cure rates are significantly lower than those of other less prevalent cancers, such as cancers of the breast and colon. More than two decades ago, very few treatments were available for lung cancer; over time, however, we have made modest strides in finding new forms of chemotherapy and new treatment targets.

Especially in the last several years, significant advances have been made in personalized chemotherapy choices, based on histology and on the availability of targeted agents that are effective and less-toxic options for lung cancer patients. The first of these targeted agents was bevacizumab (Avastin), a humanized monoclonal antibody directed at vascular endothelial growth factor (VEGF), which was associated with an improvement in overall survival (OS) in non-small-cell lung cancer (NSCLC) when added to carboplatin and paclitaxel.[1] With the success of bevacizumab as a model, newer therapies are constantly being investigated, and this review aims to provide an overview of current practice, with insights into future management. (Figure 1 highlights some current and emerging targets and targeted therapies in lung cancer.)

Epidermal Growth Factor Receptor (EGFR)

The evolution of the epidermal growth factor family’s importance in malignancy and as a therapeutic target dates back to 1962, when Stanley Cohen isolated a novel protein from mice that demonstrated increased growth of incisors and eyelids in newborn animals.[2] This protein, now called epidermal growth factor, includes a family of ligands and receptors; somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are found in 15% to 20% of lung adenocarcinomas, with deletion 19 and L858R representing almost 90% of these EGFR mutations. Two classes of agents targeting EGFR have been investigated extensively in patients with NSCLC: the tyrosine kinase inhibitors (TKIs) and the monoclonal antibodies (mAbs). Gefitinib and erlotinib (Tarceva) bind in a reversible fashion to the adenosine triphosphate (ATP) binding site of EGFR tyrosine kinase, inhibiting initiation of signaling cascades. Through numerous studies, it became clear that responses to these targeted agents did not emerge from unselected populations. Significant results were not seen just with specific patient characteristics or even EGFR amplification but instead noted in patients with specific EGFR mutations.

With this evolving knowledge, gefitinib and erlotinib were brought to the front-line treatment of patients with advanced NSCLC harboring EGFR mutations, and by December 2010, results of multiple randomized phase III trials comparing front-line erlotinib or gefitinib against platinum-based chemotherapy in patients with advanced NSCLC were reported. The Iressa Pan-Asia Study (IPASS), First-SIGNAL, the North-East Japan Study Group NEJ002 trial, and the West Japan Thoracic Oncology Group trial 3405 (WJTOG3405) are four studies that involved gefitinib, while EURTAC and OPTIMAL utilized erlotinib; all of these investigations highlighted the distinct nature of EGFR-mutated lung cancer and its selected response to TKI intervention.[3-10] In EGFR-mutated tumors, erlotinib/gefitinib consistently provided benefit across these studies in terms of progression-free survival (PFS), response rate (RR), and quality of life (QoL) compared with chemotherapy. Specifically, EURTAC randomized 165 patients between erlotinib and carboplatin/gemcitabine, and showed a PFS improvement of 8.5 months (13.1 vs 4.6 months; P < .0001); OPTIMAL randomized...
173 patients between erlotinib and chemotherapy (platinum with docetaxel or gemcitabine) and showed an improvement in PFS of 4.5 months (9.7 vs 5.2 months; $P < .0001$).[9,10] None of the studies demonstrated an OS advantage, likely due to high rates of cross-over to the alternative therapy at the time of disease progression. The results of these trials demonstrate that testing for EGFR mutations should be a standard, to identify those who would benefit from front-line EGFR-TKI treatment.

Despite the benefits derived from treatment with gefitinib/erlotinib, acquired resistance develops. The mechanisms of resistance and means of overcoming them have become active areas of research. Amplification of MET and T790M mutations account for 20% and 50%, respectively, of these cases.[11] Irreversible EGFR inhibitors, targeted therapies against MET, and dual-pathway blockades have activity in this resistant population.

Afatinib is an irreversible ErbB family blocker that covalently binds to the cysteine residue of EGFR, providing longer inhibition of EGFR. Compelling data on afatinib from LUX-Lung 3 have been reported. In this open-label, randomized phase III study, patients with EGFR-mutated, advanced lung adenocarcinoma received front-line treatment with either afatinib or cisplatin-pemetrexed. Those treated with afatinib demonstrated a prolonged PFS (11.1 vs 6.9 months; hazard ratio [HR] = 0.58; $P = .0004$).[12] In the preplanned analysis, those with common mutations (Del19 or L858R) had a median PFS of 13.6 vs 6.9 months (HR = 0.47; $P < .0001$). The RR was significantly higher with afatinib (56.1% vs 22.6%, $P < .001$ in all patients; and 60.8% vs 22.1%, $P < .0001$ in patients with common mutations). There were also improvements in the 1-year disease-control rate, cancer-related symptoms, and QoL with afatinib. The most frequent adverse events were diarrhea and rash, although no patients discontinued afatinib because of rash. LUX-Lung 3 is the first randomized study to demonstrate benefit of an oral targeted therapy vs chemotherapy in a molecularly selected population. Afatinib has also demonstrated benefit in those previously treated with EGFR TKIs.[13] Based on these results, afatinib is currently available to those who are both TKI-naive and TKI-resistant, through an open-label expanded-access program.

Cetuximab (Erbitux), a chimeric monoclonal IgG1 antibody that blocks EGFR signaling, has been investigated in the front line in combination with platinum-based chemotherapy in advanced NSCLC through two multicenter, randomized phase III trials. The First-Line Erbitux in lung cancer (FLEX) trial and the Bristol-Myers Squibb (BMS) 099 study both revealed statistically significant increases in RR with the addition of cetuximab to chemotherapy, and both demonstrated about a 1.3-month increase in OS, although BMS 099 lacked the power to detect a statistically significant difference of this magnitude.[14,15] These results are in contrast to those found with EGFR-TKIs combined with chemotherapy, which may be attributed to the different mechanism of action of the monoclonal antibody. Despite the positive results from FLEX, cetuximab has not been approved for treatment of NSCLC.

However, cetuximab is being investigated further in combination with other targeted therapies. Bevacizumab and cetuximab have shown promising results in the Southwest Oncology Group (SWOG) 0536 trial.[16] In this safety-and-efficacy phase II single-arm study, approximately 100 patients with advanced NSCLC were treated front-line with carboplatin, paclitaxel, bevacizumab, and cetuximab. The feasibility endpoint was met, and secondary endpoints revealed an RR of 53%, PFS of 7 months, and OS of 14 months. These results have led to the ongoing phase III SWOG 0819 trial of carboplatin-paclitaxel and bevacizumab (in eligible patients), with or without cetuximab, in patients with advanced NSCLC.

Additionally, cetuximab has shown response in combination with afatinib. In a trial with combination afatinib-cetuximab in patients with EGFR mutations and disease progression on erlotinib, disease control was observed in all 22 patients treated with the 40-mg dose of afatinib, with tumor size reduction of up to 76%.[17] This is under further investigation with an ongoing expanded cohort. Dacomitinib (PF-00299804) is a pan-HER inhibitor that binds irreversibly to the ATP domain of EGFR, HER2, and HER4 and has demonstrated EGFR inhibition in cell lines harboring L858R and T790M mutations.[18,19] In a global phase II study, 188 patients were randomized to dacomitinib or erlotinib after progression on chemotherapy. PFS (primary endpoint) was improved with dacomitinib (2.86 vs 1.91 months; HR = 0.66; $P = .012$), suggesting that dacomitinib is another potential treatment option.[20]

KD019/XL647 is a small-molecule TKI that targets EGFR, VEGFR-2, HER2, and Ephrin type B receptor 4. In a phase II study evaluating two dosing regimens, the RR was 20% and the PFS was 5.3 months. In patients with EGFR mutations, the RR was 57% and the PFS was 9.3 months.[21] This is a compound that will continue to undergo clinical evaluation.

A number of agents targeting parallel and downstream signaling of the EGFR pathway are under
development for the treatment of NSCLC, including MET inhibitors. The rationale for dual inhibition of EGFR and MET for treatment of NSCLC is based on evidence that MET is associated with resistance to erlotinib and gefitinib, and preclinical and clinical data suggest that this combination has additive or synergistic antitumor activity which may overcome resistance.[22-24] Tivantinib (ARQ 197) is an oral, selective, non–ATP-competitive inhibitor of MET receptor tyrosine kinase. A global randomized, double-blind, placebo-controlled phase II trial compared erlotinib plus ARQ 197 vs erlotinib plus placebo in EGFR inhibitor-naive patients with advanced NSCLC. In this 167-patient trial, median PFS (primary endpoint) was prolonged with combination therapy (16.1 vs 9.7 weeks; HR = 0.81; 95% confidence interval [CI], 0.57–1.15; P = .23).[25] Based on these promising data, the MARQUEE (Met inhibitor ARQ 197 plus Erlotinib vs Erlotinib plus placebo in NSCLC) trial was designed as a phase III, randomized, double-blind study of tivantinib plus erlotinib vs placebo plus erlotinib in previously treated patients with advanced non-squamous NSCLC, with a primary endpoint of OS.[26] The agent onartuzumab/MetMAb (OAM4558) inhibits hepatocyte growth factor/scatter factor (HGF/SF)—a tissue-derived cytokine—from binding to MET, while its monovalent structure prevents dimerization/activation of the MET signaling pathway.[27] Studies have shown that the activation of MET by the binding of HGF/SF in tumors may lead to cell proliferation, increased cell survival, and induction of motility and invasion via modification of cell-to-cell adhesion, thus leading to poor prognosis, especially in lung cancer.[28,29] A global randomized, double-blind, placebo-controlled phase II study compared erlotinib plus onartuzumab vs erlotinib plus placebo in the second- or third-line management of advanced NSCLC. The addition of MetMAb to erlotinib significantly improved PFS and OS in patients who had high expression of MET in their tumors, resulting in a near two-fold reduction in the risk of disease progression and a three-fold reduction in the risk of death.[30] This is being followed by the MetLung study, a randomized, phase III, multicenter, double-blind, placebo-controlled study in patients with advanced NSCLC and MET-positive tumors who have failed at least one line but no more than two prior lines of platinum-based chemotherapy; the primary endpoint is OS.[31]

In conclusion, targeting the EGFR pathway for treatment of NSCLC continues to expand from the reversible EGFR TKIs to the irreversible EGFR TKIs and other monoclonal antibodies that, used as single agents and in combination with other novel therapies, remain a backbone of management for those who harbor EGFR mutations.

**Anaplastic Lymphoma Kinase (ALK)**

ALK was originally identified in patients with anaplastic large cell lymphoma, a subset of B-cell non-Hodgkin lymphoma.[32] The ALK gene also plays a key role in the pathogenesis of inflammatory myofibroblastic tumors and in neuroblastoma, but it was never observed to be important in lung cancer until two groups discovered ALK rearrangement in NSCLC in 2007.[33,34] The potential driver mutation is a fusion of an intrachromosomal inversion on the short arm of chromosome 2 that joins exons 1–13 of the Echinoderm microtubule-associated-protein like 4 gene (EML4) to exons 21–29 of ALK.[33-35] The resulting EML4-ALK is a fusion of the N-terminal portion of the protein encoded by EML4, with the intracellular signaling portion of the receptor tyrosine kinase encoded by the ALK gene.[33,34] This EML4-ALK fusion gene seems novel to NSCLC. Generally, the incidence of ALK-rearranged NSCLC is 3% to 5%.[35-37] One study showed a 13% incidence in metastatic NSCLC in Western populations and a 22% incidence in never/light smokers.[35] In Asian patients negative for EGFR and KRAS mutations, ALK fusion was seen in 17%.[38] Clinical signs of ALK rearrangement in NSCLC are unclear; hence, molecular testing is necessary. There are three methods of detecting ALK rearrangement: a fluorescence in situ hybridization (FISH) break apart assay, immunohistochemistry (IHC), and reverse-transcriptase polymerase chain reaction (RT-PCR). FISH is the current gold standard and is the companion diagnostic test (Vysis ALK break apart FISH probe kit; Abbott Molecular Inc) approved by the US Food and Drug Administration (FDA) in conjunction with conditioned approval of crizotinib (Xalkori) in the United States.[35,39-41]

Crizotinib is an oral, small-molecule competitive ATP inhibitor, primarily of MET, and it also has selective ALK inhibition.[35,36,39] It was first studied in humans in 2006 in the PROFILE 1001 study, using an initial standard dose-escalation pharmacokinetic schema followed by a clinical efficacy evaluation. After two patients in this phase I study had a dramatic response (coinciding with the discovery of ALK gene rearrangements in patients with NSCLC), an expanded prospective cohort was enrolled, with testing for ALK rearrangement.[42] Updated results from September 2012 showed a
60% RR (3 complete responses, 84 partial responses), a median time to first documented objective response of 8 weeks, and a median duration of response of 49 weeks. Overall survival data are not yet mature, but estimated 6- and 12-month OS rates are 87.9% and 74.8%, respectively.[43] Response to crizotinib is independent of age, sex, performance status, and prior treatment.[43] Upon the initial results of PROFILE 1001, a multicenter open-label phase II study (PROFILE 1005) was initiated. Recent data from this study showed a response rate of 60%; the median PFS was 8.1 months and the median response duration was 46 weeks, with responses appearing at 6 weeks.[44] Crizotinib gained FDA approval in August 2011 for locally advanced or metastatic NSCLC that is ALK-positive, based on the previously described studies reporting response rates alone. Preliminary results of the prospective randomized phase III trial (PROFILE 1007) comparing crizotinib and either pemetrexed (Alimta) or docetaxel in the second-line setting were recently presented in Vienna at the 2012 meeting of the European Society for Medical Oncology (ESMO). The primary endpoint of PFS was 7.7 months in the crizotinib arm and 3 months in the chemotherapy arm. The RRs were 65% and 20%, respectively. Interim OS data showed no difference, but OS may be skewed secondary to patient crossover.[45]

Currently, the National Comprehensive Cancer Network (NCCN) guidelines give a category 2A recommendation for the ALK inhibitor crizotinib in the first-line setting in patients with locally advanced or metastatic NSCLC who have the ALK gene rearrangement.[46] The NCCN also recommends FISH as the standard diagnostic test until further evidence regarding use of RT-PCR and IHC for assessing ALK status becomes available.

ALK-rearranged NSCLC has developed resistance to crizotinib. Some mechanisms of resistance include acquired or secondary resistance via mutations in six amino acid residues in ALK, coactivation of EGFR signaling, secondary point mutations in the ALK TKI domain, ALK gene amplification, and loss of the ALK fusion gene and the activation of other kinases.[47] Several other ALK inhibitors are in the development pipeline, with investigative goals aiming for more selective ALK inhibition and the overcoming of crizotinib resistance. Some are selective ALK inhibitors like AP26113, CH5424802, LDK378, ASP3026, and X396. AP26113 is ALK/EGFR-specific, hence it has the potential to overcome crizotinib resistance mediated by EGFR activation. Recently, the FDA granted “breakthrough therapy” designation to LDK378, allowing expedited development of the drug (of note, this designation is distinct from that of priority review or that of accelerated approval.)[48] Two heat shock protein 90 (HSP90) inhibitors, retaspimycin and ganetespib, have demonstrated clinical activity in patients with ALK-rearranged NSCLC. HSP90 is a chaperone protein, and its inhibition leads to rapid degradation of EML4-ALK, resulting in tumor regression and cell death.[35,36]

ROS1

ROS1 is another human receptor tyrosine kinase of the insulin receptor family. At least 12 ROS1 fusion variants have been identified in NSCLC. These are mainly seen in nonsquamous lung cancer with clinical pathologic features similar to ALK rearrangement. ROS1 rearrangements are very rare and seen in 1% to 2% of patients with NSCLC, and there is no difference in prevalence between Asian and non-Asian patients. After the initial in vitro discovery of ROS1 inhibition by an ALK inhibitor in the HCC78 cell line, the expanded cohort of ROS1 in PROFILE 1001 (18 patients) was treated with crizotinib. The overall RR was 57%, and 8 of 12 patients achieved a complete response.[49] FISH is the standard diagnostic test, although RT-PCR and IHC are being developed to detect ROS1. Crizotinib works in ROS1 rearrangements because of homology with ALK. Future studies are being designed to investigate the response to various specific ALK inhibitors and to identify other homologous molecular targets.

KRAS/MEK/mTOR/AKT

The RAS/RAF/MAPK pathway is downstream from the aforementioned cell surface receptors and is an evolving target for non–small-cell lung cancer therapy. (RAS is an abbreviation for “rat sarcoma,” RAF is an acronym for “rapidly accelerated fibrosarcoma,” and MAPK stands for “mitogen-activated protein kinases.”) KRAS mutations are the most common oncogenic mutation in NSCLC, and their implications as an early mutation in the development of lung adenocarcinoma have been studied for more than two decades.[50] KRAS mutations have been found more frequently in smokers, and they portend a worse prognosis via potential refractoriness to EGFR TKI therapy and to selected cytotoxic regimens.[51-53] Unlike colon cancer, the utility of cetuximab as EGFR therapy based on KRAS mutational status in lung cancer was met with significantly less success and predictability. The
published subset data from both the FLEX and BMS 099 trials demonstrate response correlations with mutational status similar to those seen in colorectal adenocarcinomas. BMS 099, a phase III randomized controlled trial for patients with advanced NSCLC, used carboplatin/paclitaxel (TC) with or without cetuximab. There was no correlation with PFS or OS with the addition of cetuximab therapy (median OS was 9.69 months with cetuximab/TC vs 8.38 months with TC; HR = 0.890; 95% CI, 0.754–1.051; P = .169).[54] While there was a statistically significant improvement in RR, neither PFS nor OS achieved statistical significance.[57] Additionally, in a subset analysis, a patient’s EGFR or KRAS mutational status had little to no effect on predicting response.[54] In FLEX, a comparison of cytotoxic cisplatin/navelbine with or without cetuximab, patients who received cetuximab therapy had improved OS (median, 12.0 months vs 9.6 months; HR = 0.73; 95% CI, 0.58–0.93; P = .011) irrespective of their EGFR, PTEN, and KRAS mutational status.[55] At present, choosing molecular therapies based on KRAS mutational status alone has not been adopted as a reliable clinical strategy.

The importance of KRAS mutations in NSCLC may change with further exploration of downstream pathways. The data reported from a published trial of the mitogen-activated protein kinase–1 (MEK1) inhibitor selumetinib have drawn interest for patients with KRAS mutations. At the 2012 meeting of the American Society of Clinical Oncology (ASCO), the use of selumetinib with docetaxel in patients with KRAS-mutated refractory NSCLC demonstrated a RR of 37% (P < .001), an improved PFS (median 5.3 vs 2.1 months, HR = 0.58; 80% CI, 0.42–0.79), and a trend toward improved OS (9.4 vs 5.2 months; HR = 0.80; 80% CI, 0.56–1.14).[56] A randomized phase II trial is currently underway utilizing selumetinib with or without erlotinib, with patients being stratified based on KRAS mutational status. A second MEK inhibitor, tivantinib, has shown activity in KRAS-mutant NSCLC patients (for PFS, HR = 0.18; 95% CI, 0.05–0.70; P = .006).[57] Although the number of patients was small, the drug is being explored with erlotinib both in a phase III trial that is not stratifying patients by mutation status, and in a phase II trial that stratifies based on KRAS mutational status. Other MEK inhibitors currently in development include XL518, which is under investigation in a phase I dose-escalation trial for patients with solid tumors, and MEK162, which will be investigated in a phase II trial targeting melanoma that is now enrolling patients. Trametinib and dabrafenib are MEK inhibitors in multiple phases of development, primarily for melanoma, but investigations will include patients with additional solid tumors as well as hematologic malignancies.

Another intracellular signaling pathway of interest is the PTEN/PI3K/AKT/mTOR pathway. Important in cellular apoptosis, growth, and drug resistance, mutations in PI3K and PTEN have been linked to lung cancer, in particular squamous cell NSCLC.[58] A downstream target of the PI3K/PTEN pathway is mammalian target of rapamycin (mTOR). In a randomized discontinuation trial reviewed in poster form at the ASCO meeting in 2012, the mTOR inhibitor ridaforolimus was provided as a single agent in a subset of pretreated patients with advanced NSCLC. The RR was noticeably low at 1%, yet there was a near doubling of PFS for patients with stable disease at 8 weeks compared with patients who discontinued the drug (4 months vs 2 months; HR = 0.36; P = .013). There was also a trend toward improved OS (18 months vs 5 months; HR = 0.46; P = .09).[59] Although not as widely explored to date, new compounds have sparked an interest in targeting AKT (serine/threonine protein kinase). Like mTOR, AKT is another step in the aforementioned pathway. AKT is believed to be critical to the development of erlotinib resistance; the addition of the AKT inhibitor MK2206 re-sensitized cell lines that had become previously resistant.[60] This approach is being pursued in human subjects who likewise have failed erlotinib therapy, and a phase II study is now enrolling patients.

**Fibroblast Growth Factor Receptor (FGFR)**

The FGFR tyrosine kinase family comprises four kinases: FGFR1, FGFR2, FGFR3, and FGFR4. They contribute to cancer development by stimulating proliferation of various cell types, inhibiting differentiation of some precursor cells, and playing a crucial role in cell differentiation and growth.[61,62] Mutations in these receptors have been seen in 20% of lung squamous cell carcinomas and rarely in adenocarcinoma. **FGFR1** amplification seems to be directly correlated with smoking dose and does not differ by ethnicity. **FGFR1** amplification develops early and hence is seen in biopsy specimens of primary and metastatic lesions.[61,62] FISH and IHC testing are well correlated. Several inhibitors (BGj 398, investigated in NCT01004224; AZD 4547, investigated in NCT00979134; and dovitinib) are in early clinical development. Final data are pending from a European study comparing cisplatin and gemcitabine with or without BIBF 1120, and a phase III trial combining docetaxel with BIBF 1120. Squamous cell carcinoma is consistently related to smoking, and compared with adenocarcinoma
there are no specific molecular targets identified, limiting therapeutic options. Discovery of FGFR amplification in 20% of squamous cell carcinomas could be important. With new drugs in clinical trials, better patient outcomes are expected.

Immunotherapy

As immunotherapy has become an exciting area in oncology, with new therapies directed at tumors such as melanoma, more research is being conducted in NSCLC. Three separate areas are currently being evaluated: vaccine therapy, new monoclonal antibody therapy (passive immunotherapy; discussed in other sections of this article), and immune system modulation.

Vaccine therapy has been studied for decades in lung cancer. Initially vaccine therapy was centered on small-cell lung cancer, with investigations of nonspecific vaccines such as Bacille Calmette-Gurin (BCG), but initial trials were negative.[63] Currently in NSCLC, several vaccines are in phase III trials based on benefits seen in early-phase studies, and we recently received results from a trial using the vaccine L-BLP25 (Stimuvax). L-BLP25 targets the exposed core peptide of MUC1, a heterodimeric glycoprotein overexpressed in lung cancers that is associated with poor prognosis, due to its association with cellular transformation caused by upregulation of the PI3K-AKT cellular pathway.[64,65] In 2005, Butts et al demonstrated an improvement of 4.4 months (P = .112) in patients with advanced-stage NSCLC who received the L-BLP25 vaccine after initial first-line chemotherapy.[66] There was also a strong trend for greater than 2-year survival in patients with locoregional stage IIIb NSCLC. With these preliminary phase II results, a phase III trial (Stimulating Targeted Antigenic Responses To NSCLC [START]) was initiated to investigate vaccine vs placebo in unresectable stage III patients who were stable or responding after combined-modality therapy with chemotherapy and radiation. Unfortunately, a recent press release from Merck in December 2012 detailed that the trial did not meet its primary endpoint of OS, but it stated that “notable treatment effects were noticed in some subgroups.”[67] We are awaiting further delineation of these results in upcoming meetings, as well as results from a companion study that was being conducted in Asian patients (INSPIRE: Cancer Vaccine Study for Stage III, Unresectable, Non–small -cell Lung Cancer in the Asian Population). While the results with L-BLP25 did not meet their primary endpoint, we must await results of phase III trials involving other vaccine therapies (eg, MAGRIT: MAGE-A3 as Adjuvant Non–small-cell Lung Cancer Immunotherapy Lung Cancer Vaccine Trial, using the MAGE-A3 vaccine) before we can make definitive conclusions.

A significant amount of research is studying immune modulation with compounds targeting CTLA-4 or PD-1 (see Figures 2 and 3). Currently, ipilimumab (Yervoy, a monoclonal antibody that improves antitumor immunity via blockade of the cytotoxic T-cell lymphocyte antigen 4 [CTLA-4], impeding immune downregulation) is approved for use in advanced-stage melanoma. In NSCLC, a recent phase II study of chemotherapy and ipilimumab reported by Lynch et al showed a statistically significant improvement (P = .02) in PFS in advanced NSCLC patients initially treated with carboplatin and paclitaxel for 2 cycles who then received ipilimumab with chemotherapy for 4 more cycles.[68] Overall survival was 12.2 months, similar to results from the combination of carboplatin, paclitaxel, and bevacizumab. Interestingly, subset analysis showed a benefit in patients with squamous histology, compared with no observed benefit in those with nonsquamous histology. Given these results, a current phase III study will randomize 920 patients with squamous histology in a 1:1 fashion to phased-in ipilimumab with carboplatin and paclitaxel vs chemotherapy alone.[69] Recently in the New England Journal of Medicine (NEJM), Topalian et al reported responses in patients with multiple tumor types (including NSCLC) using an anti-PD1 antibody (MDX-1106) in a phase I trial while, in the same NEJM issue, Brahmer et al showed equally positive results using an anti-PD-L1 antibody (MDX-1105) in a similar phase I trial.[70,71] Programmed death protein 1 (PD1) is an immune checkpoint receptor that can mitigate immunosuppression of cytotoxic T cells. An active form of immune evasion used by tumor cells involves the joining of PD1 to its ligand (PD-L1), found on many tumor cells or in the tumor microenvironment. The anti-PD1 antibody showed an objective response in 14 of the 122 NSCLC patients, with a PFS of 26% at 24 weeks, while the anti-PD-L1 antibody showed an objective response in 5 of 49 patients treated, with a PFS of 31% at 24 weeks. Of note, both studies showed an increase in immune-related adverse events but more importantly, there were three deaths in the anti-PD1 study, due to pneumonitis.

With the initial positive results described above in both the phase I trial of anti-PD1 and the phase I trial of anti-PD-L1 antibodies, ongoing phase II and III trials are being undertaken in NSCLC. Two other compounds, in addition to the medications described above, are also being studied in phase I trials (AMP-224, a Fc fusion protein targeting PD-L2) and phase II trials (MK-3475, a PD-1
inhibitor).[72] Although response rates initially seem small, the rates are comparable to reported responses with chemotherapy. We eagerly await final results of these new studies, as immune-modulation therapy may become a new modality for the treatment of NSCLC.

**Cytotoxic Chemotherapy**

Even with the advances in targeted therapy and the prospect of immunotherapy, cytotoxic chemotherapy is still the backbone of therapy for patients with lung cancer. One notable unmet need concerns patients with squamous cell histology. For many years, patients with squamous cell carcinoma and adenocarcinoma had similar OS; however, more recent studies have shown improved outcomes in those with adenocarcinoma, likely due to new treatment options for lung adenocarcinoma.[73] Several agents known to be effective in adenocarcinoma, such as bevacizumab and pemetrexed, may be toxic or detrimental in patients with squamous cell carcinoma. Standard front-line chemotherapy for squamous cell carcinoma has remained a platinum-based doublet; new treatment options are needed.

Nab-paclitaxel (Abraxane) is a biologically interactive albumin-bound paclitaxel. After determining that clinical outcomes were improved with weekly rather than every-3-week administration of nab-paclitaxel in phase II trials, a phase III randomized trial was conducted in patients with advanced NSCLC to evaluate carboplatin with nab-paclitaxel vs carboplatin-paclitaxel in the front-line setting. The RR (primary endpoint) was higher in those treated with nab-paclitaxel (33% vs 25%, *P* = .005), and this was even more pronounced in those with squamous cell carcinoma (41% vs 24%). PFS was 6.3 months with nab-paclitaxel vs 5.8 months in the control group (*P* = .214), and OS was 12.1 months with nab-paclitaxel vs 11.2 months in the control group (*P* = .271).[74] Based on this trial, regulatory agencies approved nab-paclitaxel in combination with carboplatin for front-line treatment of patients with advanced NSCLC. Nab-paclitaxel–carboplatin should be considered a preferred front-line regimen for patients with advanced squamous cell carcinoma of the lung. Interestingly, nab-paclitaxel provides a novel treatment approach by increasing intratumoral concentrations of drug through a receptor-mediated transport process that involves binding to a gp60 receptor, activation of a caveolin-1 protein, and formation of caveolae transporters.[75] SPARC (secreted protein, acidic, cysteine-rich [osteonectin]) is a protein secreted by tumor that binds to albumin and thus may be affected by this biologically interactive albumin-bound paclitaxel. The SPARC pathway may be a new target in NSCLC and is being evaluated further through biomarker assays in patients treated with nab-paclitaxel.

**Future Directions**

As the rapid evolution of genome technology coupled with a fall in sequencing costs has increased the technical and economic feasibility of complete molecular profiling of a patient’s tumor, molecular diagnostic kits are being developed to guide the use of an increasing number of therapies. The International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) are examples of large-scale integrative programs whose goal is to harness the full potential of the cancer genome to deliver personalized cancer medicine through multidisciplinary programs. To get closer to our goal of personalized medicine, we suggest a potential approach to patient care (**Figure 4**). The aim will be to establish a consistent and robust validation workflow of the discovered genomic abnormalities with next-generation sequencing analysis, to enable real-time predictive targeted patient therapy by analyzing tissue specimens and circulating tumor cells (CTCs) for molecular markers in a Clinical Laboratory Improvement Amendments (CLIA)-certifiable manner. A number of different platforms include high-throughput mutation analysis and quantitative-PCR methodologies. Studies such as the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial have highlighted the feasibility and value of obtaining more patient specimens and subsequently planning for discovery of new markers correlated with clinical outcome.[76] The schema not only underscores the obvious importance of initial tissue acquisition leading to biomarker testing, but it also shows the importance of considering rebiopsy at the time of progression. Although rebiopsy is not currently a standard practice in patients with lung cancer, we propose that this should be considered more frequently, as it is clear that lung cancer is not a homogenous entity and that any histologic change, or any change in mutational status, could lead to the gains or losses of new therapies for our patients. We have recently reported up to 25% changes in mutational status (gains and losses) in tissue treated with chemotherapy compared with baseline.[77]

**Conclusions**
In conclusion, multiple advances have been made in the number and types of therapy available for treatment of patients with lung cancer. One overriding theme that is present with all our new therapies is the importance of identifying specific characteristics in our patients that will guide or even change our therapeutic options. This requires an even more careful selection of patients based on information gathered from their tumors. To provide the best therapy for our patients, we must accept that their tumor characteristics can change over time, especially after chemotherapy, and that truly personalized treatment of the patient, in real time, is only possible with the most up-to-date information about their tumor status.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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Figure 1: Therapeutic Targets in Lung Cancer

Figure 2: Schematic of Immune Checkpoint Mechanisms—CTLA-4

Figure 3: Schematic of Immune Checkpoint Mechanisms—Anti-PD1/PD-L1

Figure 4: A Proposed Algorithm for a Personalized Systematic Approach ...

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