Recent advances in the management of advanced non–small-cell lung cancer

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Lung cancer is the leading cause of cancer-related mortality among men and women in the United States. Non–small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancers. Most patients with NSCLC present with advanced disease and median overall survival in this incurable setting remain dismal. Accumulating evidence suggests that both histology and molecular signature have prognostic and predictive value for NSCLC. Recent advances in the molecular characterization of NSCLC tumors have made individualized treatment approaches feasible. Personalized chemotherapy and targeted biological therapy based on a tumor's individual biologic and molecular profile can optimize efficacy while minimizing toxicity. Molecular testing for activating mutations in the epidermal growth factor receptor (EGFR) domain and *EML4-ALK* translocation are routinely used to guide therapeutic decisions. Several new treatments that irreversibly target EGFR family members are in development for patients with NSCLC. Novel *EML4-ALK* inhibitors such as LDK378 are promising agents with encouraging early efficacy data. *KRAS* mutations are the most common mutation in adenocarcinomas. Although no agents for this subset of NSCLC have been approved, there are several agents in clinical development, including selumetinib, an MEK inhibitor, that seem promising. A growing body of evidence suggests that NSCLC is subject to immune surveillance. Immunotherapeutic interventions, including vaccine therapy and antigen-independent immunomodulatory strategies, may improve outcomes in NSCLC. In this review, we summarize recent advances in non–small-cell lung cancer, with an emphasis on investigational strategies for individualized treatment.

Lung cancer is the most common cause of cancer-related death worldwide.[1] Between 85% and 90% of lung cancers are non–small-cell lung cancer (NSCLC), and 40% of patients with newly diagnosed NSCLC present with advanced disease. Adenocarcinoma is the most common subtype of NSCLC, accounting for 40%-50% of cases, with squamous cell carcinoma (25%-30% of cases) and large cell carcinomas (10%-15% of cases) being the second and third most common subtypes.

Early stage NSCLC represents a minority of cases and is often curable with surgery with or without adjuvant chemotherapy, which has been shown to improve outcome in resected patients with nodal involvement. In the locally advanced setting, radiation therapy (XRT), surgery, and chemotherapy are used alone or in combination to maximize therapeutic benefit. In this regard, chemotherapy that is given concurrently with XRT is superior to XRT alone. However, most patients with NSCLC present with distant metastases where chemotherapy is the mainstay of treatment.

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For patients with advanced NSCLC, 4-6 cycles of platinum-based chemotherapy is the usual approach.[2] Histology plays an important role in outcomes. For patients with adenocarcinoma, frontline pemetrexed and platinum have been shown to yield superior efficacy and an improved side effects profile compared with the gemcitabine–platinum combination.[3,4] Maintenance therapy for patients without disease progression after first-line chemotherapy has recently emerged as a new treatment paradigm for some patients.[5] Erlotinib and pemetrexed has been shown to improve survival both as "continuation" and "switch" maintenance[6,7] in patients with nonsquamous carcinoma histology. Bevacizumab added to first-line chemotherapy produces modest improvement in outcomes compared with chemotherapy alone; however, it is generally reserved for nonsquamous tumors and patients without ongoing hemoptysis and other contraindications for bevacizumab use.[8] Patients with activating mutations in the epidermal growth factor receptor (EGFR) domain or *EML4-ALK* translocation benefit from first-line treatment with erlotinib or crizotinib, respectively.[9-12] These mutations are seen in a relatively small subset of NSCLC patients. They are common in patients

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with adenocarcinoma, never smokers, and patients of East Asian origin. Even though *KRAS* is the most common mutation found in NSCLC, we currently do not have an effective targeted therapy for this subset of NSCLC. More recently, immunotherapy has been demonstrated to be an attractive option for the treatment of NSCLC.[13-15] Despite the addition of new therapies, the median overall survival of patients in advanced stages of disease remains dismal. One-year survival rates are 40%-50% at best, and 2-year survival rates are consistently below 15%-20%. Although these percentages are starting to improve, only 3%-5% of advanced NSCLC patients survive 5 years after diagnosis. Personalized chemotherapy based on a patient's individual biologic and molecular profile is a promising approach to optimize efficacy with the available agents. This review focuses on recent advances in treatment approaches for advanced non–small-cell lung cancer, with a special emphasis on novel molecularly targeted agents and the emerging role of immunotherapy.

New agents for NSCLC with EGFR mutation

Erlotinib, a reversible oral tyrosine kinase inhibitor that targets the EGFR domain, was originally approved in unselected patients in the second- and third-line setting after progression on platinum-based therapy. The results of several large phase 3 randomized trials have established the place of the EGFR TKIs in the treatment algorithm,[10,16] and erlotinib is currently considered the standard of care for front-line treatment of patients whose tumors harbor an activating mutation in the EGFR domain. Despite this advance with response rates (RRs) in the 50%-70% range, the median progression-free survival (PFS) is about 9-10 months in most studies, with most patients with EGFR-mutant tumors sustaining disease progression by 1 year, mostly because of the development of resistance by multiple disparate pathways. Several new treatments that irreversibly target EGFR family members are under development for patients with NSCLC. One such agent is afatinib, an oral irreversible ErbB family inhibitor that targets EGFR and HER2, that has shown activity in an erlotinib- and gefitinib-resistant lung cancer model.[17] A randomized, double-blind, phase 2b/3 study (LUX-Lung 1) evaluated afatinib plus best supportive care (afatinib–BSC) compared with placebo–BSC in patients who had received 1 or 2 previous chemotherapy regimens and had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib.[18] Most of the patients (81%) had received 24 weeks or more of prior EGFR TKI, so that they represented a population that had previously derived benefit from this class of agents. The disease control rate at 8 weeks was 58% for the afatinib–BSC patients and 19% for the placebo–BSC patients ($P < .0001$). No complete responses to treatment were noted; 29 patients (7%) had a partial response in the afatinib group, as did 1 patient in the placebo group. Objective RRs (ORRs) confirmed by independent analysis were 7.4% and 0.5%, in the afatinib and placebo groups, respectively ($P < .01$). Median PFS was longer in the afatinib group (3.3 months) than it was in the placebo group (1.1 months; hazard ratio [HR], 0.38; $P < .0001$). However, this benefit failed to translate into a survival advantage. Median overall survival (OS) was 10.8 months in the afatinib group and 12 months in the placebo group (HR, 1.08; $P = .74$). The 2 most common adverse events associated with afatinib were diarrhea (87%; grade 3, 17%) and rash/acne (78%; grade 3, 14%).

LUX-Lung 2 was a subsequent multicenter phase 2 open-label single-arm study that evaluated the efficacy of afatinib in patients with advanced NSCLC with an EGFR-activating mutation.[19] Afatininb at a dose of 40 mg or 50 mg once daily was administered to 129 patients. The investigators reported an ORR of 67% (confirmed ORR of 60%), a disease control rate (DCR) of 86%, median PFS of 14 months, and median OS of 24 months. Comparable efficacy was observed in the first- and second-line settings. In patients with an exon 19 deletion or a L858R mutation, the ORRs were 69% and 59%, respectively; DCRs were 93% and 83%; and PFS was 13.7 months and 16.1 months. Again, the most common drug-related adverse events were diarrhea (95%; grade 3, 19%) and rash/acne (91%; grade 3, 21%).

The LUX-Lung 3 trial was reported at the 2012 annual meeting of the American Society of Clinical Oncology. In this phase 3 trial, the investigators compared 40 mg afatinib and intravenous pemetrexed plus cisplatin (pemetrexed–cisplatin; 500 mg/m^2 + 75 mg/m^2 q21 days up to 6 cycles) as first-line therapy in 345 NSCLC patients who harbored an EGFR-activating mutation. The ORR was significantly higher in patients who received afatinib than in those who received the pemetrexed–cisplatin combination (56% vs 23%, respectively; $P < .0001$). Median PFS was significantly better for afatinib than for pemetrexed–cisplatin (11.1 vs. 6.9 months; HR, 0.58; $P = .0004$). In 308 patients with common mutations (exon 19 deletion or L858R), the median PFS was 13.6 months. This is the largest trial to date to demonstrate the superiority of an EGFR TKI to a state-of-the-art platinum-based doublet and the first trial to use pemetrexed–cisplatin as a comparator. It was also the first trial to examine an irreversible HER1/HER2 TKI in this setting. It will likely lead to approval of this drug by the Food and Drug Administration.[20]

Besides afatinib, several other irreversible kinase inhibitors are currently under development, mostly in

early clinical phases. Drugs that act by irreversible competitive binding include neratinib (HKI-272) and dacomitinib (PF00299804). Despite promising preclinical data, neratinib has shown marginal activity in TKI-naïve patients and patients with prior benefit from TKIs, and was therefore discontinued from further development in NSCLC.[21]

Dacomitinib has been studied in the treatment of NSCLC. In a randomized phase 2 trial, 188 unselected patients with advanced NSCLC and who had been previously exposed to platinum-based therapy were randomly assigned to receive dacomitinib or erlotinib. The median PFS was 2.86 months for patients treated with dacomitinib and 1.91 months for those treated with erlotinib (HR, 0.66; $P = .012$). Median OS was 9.53 months for the dacomitinib patients and 7.44 months for the erlotinib patients (HR, 0.80 [95% CI, 0.56 to 1.13]; two-sided $P = .205$).[22] The overall improvement in PFS that was seen with dacomitinib was noted across most of the clinical and molecular subsets that were assessed. For the EGFR-mutant subset, median PFS was 7.44 months for both dacomitinib and erlotinib. The ORR for dacomitinib was 17.0%, with 1 complete response, and 5.3% for erlotinib ($P = .011$). This trial, the first to directly compare an irreversible pan-HER TKI with erlotinib, demonstrated improved PFS after treatment with dacomitinib. A phase 3 study is underway to confirm the findings of this study for second- and third-line therapy in patients with advanced NSCLC.[23]

MET, another tyrosine kinase, is a receptor of hepatocyte growth factor or scatter factor, which is known to be essential for normal development and cell survival. It plays an important role in signaling pathways, especially as a resistance mechanism after EGFR TKI blockade. Several MET inhibitors are currently in clinical development. Among others, onartuzumab and tivantinib are the most prominent members and the furthest along in clinical trials.

Onartuzumab is a monovalent (one-armed) monoclonal antibody that binds specifically to the extracellular domain of the MET receptor and therefore blocks ligand-mediated activation and further downstream signaling. In a phase 2 study, onartuzumab was evaluated in combination with erlotinib and compared with erlotinib alone in 128 erlotinib-naïve NSCLC patients whose disease had progressed on 1 or 2 lines of treatment. In patients with MET overexpression (MET diagnostic-positive), PFS (HR, 0.56; $P = .05$) and OS (HR, 0.55; $P = .11$) were increased in favor of the combined onartuzumab–erlotinib treatment. MET diagnostic-negative patients who received the onartuzumab–erlotinib combination had inferior outcomes compared with those who received erlotinib alone. No subgroup of patients other than those in the MET diagnostic-positive group derived any clinical benefit from onartuzumab.[24] On the basis of these phase 2 results, a global randomized phase 3 trial in MET diagnostic-positive patients is currently ongoing.[25]

Tivantinib is a small-molecule inhibitor of c-MET. In a phase 2 study, patients who were EGFR-TKI-naïve were randomized to receive erlotinib plus placebo or erlotinib plus tivantinib as second- or third-line treatment after failure of at least 1 line of platinum-containing chemotherapy.[26] The trial failed to meet its primary endpoint of PFS. However, several subgroups of patients showed some clinical benefit, including patients with nonsquamous histology, those with EGFR wild-type status, and those with *KRAS* mutations. A phase 3 study of tivantinib plus erlotinib compared with erlotinib alone has just completed accrual in patients with nonsquamous NSCLC as second- or third-line treatment, but preliminary reports failed to show a survival benefit.

New agents for NSCLC with *KRAS* mutation

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is a member of the rat sarcoma family and an important downstream signaling target in the survival pathways. Mutations in the *KRAS* gene are seen in about 15%-25% of adenocarcinomas, more commonly in smokers. A meta-analysis has shown that the mutations were more common in adenocarcinoma than in other histologic types (odds ratio [OR], 1.98; $P < .01$) and in current or former smokers than in never smokers (OR, 4.36; $P < .01$).[27] In metastatic colorectal carcinomas, *KRAS* status has significant predictive value because clinical benefit from cetuximab-based therapy is largely limited to patients whose tumors are *KRAS* wild-type. In contrast, *KRAS* mutation status does not seem to predict benefit with cetuximab in NSCLC patients.[28-30] NSCLC with *KRAS* mutation forms a distinct subset and remains a therapeutic challenge; we currently do not have any agents that have been approved for use in this cohort.

There has been interest in the development of inhibitors of MEK, a cell signaling pathway downstream from *KRAS*. Several studies are ongoing; the most noteworthy was presented at the 2012 ASCO meeting.[31] In that phase 2 study, 87 patients with *KRAS*-mutant advanced stage NSCLC who had received prior chemotherapy were randomized to receive docetaxel alone or in combination with oral selumetinib (a *BRAF* and MEK inhibitor). OS was longer for the selumetinib–docetaxel patients than it was for those who received docetaxel alone (9.4 vs 5.2 months, respectively) but it did not reach statistical significance (HR, 0.80 [80% CI, 0.56]; $P = .2069$). All secondary endpoints were significantly improved for the

selumetinib–docetaxel combination (RR: 37% vs 0%, $P <$ .0001, and PFS: 5.3 vs 2.1 months, $P = .0138$). The combination therapy was also more toxic, however. The most frequent toxicities (selumetinib–docetaxel vs dcoetaxel alone) included neutropenia (67.4% vs 54.8%), febrile neutropenia (15.9% vs 0%), dyspnea (2.3% vs 11.9%), and asthenia (9.1% vs 0%). Based on these promising early data, a phase 3 trial is being designed.

New agents for NSCLC with *EML4-ALK* translocation

The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is normally expressed only in the central nervous system, small intestine, and testis. The ALK gene translocation [t(2;5)(p23;q35)] was originally found in a subset of anaplastic large-cell lymphomas in 1994.[32,33] In 2007, Soda and colleagues[33] described the presence of this translocation between the C-terminal kinase domain of ALK and the N-terminal portion of the echinoderm microtubule-associated protein-like 4 (EML4) in patients with NSCLC. This translocation causes aberrant activation of downstream oncogenic signaling pathways such as MAP kinase, PI3-kinase, and signal transducers and activators of transcription, leading to cell proliferation, invasion, and inhibition of apoptosis. As with the EGFR mutation, the ALK gene translocation is more frequently seen in adenocarcinoma of the lung and in never smokers or light smokers. Patients with ALK gene translocation tend to be younger, with a higher distribution of men compared with those with EGFR mutations. Histologically, signet ring features are often present. Even though *EML4-ALK* translocation is found in a limited subset of patients (only 3%-6% of all cases of NSCLC), it constitutes 35,000-40,000 cases annually worldwide.

Crizotinib is currently approved for treatment of advanced NSCLC harboring an *EML4-ALK* translocation. This approval was granted based on response rates of 60% or higher observed in various early clinical studies.[9,34] A phase 3 trial (PROFILE 1007) that compared second-line crizotinib with either pemetrexed or docetaxel in NSCLC with ALK translocation was recently completed. Preliminary data were presented at the 2012 annual meeting of the European Society for Medical Oncology.[35] The response rate was considerably higher in the crizotinib arm, with a markedly improved PFS of 7.7 months compared with 3 months for the control arm. In addition, PROFILE 1014, a randomized open-label phase 3 study of a comparison of crizotinib and pemetrexed plus cisplatin or pemetrexed plus carboplatin in previously untreated metastatic nonsquamous cell carcinoma of the lung is currently enrolling patients.

LDK378 is a novel, potent, and selective small-molecule ALK inhibitor. Potent activity was demonstrated in enzymatic and cell based assays. Recently, the results from a first-in-human, phase 1 study of this agent were reported. The study was conducted in patients with tumors with ALK rearrangement, amplification, or mutation who received once daily oral LDK378 on a continuous 21-day schedule. A response rate of 81% was reported in 21 of the 26 NSCLC patients who were treated at $\geq$ 400 mg LDK378 and whose disease had progressed following treatment with crizotinib. There were also hints of antitumor activity against brain metastases at the 750-mg dose.[36] The most common adverse events included nausea, vomiting, and diarrhea.

New immunotherapy agents

Epithelial cancers express antigens, many of which are potentially recognizable by the immune system. Therefore, immunotherapy is a promising approach for the treatment of malignancies. Its application, however, has been limited because of the presence of several resistance mechanisms that include local immune suppression, induction of tolerance to self-antigens, and systemic dysfunction in T-cell signaling. In addition, tumors may exploit several distinct pathways to actively evade immune destruction, including endogenous "immune checkpoints" that normally terminate immune responses after antigen activation. These observations have resulted in intensive efforts to develop immunotherapeutic approaches for cancer that would include inhibitors of the immune checkpoint pathway, such as the anti-CTLA-4 antibody, ipilimumab.

Ipilimumab showed promising results in the treatment of NSCLC in a phase 2 study (CA184-041) that randomized previously untreated patients with advanced NSCLC to receive chemotherapy with carboplatin (area under the curve [AUC] 6) and paclitaxel (175 mg/m^2) alone or with concurrent ipilimumab (10 mg/kg from cycle 1 to cycle 4) or phased ipilimumab (10 mg/kg from cycle 3 to cycle 6). Overall, 204 patients were included in the study. Response was determined by using immune response (IR) criteria.[37] IR-PFS was improved in the ipilimumab arms compared with chemotherapy alone. There was no significant difference in OS between the arms ($P = .104$) but a trend seemed to favor the sequential combination of ipilimumab plus chemotherapy over placebo (9.7 months in the concurrent arm [HR, 0.98; $P = .47$] and 12.2 months in the phased arm [HR, 0.86; $P = .23$] vs 8.3 months in the placebo arm).[15] In 2011, Lynch and colleagues presented the results of a subgroup analysis of the CA184-041 phase 2 study that looked at efficacy by histologic subtypes. Median IR-PFS was 6.2

months for squamous NSCLC and 5.7 months for nonsquamous NSCLC for the phased ipilimumab arms, compared with 4.2 months for squamous NSCLC and 5.3 months for nonsquamous NSCLC for chemotherapy alone (HR, 0.55 and 0.82, respectively).[38] This subgroup hypothesis-generating analysis suggested that patients with squamous NSCLC might derive a greater benefit with the ipilimumab plus chemotherapy combination compared with patients with nonsquamous NSCLC, especially for the phased combination. A phase 3 trial is currently underway evaluating the incorporation of ipilimumab in the first-line treatment of patients with squamous NSCLC.

Programmed death 1 (PD-1) protein is a T-cell coinhibitory receptor, and one of its ligands, PD-L1, plays a pivotal role in the ability of tumor cells to evade the host's immune system.[13,14] The blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models. In a recent report by Topalian and colleagues,[14] 18% of patients with NSCLC had a response after treatment with a PD-1 inhibitor that was administered every other week for 2 months or more. Most of these responses were seen in patients who had received at least 3 lines of prior systemic therapy. These data are intriguing, especially because metastatic NSCLC is generally not considered to be responsive to immunotherapy. Responses were durable; 20 of 31 responses lasted 1 year or more in patients with 1 year or more of follow-up. Like ipilimumab, there may be preferential activity in squamous cell carcinoma. Based on these encouraging data, the drug is being developed further as a single agent. In addition, a broad ongoing phase 1 safety study of PD-1 inhibitor is being conducted in combination with gemcitabine and cisplatin, pemetrexed and cisplatin, carboplatin and paclitaxel, bevacizumab maintenance, and erlotinib in patients with advanced NSCLC. Several other PD-1 and PD-L1 inhibitors are also being studied in the phase 1 setting.

Conclusion

In this review, we have summarized recent advances and investigational strategies for individualized treatment for patients with advanced NSCLC. New insights into disease biology have changed the therapeutic landscape. Molecular characterization is now routinely used to guide therapeutic decisions, and oral small-molecule inhibitors have firmly secured their place in the treatment paradigm. Several promising new agents are being developed, and the availability of whole genome sequencing may uncover additional targets. The approval of immunotherapeutic agents for prostate cancer and melanoma has spurred a renewed interest in such therapies for NSCLC.

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