Evolving Treatment Paradigms in Non-Small Cell Lung Cancer

Kathryn F. Mileham, MD
Staff Oncologist

Heather D. Brooks, MD
Staff Oncologist

Edward S. Kim, MD
Chair, Solid Tumor Oncology and Investigational Therapeutics
Donald S. Kim Distinguished Chair for Cancer Research
Levine Cancer Institute
Carolinas HealthCare System
Charlotte, North Carolina

Lung cancer remains the leading cause of cancer-related death in the United States, accounting for 30% and 26% of all cancer deaths in men and women, respectively, and exceeding the predicted death rates for breast and colorectal cancers combined. The overall 5-year relative survival is a staggering 15.6%. Non-small cell lung cancer (NSCLC) is the most common histologic subtype, accounting for more than 85% of all lung cancer cases.

The evolution of conventional lung cancer treatment and personalized therapy continues. Screening studies finally have established a role for early detection. However, very few patients present with early-stage disease. With the majority of patients presenting with advanced disease, better evaluation and treatment decisions using histology and molecular therapies are desperately needed. Current treatment plans have resulted in an increased median overall survival (OS) from 2 months to more than 12 months. Still, the need for improved outcomes with reduced treatment toxicity persists in a time when personalized therapy is evolving into a standard.

Conventional Chemotherapy
Since 1997, the American Society of Clinical Oncology (ASCO) has recommended the use of cisplatin-based chemotherapy for patients with advanced NSCLC and an adequate performance status. This was based on a meta-analysis of 52 clinical trials with more than 9,000 patients. Cisplatin-based chemotherapy showed a 27% reduction in the risk for death at 1 year.
Subsequent clinical trials focused on increasing efficacy using newer agents and decreasing toxicity by substituting carboplatin for cisplatin. Although the role of platinum-based doublet regimens as a mainstay has been well established, this paradigm is changing dynamically as newer agents are developed and molecular targets are identified.

Two variables must be considered in the choice of a platinum-based doublet: the platinum agent used (cisplatin or carboplatin) and the agent combined with the platinum. Chemotherapeutics approved for use in this setting include paclitaxel, gemcitabine, vinorelbine, docetaxel, and pemetrexed (Alimta, Lilly). Results from a large trial comparing cisplatin-paclitaxel with 3 other regimens (carboplatin-paclitaxel, cisplatin-docetaxel, and cisplatin-gemcitabine) found no significant difference in OS (median 7.9 months) among the 4 regimens. Of note, there were less serious toxicities reported in patients treated with carboplatin-paclitaxel.

More recently, nanoparticle albumin-bound paclitaxel (Abraxane, Celgene) has been shown to be effective as well as tolerable in NSCLC. Preliminary results from a Phase III trial comparing carboplatin-nab-paclitaxel with carboplatin-paclitaxel showed higher response rates (RR) in the nab-paclitaxel arm. When compared with paclitaxel, nab-paclitaxel was associated with reduced incidence of grade 3 or higher nonhematologic toxicities, specifically neuropathy, myalgia, and arthralgia (3% vs 10%), despite the higher paclitaxel dose delivered.

A Phase III study of 1,725 patients with advanced NSCLC compared front-line treatment with cisplatin-pemetrexed and cisplatin-gemcitabine. This trial showed similar overall efficacy between the regimens, and, importantly, demonstrated a benefit difference based on histology. When examined by histology, patients with nonsquamous NSCLC treated with cisplatin-pemetrexed sustained a statistically significant survival advantage over those treated with cisplatin-gemcitabine (median OS, 11.8 and 10.4 months, respectively), including significantly better survival in those with adenocarcinoma (12.6 vs 10.9 months; hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.71-0.99; P=0.03). In contrast, patients with squamous cell histology had a shorter median survival when treated with cisplatin-pemetrexed. Identification of specific NSCLC histology has become important in the overall evaluation of patients with lung cancer.

**Changing Paradigms**

The increasing influence of histologic subtype in the choice of agents, the identification of new molecular targets, and the availability of targeted agents is changing the strategy for front-line treatment selection in advanced NSCLC. Molecular testing of lung tumors (eg, epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK]) to facilitate treatment selection is readily available and can be considered a standard of care, as it is for other solid tumors, including breast and colorectal. This truly allows clinicians to personalize therapy for individual patients.

Bevacizumab (Avastin, Genentech), a humanized monoclonal antibody (mAb) that inhibits vascular endothelial growth factor (VEGF)-A, not only was the first targeted agent proven to extend survival when added to conventional chemotherapy (carboplatin-paclitaxel) in the front-line treatment of advanced NSCLC, but in Eastern Cooperative Oncology Group (ECOG) 4599, it also was the first treatment regimen to demonstrate a median OS greater than 1 year in any Phase III trial of metastatic NSCLC (12.3 vs 10.3 months; HR, 0.79; CI, 0.67-0.92; P=0.003). Prudent patient selection is essential with the use of bevacizumab because increased toxicity and patient deaths have been reported.

Somatic mutations in the tyrosine kinase domain of *epidermal growth factor receptor* (*EGFR*) gene have been reported in lung cancers (predominantly adenocarcinomas). *EGFR* mutations are associated with sensitivity to EGFR-targeted therapies.

Erlotinib (Tarceva, Genentech), a reversible tyrosine kinase inhibitor (TKI), acting directly at EGFR, is FDA-approved for the treatment of NSCLC after platinum-failure. More recently, 2 notable trials investigated the use of erlotinib in the front-line management of advanced NSCLC patients with *EGFR* mutations. EURTAC (European Erlotinib Versus Chemotherapy) is a prospective, randomized Phase III trial that investigated whether front-line treatment with erlotinib is superior to platinum-based chemotherapy in patients with *EGFR* mutations. At the time of interim analysis, progression-free survival (PFS) in the erlotinib arm was superior to that in the chemotherapy arm (9.4 vs 5.2 months; HR, 0.42; P<0.0001). Median OS was not significantly different (22.9 vs 18.8 months; HR, 0.80; P=0.42). The Phase III OPTIMAL (Erlotinib Versus Gemcitabine/Carboplatin in Chemo-naive State IIIb/IV Non-Small Cell Lung Cancer Patients With Epidermal Growth Factor Receptor Exon 19 or 21 Mutation [ML20981]) trial is evaluating the efficacy of front-line erlotinib versus gemcitabine-carboplatin in 165 patients with advanced NSCLC who harbor EGFR-activating mutations. Treatment with erlotinib improved median PFS (primary end point) when compared with chemotherapy (13.1 vs 4.6 months). Common toxicities associated with erlotinib treatment are rash and diarrhea.

Gefitinib (Iressa, AstraZeneca), an inhibitor of the EGFR tyrosine kinase domain, was evaluated in several trials. INTEREST (Iressa Non-small cell lung cancer Trial Evaluating Response and Survival Against Taxotere) compared gefitinib and docetaxel in patients with advanced NSCLC who had received previous platinum-based chemotherapy. Results for all 1,433 patients confirmed noninferiority of gefitinib compared with docetaxel for OS (7.6 vs 8 months; HR, 1.020; CI, 0.905-1.150). Patients with *EGFR* mutations...
treated with gefitinib had longer PFS compared with those treated with docetaxel. In IPASS (Iressa Pan Asia Study), patients with advanced NSCLC who never smoked or formerly were light smokers received either carboplatin-paclitaxel or gefitinib in the front-line setting. Although median PFS was similar in both arms (5.7 vs 5.8 months), patients treated with gefitinib had a significantly higher PFS at 12 months (24.9% vs 6.7%; HR, 0.74; CI, 0.65-0.85; P<0.0001). Other strategies targeting the EGFR pathway have been reported. Cetuximab (Erbilux, Bristol-Myers Squibb) is a chimeric mAb that inhibits EGFR. The FLEX (First-Line Erbitux in Lung Cancer) trial evaluated front-line cisplatin-vinorelbine with or without cetuximab in patients with EGFR-expressing advanced NSCLC. Cetuximab was then given as continuation maintenance until progressive disease or intolerable side effects developed. The addition of cetuximab improved OS (11.3 vs 10.1 months; HR, 0.871; CI, 0.762-0.996; P=0.044). Interestingly, first-cycle rash (commonly associated with EGFR inhibitors) was associated with improved survival.

The combination of targeted agents against VEGF and EGFR with platinum-based chemotherapy may result in improved survival benefit. SWOG (Southwestern Oncology Group) 0536 was a Phase II study that combined carboplatin, paclitaxel, cetuximab, and bevacizumab for up to 6 cycles followed by weekly maintenance bevacizumab until disease progression in patients with advanced NSCLC. The combination was found to have an adequate safety profile and has led to an ongoing Phase III trial (SWOG 0819) investigating carboplatin-paclitaxel or carboplatin-paclitaxel-bevacizumab with or without concurrent cetuximab in advanced NSCLC.

The EML (echinoderm microtubule-associated protein-like) 4-ALK fusion oncogene is a new biomarker that has been identified in a small subset of patients with NSCLC (approximately 4%). Patients with ALK rearrangements have similar characteristics as those with EGFR mutations (adenocarcinoma, nonsmokers, or light smokers); however they often are young and male. Because these patients are resistant to EGFR tyrosine kinase inhibitors (TKIs), identifying patients with ALK rearrangements and customizing therapy to this target has been a focus of research efforts. Fluorescence in situ hybridization (FISH) rather than immunohistochemistry is the diagnostic test of choice to uncover ALK rearrangements.

Crizotinib (Xalkori, Pfizer) is an ALK and MET TKI that recently was approved by the FDA for patients with ALK-positive advanced NSCLC. Of the 82 patients in the seminal Phase I study, 46 had a confirmed partial response and 1 had a confirmed complete response, for an overall RR of 57% (primary end point). At the mean treatment duration of 6.4 months, 33% had stable disease with minimal toxicities. Evaluation of an expansion cohort suggests a survival advantage in ALK-positive patients treated with crizotinib versus crizotinib-naive ALK-positive patients. Although crizotinib is a new standard of care for patients with ALK-positive advanced NSCLC, 3 ongoing clinical trials (PROFILE 1007, 1005, and 1014) continue to evaluate the role of this targeted therapy. Chromosomal rearrangements involving the ROS1 receptor, a tyrosine kinase, have recently been described in a subset of NSCLC and appear to be therapeutic targets for ALK therapies (e.g., crizotinib). The incidence of ROS1 abnormalities has been reported to be between 1% and 2% and seems to be independent of ALK status.

**Maintenance Therapy**

Data from multiple trials consistently have shown improvements in survival with maintenance therapy (Table). Strategies include either continuation of one or more of the initial agents (continuation maintenance), the introduction of an additional agent (switch maintenance), or a combination. Pemetrexed and erlotinib are FDA-approved as maintenance therapy.

Several trials adding targeted agents to chemotherapy have included a continuation maintenance strategy. In the previously mentioned ECOG 4599 trial, patients receiving bevacizumab with carboplatin-paclitaxel in the experimental arm continued bevacizumab every 3 weeks until progression of disease or intolerable side effects. The FLEX trial also examined the role of cetuximab maintenance after front-line treatment. Patients with EGFR-expressing advanced NSCLC who received cetuximab with chemotherapy in the experimental arm continued cetuximab after chemotherapy until progression or intolerable side effects.

In July 2009, the FDA approved pemetrexed for maintenance treatment of patients with advanced NSCLC with nonsquamous histology who had not progressed after initial chemotherapy. This approval was based on data from a Phase III trial of 664 patients with advanced NSCLC who did not progress on an initial platinum-based doublet (non-pemetrexed based) and then received maintenance pemetrexed or placebo. Compared with patients receiving placebo, those who received maintenance pemetrexed had both improved PFS (4.3 vs 2.6 months; HR, 0.50; CI, 0.42-0.61; P<0.0001) and OS (13.4 vs 10.6 months; HR, 0.79; CI, 0.65-0.95; P=0.012). This provides an example of the efficacy of a switch maintenance strategy.

Preliminary data from the PARAMOUNT trial presented at ASCO 2011 support the use of pemetrexed in a continuation maintenance treatment strategy. This Phase III international trial examined 939 patients with advanced nonsquamous NSCLC. Those who did not progress during cisplatin-pemetrexed induction therapy were randomized to receive either maintenance pemetrexed every 3 weeks plus best supportive care (BSC) or placebo plus BSC until evidence of progression. Patients receiving maintenance pemetrexed sustained an improved PFS (HR 0.64; CI, 0.51-0.81; P=0.00025), with a 36% reduction in risk for progression. The favorable tolerability profile and ease of administration make...
pemetrexed an appealing option for maintenance therapy in advanced NSCLC.

The FDA approved erlotinib in April 2010 for maintenance treatment of patients with advanced NSCLC with nonprogressive disease after front-line platinum-based chemotherapy. This approval was based on the large Phase III SATURN (Sequential Tarceva in Unresectable NSCLC) trial.\(^\text{28}\) This trial was one of the first to evaluate maintenance therapy versus placebo in a prospective fashion. Patients with advanced NSCLC (N=1,949) received erlotinib or placebo after platinum-based doublet chemotherapy. Maintenance erlotinib was associated with a statistically significant improvement in both PFS (HR, 0.71; CI, 0.62-0.82; P<0.0001) and OS (12 vs 11 months). In an exploratory analysis, patients with EGFR mutations sustained an even greater benefit from maintenance erlotinib.

In the Phase III IFCT-GFPC 0502 study, treatment-naive patients with advanced NSCLC were treated with 4 cycles of cisplatin-gemcitabine.\(^\text{25}\) Those who did not progress were randomized to observation, continuation maintenance gemcitabine, or switch-maintenance erlotinib. PFS was significantly prolonged in patients receiving either maintenance with gemcitabine or erlotinib versus observation alone (HR, 0.51; CI, 0.39-0.66 and HR, 0.83; CI, 0.73-0.94, respectively).

Additional strategies for maintenance include a combination of continuation and switch, in which one of the agents from initial therapy is continued, and an additional agent that was not used previously is added. This concept was tested in the ATLAS trial, a Phase III evaluation of bevacizumab with or without erlotinib after completion of chemotherapy with bevacizumab for front-line treatment of advanced NSCLC.\(^\text{30}\) Patients who were treated with combination maintenance showed a significant improvement in PFS (4.8 vs 3.7 months; HR, 0.722; CI, 0.592-0.881; P=0.0012) over those treated only with continuation maintenance.

### Table. Selected Trials of Maintenance Therapy in Advanced NSCLC

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Treatment Arms</th>
<th>N</th>
<th>PFS, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias et al(^\text{29})</td>
<td>GC, then immediate docetaxel GC, then delayed docetaxel</td>
<td>309</td>
<td>5.7 (P=0.001)</td>
<td>12.3 (P=0.0853)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.7</td>
<td>9.7</td>
</tr>
<tr>
<td>Capuzzo et al(^\text{28})(SATURN)</td>
<td>CT, then E CT, then P</td>
<td>438/451</td>
<td>PFS was significantly prolonged with E versus P in all patients (HR, 0.71; 95% CI, 0.62-0.82; P&lt;0.0001)</td>
<td>12/11</td>
</tr>
<tr>
<td>Ciuleanu et al(^\text{26})</td>
<td>Pemetrexed + BSC P + BSC</td>
<td>441/222</td>
<td>Overall/NSQ/SQ 4.3/4.5/2.8 2.6/2.6/2.6</td>
<td>Overall/NSQ/SQ 13.4/15.5/9.9 10.6/10.3/10.8</td>
</tr>
<tr>
<td>Miller et al(^\text{30})(ATLAS)</td>
<td>CT + B, then B + P CT + B, then B + E</td>
<td>768</td>
<td>3.7 (P=0.0012)</td>
<td>4.8</td>
</tr>
<tr>
<td>Paz-Ares et al(^\text{27})(PARAMOUNT)</td>
<td>Cisplatin + pemetrexed, then pemetrexed + BSC Cisplatin + pemetrexed, then P + BSC</td>
<td>359/180</td>
<td>3.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Barlesi et al(^\text{31})(AVAPERL)</td>
<td>Cisplatin + B + pemetrexed, then B + pemetrexed Cisplatin + B + pemetrexed, then B</td>
<td>128/125</td>
<td>10.2 (P=0.001)</td>
<td>6.6</td>
</tr>
<tr>
<td>Patel et al(^\text{32})(PointBreak)</td>
<td>Carboplatin + B + pemetrexed, then B + pemetrexed Carboplatin + B + paclitaxel, then B</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(\text{B, bevacizumab; BSC, best supportive care; CI, confidence interval; CT, first-line platinum-based chemotherapy; E, erlotinib; GC, gemcitabine-carboplatin; HR, hazard ratio; NA, not available; NSQ, nonsquamous; OS, overall survival; P, placebo; PFS, progression-free survival; SQ, squamous}\)
Final efficacy outcomes of AVAPERL were presented at the 16th ECCO (European CanCer Organisation)—36th ESMO (European Society for Medical Oncology) Multidisciplinary Cancer Congress in September 2011. This ongoing Phase III study is evaluating continuation maintenance with bevacizumab with or without pemetrexed following 4 cycles of front-line cisplatin-bevacizumab-pemetrexed in advanced nonsquamous NSCLC. Those who had at least stable disease after front-line treatment were randomized to either bevacizumab alone or bevacizumab plus pemetrexed. The median PFS (primary end point) from the start of induction therapy was 6.6 versus 10.2 months, respectively (HR, 0.50; P<0.001). When evaluated from time of randomization, the median PFS was 3.7 months versus 7.4 months, respectively (HR, 0.48; P<0.001).

These encouraging findings will be further evaluated with large Phase III trials. ECOG 5508 is a Phase III study that will randomize 1,282 patients to bevacizumab, pemetrexed, or a combination of bevacizumab and pemetrexed after 4 cycles of initial therapy with carboplatin-paclitaxel-bevacizumab in advanced nonsquamous NSCLC. PointBreak is a separate randomized, open-label Phase III study comparing carboplatin-pemetrexed-bevacizumab followed by maintenance pemetrexed-bevacizumab with carboplatin-paclitaxel-bevacizumab followed by maintenance bevacizumab in advanced nonsquamous NSCLC; patients will receive up to 4 cycles of induction treatment followed by maintenance until progression or treatment discontinuation.

Although observation is still an option in patients with disease control after initial chemotherapy, consideration should be made for maintenance therapy, especially in patients with preserved performance status. Options for maintenance therapy in advanced NSCLC include continuation of front-line therapy with bevacizumab, cetuximab, pemetrexed, or gemcitabine, or
switching to pemetrexed for patients with nonsquamous histologies and erlotinib for those with \textit{EGFR}-mutated tumors. Additional considerations can be made for doublet maintenance therapy.

\textbf{Overcoming Resistance}

\textbf{EGFR and Acquired EGFR Resistance}

An active area of research centers on mechanisms of resistance to EGFR TKIs, including amplification of the \textit{MET} oncogene and secondary mutations in \textit{EGFR}, such as the \textit{T790M} mutation in exon 20. The \textit{T790M} mutation is the most common mechanism of acquired resistance, accounting for more than 50\% of the cases. Dual EGFR-MET inhibition is a potential approach for overcoming MET-mediated resistance to EGFR inhibitors. ARQ 197 is an oral, selective, non-ATP competitive inhibitor of c-MET, a receptor tyrosine kinase implicated in cancer cell migration, invasion, and proliferation. A global randomized, double-blind, placebo-controlled Phase II trial compared erlotinib plus ARQ 197 with erlotinib plus placebo in previously treated EGFR inhibitor-naive patients with advanced NSCLC. Median PFS (primary end point) was prolonged with combined treatment (16.1 vs 9.7 weeks; HR 0.81; CI, 0.57, 1.15; \textit{P}<0.0004). The objective response rate also was significantly higher with afatinib versus chemotherapy (56\% vs 23\%; \textit{P}<0.0001). This is the first randomized study to demonstrate benefit of an oral targeted therapy versus chemotherapy in a molecularly selected population.

\textbf{EML4-ALK and Crizotinib Resistance}

\textit{EML4-ALK} is a novel fusion oncogene occurring in about 3\% to 7\% of NSCLC cases.\textsuperscript{24} The fusion results from a small inversion within chromosome 2p, leading to expression of a constitutively activated, chimeric tyrosine kinase. \textit{EGFR} mutations and \textit{EML4-ALK} rearrangements are generally mutually exclusive.\textsuperscript{59} Patients tend to respond rapidly to crizotinib, but many develop resistance after about 1 year of therapy, and increased brain metastases have been reported.\textsuperscript{40} The FDA recently approved crizotinib for patients with advanced NSCLC with \textit{ALK}-positive rearrangements as demonstrated via the Abbott Vysis test. Second-generation ALK TKIs and heat shock protein 90 inhibitors as strategies to treat crizotinib-resistant tumors are under way.\textsuperscript{41}

\textbf{Newer Targeted Therapies}

The recent advances in the treatment of NSCLC have involved the integration of targeted therapeutics and more accurately defining the subset of patients who are most likely to benefit from a given treatment. We have attempted to use clinical factors such as tobacco history, gender, and ethnicity to determine appropriate therapy. However, because 60\% of lung cancers carry an identifiable mutation,\textsuperscript{42} there is movement toward assessing genetic factors more quickly. The Lung Cancer Mutation Consortium (LCMC) has reported the frequencies, characteristics, and therapeutic options for genetic mutations found in lung cancer. Additionally, appropriate patients are offered participation in LCMC-linked clinical trials of agents targeting the identified mutation.

The importance of histology cannot be underestimated. Although targeted therapies have improved outcomes for patients with adenocarcinoma of the lung, patients with squamous cell carcinoma very rarely respond to these same agents. In addition to EGFR, the other promising targets including \textit{EML4-ALK}, \textit{KRAS}, and \textit{MET} also may be limited to adenocarcinoma. Given that squamous cell lung cancers account for about 25\% of new lung cancer cases and 40,000 deaths per year in the United States, it is important to identify and understand the genomic alterations that drive this histologic subtype. To date, 3 molecular targets have been...
identified in squamous cell carcinomas: Fibroblast growth factor receptor 1 (FGFR1) is amplified in about 20% of squamous cell lung cancer and PI3KCA and DDR2 mutations each have been identified in about 3% of squamous cell carcinomas. All of these mutations represent promising targets for future therapy, and they are already being considered for clinical trials.

Although studies continue to evaluate therapies based on tumor histologic profiles, the BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial tackled personalized treatment based on tumor molecular biomarker profiles. This was the first completed prospective, biopsy-managed, biomarker-based, adaptively randomized study in patients with heavily pretreated NSCLC. Based on results from core needle biopsy specimens, patients were treated with erlotinib, vandetanib (Caprelsa, AstraZeneca), erlotinib plus bexarotene (Targretin, Eisai), or sorafenib (Nexavar, Bayer). Patients with mutant-KRAS tumors benefited from sorafenib. Attention has also been placed on targeting BRAF mutations, especially because most of the identified mutations in NSCLC seem to be mutually exclusive. Thus, agents such as vemurafenib (Zelboraf, Genentech) and dasatinib (Sprycel, Bristol-Myers Squibb), which have shown activity in V600E BRAF mutations and DDR2 mutations, respectively, are being evaluated in these settings. All of these efforts are substantial steps toward individualized lung cancer therapy.

Conclusion

Paradigms in all stages of treatment of advanced NSCLC are evolving toward targeted molecular therapies with better tolerability profiles. Based on recent studies, new standards of management in advanced NSCLC must be considered including maintenance strategies and targeted therapies. To improve our management of lung cancer patients, more tissue should be collected (eg, core biopsies) to evaluate upfront not only histology but also biomarker profiles. The BATTLE trial has already demonstrated the feasibility of this type of approach in advanced NSCLC. One day, we hope patients with lung cancer will be treated according to a biomarker tumor profile and not limited by their age or performance status. Unique treatment strategies can then be directed to each patient on a truly individual basis. Finally, broader clinical trial participation should be encouraged to enhance our knowledge of how to continue to improve outcomes in a disease that remains the leading cause of cancer death in the United States.

References


8. Socinski MA, Bondarenko IN, Karaseva NA, et al. Results of a randomized, phase III trial of nab-paclitaxel (nab-P) and carboplatin (C) compared with cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2017;35(28 suppl):Abstract 7515.


