Exciting advances in understanding the biology of lung cancer have occurred over the last few years. These biological advances, coupled with the availability of newer agents and newer surgical techniques and radiation modalities, have led to the design of trials exploring the clinical value of newer treatment approaches. The rapidity of advances across several disciplines makes the task of keeping up with these advances formidable not only for the general oncologist, but also for specialists in lung cancer. This review aims to summarize the most important recent clinical advances that could impact the management of lung cancer.

**Prevention**

Selenium has long been thought to protect against development of cancer.[1] Secondary analysis of a double-blind placebo-controlled trial showed that selenium supplementation decreased the incidence of lung cancer.[2] In an attempt to confirm these findings, a large double-blind placebo-controlled trial was conducted. Selenium supplementation did not decrease the risk of secondary primary tumors either in the lung or overall, when administered to patients with resected stage I non–small-cell lung cancer (NSCLC).[3] The incidence of second primary tumors (lung/overall) was 1.366/3.66 per 100 person-years for placebo vs 1.91/4.11 per 100 person-years for selenium ($P = .15$).

**Screening**

Advances in imaging technology have renewed an interest in lung cancer screening. However, all published studies of low-dose helical computed tomography (CT) screening are nonrandomized observational cohorts of volunteers; these studies have not been able to determine whether lung cancer–specific mortality is decreased with CT screening.[4] The National Lung Screening Trial (NLST) was a prospective randomized study of high-risk individuals ($\geq$ 30 pack-years, ages 55 to 74 years) in which individuals were randomized to CT scans or chest x-rays annually for 3 years. The recently announced results of this study demonstrated that CT scan screening decreased lung cancer–specific mortality by approximately 20% and reduced all-cause mortality by about 7%, leading to early closure of the study. (For more information, please link to [http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease](http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease).)
Staging

The revised staging system (AJCC [American Joint Committee on Cancer] Cancer Staging Manual, 7th edition, 2010) for lung cancer has recently been implemented based on the recommendations of the International Association for the Study of Lung Cancer (Table 1).[5] The revised staging system was externally validated using a large prospective clinical trial database.[6] Using prospectively collected data from 1,037 patients enrolled in the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial, the investigators showed that use of the 7th edition of the AJCC lung cancer staging system produced results demonstrating monotonic progression, distinction between groups, and homogeneity within groups.[7]

Determining whether or not mediastinal lymph nodes are involved is critical in the management of patients with NSCLC, since that is the single most important determinant of the suitability of primary surgical resection. In the past few years newer nonsurgical approaches to sample mediastinal lymph nodes have been developed, including endobronchial ultrasound (EBUS)-guided transbronchial needle aspirate (TBNA) and transesophageal endoscopic ultrasound–guided fine needle aspiration (EUS-FNA), that appear to confer an advantage over conventional bronchoscopy with blind TBNA for sampling mediastinal lymph nodes.

Mediastinal staging with EUS-FNA and EBUS-TBNA in resectable NSCLC reduced futile thoracotomies.[8] Among the patients randomized to endoscopic ultrasound followed by surgical staging (ES-SS), nodal metastases were found in 50% of patients, compared with 35% of patients randomized to surgical staging (SS) alone (P = .019). Thoracotomy was futile in 7% of ES-SS patients versus 18% of SS patients (P = .009). The rate of complications during staging was similar in both arms. In another single-institution study, Tupayachi et al showed that EBUS-TBNA had better accuracy for nodal staging versus CT (94% vs 77%, P = .004) and PET (96% vs 73%, P = .019) scans.[9]

Local Therapies for Early-Stage NSCLC

Surgical resection is the gold-standard treatment for fit patients with early-stage NSCLC. Newer radiation techniques offer the promise of being equally effective but without the need for major surgery. These techniques are not considered standard of care, and surgery remains the treatment of choice.

Ramirez et al evaluated the quality of surgery in 746 operations performed by 21 community-based, board-certified cardiothoracic or general thoracic surgeons.[10] They found that seven surgeons failed to meet NCCN (National Comprehensive Cancer Network) criteria and five failed to meet RADIANT trial criteria of good-quality surgery in 100% of cases, affecting 168 and 134 patients, respectively. In another study, the same group compared operating surgeons’ claims of mediastinal lymph node dissection to the pathology report and to comments from an independent surgery reviewer who assessed the operative report in a blinded fashion.[11] They found a high proportion of suboptimal mediastinal lymph node excision (71% per independent surgical review; 92% based on pathology report).

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TABLE 2

| Highlights of Advances in Treatment of Lung Cancer, 2010 |

Stereotactic radiosurgery (SRS) (60 Gy in 3 fractions) appeared to be equivalent to standard radiation therapy in patients with medically inoperable early-stage NSCLC in a prospective multicenter study.[12] Among 70 patients evaluable for response, complete response was observed...
in 11 patients (16%), partial response in 37 (53%), stable disease in 20 (28%), and progression in 2 patients (3%). The probability of 2-year overall-survival for the entire group was 62% (95% CI = 42%-77%) and median recurrence-free survival (RFS) was 43 months. Volumetric image-guided (VIGRT) stereotactic lung radiotherapy (stereotactic body radiation therapy [SBRT]) produced excellent local control for stage I NSCLC.[13] This analysis of 434 patients treated uniformly by this technique showed 2-year rates of local recurrence, regional recurrence, and distant metastasis of 8%, 13%, and 26%, respectively. Overall survival (OS) and cause-specific survival rates at 2 years were 58% and 84%, respectively.

Although the baseline physical functioning and global quality of life (QOL) of patients referred for SBRT for stage I NSCLC were far poorer than those reported in the surgical literature, health-related QOL (HRQOL) scores did not decline during the first year after SBRT in an analysis of 382 consecutive SBRT patients from 70 Dutch centers.[14] This may be an advantage over surgery, since HRQOL is often compromised in the first 6 months after surgery, and generally fails to return to baseline values, particularly in elderly patients.

**Neoadjuvant chemotherapy**

Neoadjuvant chemotherapy for early-stage disease carries the theoretical advantages of earlier treatment of micrometastases, a decrease in tumor volume resulting in better local control with definitive local therapy, and better tolerance compared with adjuvant chemotherapy.

In an updated analysis of a previously published study, IFCT (Intergroupe Francophone de Cancrologie Thoracique) demonstrated that preoperative chemotherapy with two cycles of mitomycin, ifosfamide, and cisplatin, and two additional postoperative cycles for responding patients, did not significantly increase long-term survival.[15] There was a stable long-term 8% survival benefit in favor of neoadjuvant chemotherapy, however. The benefit for neoadjuvant chemotherapy seemed to be more pronounced in patients with stage I and II disease (23% vs 38% rates of 10-year survival), while the difference in stage IIIA patients was not significantly different. Patients who had a lobectomy but not a pneumonectomy seemed to benefit from chemotherapy. In patients with pathologically proven N2 or N3 disease, concurrent chemoradiation with carboplatin and paclitaxel, along with 50.4 Gy to the mediastinum and primary tumor and a boost of 10.8 Gy to gross disease, achieved a mediastinal nodal sterilization rate of 63%.[16] In this RTOG (Radiation Therapy Oncology Group) phase II study of 60 patients, median OS was 26.6 months and the 1-year OS rate was 77%. The survival rates exceed those of the SWOG (Southwest Oncology Group) phase II and III studies using neoadjuvant cisplatin-based chemotherapy combined with radiotherapy in patients with stage III disease.

**Adjuvant chemotherapy for early-stage NSCLC**

Adjuvant chemotherapy is now considered standard of care for patients with completely resected stage II and IIIA NSCLC.[17] In an analysis from the Ontario Cancer registry, Booth et al found that the proportion of cases receiving adjuvant chemotherapy increased from 7% in 2001–2003 to 31% in 2004–2006 ($P = .0001$).[18] During the study period there was a significant improvement in 4-year survival among all surgical cases, from 52.5% to 56.1% ($P = .007$). Younger age, less comorbidity, shorter length of surgical hospital stay, more extensive surgery, stage II/III disease, and region where surgery was performed were independently associated with administration of adjuvant chemotherapy.

Adjuvant gefitinib (Iressa) did not confer an advantage in disease-free survival (DFS) or OS when administered to an unselected group of patients with stages IB–IIIA NSCLC.[19] The absence of a KRAS mutation or increased EGFR gene copy number did not predict for benefit from gefitinib; however the small numbers of patients in these subgroups prior to premature study closure should temper the interpretation of this subgroup analysis. In a randomized phase III study of 158 patients, those treated with a combination of docetaxel (Taxotere) and cisplatin had similar DFS (70.1% vs 71.4%; $P = .88$) and OS rates (87.7% vs 81.8%; $P = .37$) at 20 months compared with patients who received cisplatin and vinorelbine (Navelbine).[20]

**Locally Advanced NSCLC**

The optimal treatment of patients with locally advanced NSCLC has not been clearly defined. Many treatment options are available but none yield a high probability of cure. Published trials of combined modality therapy included patients with stages I–III disease, which hampers subset analyses because of the lack of statistical power. Current data on treatment of these patients are
derived from trials with a number of significant limitations,[21] magnified by numerous preliminary reports with short follow-up, thereby obscuring the long-term benefits.

The prognostic value of the number of positive N2 lymph nodes in patients who had a curative resection was analyzed in a single-institution study from Seoul.[22] In this analysis of 250 patients, the investigators classified patients with pathologic N2 disease into three groups (1 vs 2-5 vs ≥ 6) and found that the number of positive N2 lymph nodes was an independent prognostic factor (hazard ratios [95% CI] of N2b and N2c vs N2a: 1.52 [1.07–2.17] and 2.32 [1.44–3.74] for DFS, and 1.77 [1.22–2.58] and 1.91 [1.17–3.14] for OS, respectively).

Approximately 15% of patients with unresectable stage III NSCLC could be cured with vinorelbine, cisplatin, and concurrent thoracic radiotherapy in a single arm, multi-institution phase II study of 111 patients.[23] The response rate in these 111 patients was 82.0% and the 3-, 5-, and 7-year progression-free survival (PFS) and OS rates were 20.2%, 15.2%, and 13.9%, and 43.4%, 25.2%, and 22.2%, respectively. The median PFS and OS were 13.4 and 30 months, respectively. Combinations of bortezomib (Velcade), carboplatin and paclitaxel,[24] cisplatin and S-1,[25] biweekly docetaxel and cisplatin following 3 cycles of induction therapy with the same agents,[26] pemetrexed (Alimta) and cisplatin,[27] and pemetrexed and carboplatin[28] had acceptable toxicity and encouraging outcomes when given along with thoracic radiation therapy in patients with locally advanced NSCLC.

**Metastatic NSCLC**

Treatment of metastatic NSCLC involves platinum-based doublet chemotherapy in fit patients. With the exception of bevacizumab (Avastin), addition of targeted therapy has not been shown to improve outcomes in this setting. Recent advances in our knowledge of tumor biology and development of markers predictive of response to small-molecule epidermal growth factor receptor (EGFR) inhibitors have kindled an interest in “personalized therapy” for these patients.

**Prognostic factors**

In the largest reported analysis of outcomes for patients with advanced lung adenocarcinoma with respect to KRAS and EGFR mutation status, Johnson et al showed that patients with KRAS mutations had the worst outcomes, with a median OS of 15 months, while those with EGFR mutations had the best outcomes, with a median OS of 37 months.[29] Patients with KRAS/EGFR wild type had intermediate outcomes, with a median OS of 23 months.

**First-line therapy in patients with EGFR mutations**

The final results of IPASS (the Iressa Pan-Asia Study) showed that gefitinib resulted in better PFS compared with carboplatin/paclitaxel in patients with activating EGFR mutations, but OS was no different between the two groups.[30] Two recent trials from Japan and one from China in patients with sensitive EGFR mutations confirmed these findings. The NEJ-002 trial (gefitinib vs carboplatin/paclitaxel),[31] the WJ3405 trial (gefitinib vs cisplatin/docetaxel),[32] and the OPTIMAL trial (erlotinib [Tarceva] vs carboplatin/gemcitabine [Gemzar])[33] showed that EGFR tyrosine kinase inhibitors (TKIs) improved PFS compared with chemotherapy, but there was no difference in OS between the EGFR TKI and chemotherapy groups. The QOL analysis of the NEJ-002 study, however, showed that patients treated with gefitinib maintained their QOL for a much longer period of time than the chemotherapy group.[34] Interestingly, in the OPTIMAL trial, patients with exon 19 deletions had a trend towards longer PFS than those with the L858R mutation (15.3 vs 12.5 months, respectively).[35]

In never-smokers and light smokers, the results of the CALGB 30406 trial showed that erlotinib alone was similar in efficacy but with a superior toxicity profile compared with erlotinib and chemotherapy (carboplatin and paclitaxel) in treatment-naive Caucasian nonsmokers with advanced NSCLC.[36] Patients with activating EGFR mutations had significantly better response rates, PFS, and OS compared with EGFR wild type patients. Addition of chemotherapy to treatment of patients with activating EGFR mutations did not appear to confer any additional advantage compared with erlotinib alone.

In an interesting post-hoc analysis, Inoue et al compared the efficacy of a lower dose of gefitinib (250 mg every other day; patients who decreased their dose because of toxicity) with the standard dose (250-mg daily) in patients with activating EGFR mutations.[37] They found that both groups had similar PFS and OS. This raises an interesting question: is a lower dose of gefitinib sufficient in all patients, or do patients who do not develop adverse events need the standard dose in order to attain
a clinical benefit? In a small trial addressing this question, a lower dose of erlotinib (25-mg daily) produced impressive responsive rates (5/7) and median OS (17 months) in patients with activating EGFR mutations.[38] These results, if confirmed in larger studies, could have major cost implications in the treatment of these patients.

First-line gefitinib produced excellent results in treatment-naive older patients (≥ 75 years) who harbored EGFR mutations.[39] In this trial, the overall response rate was 74% and the disease control rate was 90%, with a median PFS of 13.6 months.

Other targeted therapy

The phase II Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial adaptively randomized 255 patients with metastatic NSCLC to one of four treatment groups—erlotinib, erlotinib + bexarotene (Targretin), sorafenib (Nexavar), or vandetanib (Zactima)—based on eligibility criteria and biomarker results taken from fresh core needle biopsies at study entry.[40] The disease control rate at 8 weeks for the overall population was 46%. Median OS and PFS were 9 months and 1.9 months, respectively, and the 1-year survival rate was 39%. Disease control was superior in EGFR mutation–positive patients who received erlotinib (P = .04) and in EGFR mutation–negative patients (P = .012) or high polysomy patients who received sorafenib (P = .048). Similarly, patients with cyclin D1 immunohistochemistry (IHC) positivity (P = .011) and EGFR amplification by FISH (P = .006) had better disease control with erlotinib and bexarotene, whereas those with IHC-positive VEGFR2 (vascular endothelial growth factor receptor 2) did better with vandetanib (P = .05).

First-line therapy in unselected patients

Cytotoxic chemotherapy combinations. A phase III study of the combination of albumin-bound paclitaxel (nab-paclitaxel [Abraxane]) and carboplatin showed improvement in the response rate, which was the primary endpoint of the study, compared with standard carboplatin and paclitaxel (33% vs 25%, P = .005).[41] There was also significantly less hematological and nonhematological toxicity of grade 3 or greater in patients receiving nab-paclitaxel and carboplatin. However survival data are pending and a substitution of nab-paclitaxel for paclitaxel may be premature at this time. Patients with squamous cell carcinoma seemed to derive the most benefit from nab-paclitaxel, with a response rate of 41%, compared with 25% for patients treated with standard paclitaxel (P < .001). This may be attributable to aberrant caveolin1 overexpression in squamous cell carcinomas. Addition of targeted agent(s) to cytotoxic chemotherapy. In a number of clinical trials, addition of targeted agents to standard chemotherapy in unselected patients did not improve efficacy. In a randomized phase III trial, addition of figitumumab (CP-751871; an IGF-1R [insulin-like growth factor 1 receptor] antibody) to carboplatin and paclitaxel did not improve overall survival in patients with squamous cell carcinoma.[42] Adverse events were more common in the experimental arm and included anorexia, nausea, vomiting, diarrhea, hyperglycemia, asthenia, weight loss through dehydration, infections, and cardiovascular events. More deaths were noted in the experimental arm (8 vs 0). Addition of either NOV-002 (glutathione disulfide)[43] or mapatumumab (a fully human agonistic monoclonal antibody that targets TRAIL-R1 [tumor necrosis factor–related apoptosis-inducing ligand receptor 1]) to carboplatin and paclitaxel did not improve outcomes in treatment-naive advanced NSCLC patients. Similarly addition of dulanermin (recombinant human Apo2L/TRAIL, a proapoptotic agonist of death receptors 4 and 5)[45] or PRO95780 (a fully human, affinity-matured IgG1 monoclonal antibody that induces DRS-mediated apoptosis)[46] to a combination of carboplatin/paclitaxel/bevacizumab did not offer any survival advantage. Cediranib (also known as AZD2171; a VEGF receptor tyrosine kinase inhibitor) did not improve overall survival when added to gemcitabine (Gemzar)/carboplatin.[47] Addition of sorafenib to cisplatin/gemcitabine improved PFS and time to progression, but not OS.[48] Based on these results and the findings of previous similar studies, it is unlikely that addition of a targeted agent to a platinum-based doublet in unselected patients will lead to significant improvement in outcomes from advanced NSCLC. In a randomized phase II study of 46 patients, however, addition of the tumor vascular disrupting agent fosbretabulin tromethamine (CA4P; Zybrestat) to carboplatin/paclitaxel/bevacizumab resulted in an improvement in OS.[49] Interestingly, however, there was no improvement in the primary endpoint of PFS. Similarly, ipilimumab showed a slight improvement in PFS when combined with carboplatin/paclitaxel either concurrently or in a phased schedule, compared with carboplatin/paclitaxel alone (5.52 and 5.68 months vs 4.63 months, respectively).[50] Sequencing of therapy. A phase III trial in unselected patients comparing a strategy of using erlotinib followed by chemotherapy (cisplatin + gemcitabine) with the same combination in the reverse order...
showed that first-line erlotinib followed by chemotherapy was inferior to the chemotherapy-first strategy (HR of death = 1.40, \( P = .002 \)).[51] In an unselected population of treatment-naive patients who could not undergo chemotherapy because of poor performance status, erlotinib did not improve overall survival compared with best supportive care.[52] Females had improved PFS and OS with erlotinib, while patients with adenocarcinoma had an improved PFS. Special populations. Doublet therapy with monthly carboplatin and weekly paclitaxel was superior to single-agent gemcitabine or vinorelbine in elderly patients (70–89 years) with advanced NSCLC.[53] Patients who received the doublet therapy had superior OS (10.4 vs 6.2 months, \( P = .0001 \)) and PFS (6.3 vs 3.2 months, \( P < .0001 \)). Although grade 3–4 hematological toxicity was higher in the doublet arm (54.1% vs 17.9%), there was no increase in the early-death rate. These data provide confirmation of the previous subset analyses of phase III trials that suggested elderly people were able to receive, and achieved similar benefit from, doublet chemotherapy, as compared to younger patients. However, a meta-analysis of eight trials demonstrated that although doublets improved response rates, OS was not affected.[54] Myelosuppression was more frequent with doublets.

**Maintenance therapy**

Maintenance chemotherapy with either erlotinib or gemcitabine improved PFS after initial therapy with cisplatin-gemcitabine in patients with advanced NSCLC. Similar benefit for gemcitabine was seen after initial therapy with gemcitabine-carboplatin.[56] In a similarly designed trial, maintenance therapy with gefitinib improved PFS in patients who did not progress after first-line therapy.[57] As of this writing, however, none of these studies has shown any improvement in OS.

**Relapsed NSCLC**

Approximately 2%–7% of patients with NSCLC have EML4-ALK (anaplastic lymphoma kinase) fusion oncogenes.[58] ALK-positive adenocarcinomas are characterized by younger patient age at onset, absence of mutations in EGFR and KRAS, and prevalence in nonsmokers or light smokers.[59] The oral ALK inhibitor crizotinib (PF-02341066) demonstrated excellent disease control rates in heavily pretreated patients who harbored an ALK fusion oncogene.[60] Of the 82 patients with ALK rearrangement who were administered crizotinib at 250-mg twice daily, 1 patient had a complete response and 46 had a partial response, for an overall response rate of 57%.\[61\] An additional 22 patients had stable disease, for a disease control rate of 87%. The drug was well tolerated, with gastrointestinal toxicities being most common. MET gene expression is associated with worse prognosis in NSCLC, and MET activation has been implicated in resistance to EGFR inhibition in NSCLC with EGFR mutations. Addition of METMab (a monovalent MET receptor antibody) to erlotinib resulted in an improvement in PFS (HR = 0.56; 95% CI = 0.31–1.02; \( P = .05 \)) compared with erlotinib alone in MET-positive (expression by immunohistochemistry) patients. In contrast, MET-negative patients treated with the combination had a worse PFS (HR = 2.01; 95% CI = 1.04–3.91; \( P = .04 \)) and OS (HR = 3.26; 95% CI = 1.20–8.80; \( P = .01 \)) compared with erlotinib.[62]

**TABLE 3**

Take-Home Messages

Dual EGFR-MET inhibition using a combination of the c-MET inhibitor ARQ197 and erlotinib prolonged PFS (16.1 vs 9.7 weeks) in EGFR TKI–naive patients.[63] This study randomized 167 patients with inoperable locally advanced/metastatic disease, who had received one or more prior chemotherapy regimens but no prior EGFR TKI, to either erlotinib alone or erlotinib and ARQ197. Overall survival was not different between the two groups, however, (8.4 vs 6.8 months). The major benefit was seen in patients with nonsquamous histology, EGFR wild type status, and mutant KRAS status. The combination was well tolerated, with similar adverse-effect profiles between the two groups.[64] Afatinib (BIBW 2992), an irreversible EGFR and HER2 TKI, improved PFS (3.3 vs 1.1 months; HR =
0.38, \( P < .0001 \) compared with placebo in patients with advanced NSCLC in whom chemotherapy and EGFR TKI therapy had failed.[65] There was no improvement in OS, however (10.78 vs 11.96 months; HR = 1.08; 95% CI = 0.86–1.35). Similarly, addition of sunitinib (Sutent) to erlotinib improved PFS (15.5 vs 8.7 weeks, \( P = .0023 \)), but not OS (9 vs 8.5 months, \( P = .14 \)) in a randomized phase III trial of unselected patients with recurrent NSCLC.[66]

**Palliative care**

In an interesting single-institution study from the Dana-Farber Cancer Institute, Temel and colleagues evaluated the role of early palliative care on patient-reported and end-of-life care outcomes in newly diagnosed patients with advanced NSCLC.[67,68] They randomized 151 patients to either early palliative care with concurrent oncology care or standard oncology care alone and assessed QOL and mood. They found that patients assigned to early palliative care experienced better QOL and had lower rates of depression compared with those who received standard oncology care. Not surprisingly, fewer early palliative care patients received aggressive care at the end of life, but despite this they had longer survival compared with standard-oncology-care patients (11.6 vs 8.0 months, \( P = .02 \)). While this emphasizes the utility of the early involvement of a palliative team in patients with advanced NSCLC, the exact nature of the palliative care intervention in this study is unclear.

**Small Cell Lung Cancer**

While the incidence of small cell lung cancer (SCLC) is decreasing in the United States, SCLC remains a frustrating disease to treat.[69] Despite the exquisite sensitivity of SCLC to chemotherapy, with high response rates, survival is dismal. There have been no major advances in the chemotherapy of SCLC since the development of platinum and etoposide in the mid 1990s.[70]

**Prognostic factors**

Baseline circulating tumor cells (CTC) and early decrease in CTCs during first-line chemotherapy have been found to be independent predictors of OS in SCLC.[71] In an analysis of NCCTG (North Central Cancer Treatment Group) trials, PFS was strongly associated with OS and showed promise as a potential surrogate for OS.[72] This needs to be validated further, however. In an interesting study, Gomez et al evaluated the prognostic efficacy of the maximum standardized uptake value (\( \text{SUV}_{\text{max}} \)) in limited-stage SCLC. Unexpectedly, the investigators found that a higher pretreatment \( \text{SUV}_{\text{max}} \) at the primary site (> 14) predicted for a better OS.[73]

**First-line therapy**
# Therapeutic Agents Mentioned in This Article

- Afatinib (BIBW 2992)
- Amrubicin (INN)
- ARQ197
- Bevacizumab (Avastin)
- Bexarotene (Targretin)
- Bortezomib (Velcade)
- Carboplatin
- Cediranib (AZD2171)
- Cisplatin
- Crizotinib (PF-02341066)
- Docetaxel (Taxotere)
- Dulanermin
- Erlotinib (Tarceva)
- Etoposide
- Figitumumab (CP-751871)
- Fosbretabulin tromethamine (CA4P; Zybrestat)
- Gefitinib (Iressa)
- Gemcitabine (Gemzar)
- Ifosfamide
- Ipilimumab (MDX-010)
- Mapatumumab
- METMAb
- Mitomycin
- Nab-paclitaxel (Abraxane)
- NOV-002 (glutathione disulfide)
- Paclitaxel
- Pemetrexed (Alimta)
- Picoplatin
- PRO95780
- Selenium
- Sorafenib (Nexavar)
- Sunitinib (Sutent)
- Vandetanib (Zactima)
- Vinorelbine (Navelbine)

*Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.*
Cediranib, an oral inhibitor of VEGFR, was tested in combination with etoposide and cisplatin as first-line therapy for extensive-stage/metastatic lung cancer in a phase I trial.[74] The recommended dose of cediranib was determined to be 20 mg when used with this combination. The expansion cohort of 18 patients who received this combination showed a response rate of 67% and a median PFS of 8 months. Further study of this agent in SCLC is planned. The European Organisation for Research and Treatment of Cancer (EORTC) conducted a phase II study, EORTC 08062, comparing amrubicin (INN) with amrubicin/cisplatin and cisplatin/etoposide in previously untreated patients with extensive-stage SCLC (n = 99).[75] The study aimed to achieve a response of 80%. The response rate was highest for the combination of amrubicin with cisplatin (77%), compared with 61% for amrubicin alone and 63% for cisplatin/etoposide. Grade 3–4 neutropenia was seen in approximately 70% of patients in each arm, and cardiac toxicity did not differ among the three arms.

Relapsed/refractory disease
Picoplatin did not improve OS in the placebo-controlled phase III SPEAR trial in patients with relapsed/refractory SCLC.[76] However, patients in the worst prognostic group (refractory patients or those who relapsed within 45 days) had a significant improvement in survival with picoplatin. Picoplatin was well-tolerated with manageable hematological toxicity, and it could serve as an option for these patients.

Summary
Screening for lung cancer may soon become a reality, based on results of the NLST trial, although the specific details still need to be worked out. Successful completion of the BATTLE trial suggests that biomarker-driven personalized therapy may no longer be a distant dream. The ALK inhibitor crizotinib appears promising in individuals who carry the fusion oncogene. Platinum-based doublet therapy is superior to single-agent therapy in fit elderly treatment-naive patients with advanced NSCLC. Trials evaluating the addition of a targeted agent to platinum-based doublet therapy in unselected patients probably should not be recommended. Maintenance-therapy trials appear to show benefit in PFS, but the studies presented in 2010 have not yet shown a survival advantage. The MET inhibitor ARQ197 when combined with erlotinib seemed to overcome some of the resistance that develops with EGFR TKIs, especially in patients with KRAS mutations. Amrubicin is an exciting new agent in development for SCLC, and if the results of the study presented at the 2010 annual meeting of the American Society of Clinical Oncology (ASCO) are confirmed in phase III trials, it may replace etoposide in the first-line therapy of SCLC. Table 2 and Table 3 highlight advances in the treatment of lung cancer in 2010 and summarize the key take-home messages of this article, respectively.

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