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Educating Medical Directors of Employers, Health Plans and Provider Systems

Supplement: A CME CNE Approved Activity

New Horizons in Advanced Non-small Cell Lung Cancer: Improving Patient Outcomes with Novel Therapies and Strategies

This activity is supported by an educational grant from Lilly

New Horizons in Advanced Non-small Cell Lung Cancer: Improving Patient Outcomes with Novel Therapies and Strategies

Tom Stinchcombe, MD

Instructions for CME/CNE: Read the monograph, answer the post test, complete the evaluation form, and send completed post test and evaluation to:

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Learning Objectives:
1. Review the mechanisms of action, safety and efficacy of current and emerging treatments in the management of advanced NSCLC.
2 Analyze recent clinical data and pathological evidence on novel treatments for patients with metastatic squamous NSCLC.
3. Describe current data relating histology and biomarkers to treatment decisions and sub-typing in advanced NSCLC.
4. Evaluate new treatment options for patients who have metastatic NSCLC with disease progression.
5. Examine patient and clinical factors used to guide first-line and maintenance therapy selection in NSCLC.
6. Discuss whether switching treatment or continued use of the same treatment is most appropriate in maintenance or progressive settings of advanced NSCLC.

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Katie Eads has no real or perceived financial relationships to disclose.
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New Horizons in Advanced Non-small Cell Lung Cancer: Improving Patient Outcomes with Novel Therapies and Strategies

Post Test Questions

1. Which of the following is the most common type of lung cancer?
   a. Small Cell
   b. Non-small cell adenocarcinoma
   c. Non-small cell squamous
   d. Large cell

2. Which of the following agents is added to first-line chemotherapy for **adenocarcinoma** type of metastatic/advanced non-small cell lung cancer (NSCLC) without known oncogenic mutations to improve overall survival?
   a. Afatinib b. Sunitinib c.Bevacizumab d. Necitumumab

3. Necitumumab is the first FDA-approved biologic for the first-line treatment of patients with metastic squamous NSCLC in combination with cisplatin and gemcitabine.
   a. True
   b. False

4. Which of the following is the MAIN reason for maintenance therapy after chemotherapy in NSCLC?
   a. Reduce rate of symptoms related to anemia
   b. Re-activate tumor cell sensitivity to chemotherapy
   c. Reduce incidence of bony fractures related to mets
   d. Suppress tumor growth

5. Which of the following is an accurate statement about immunotherapy in NSCLC?
   a. This type of lung cancer is not receptive to immunotherapy.
   b. One in five patients who receive immunotherapy will have long-lasting, durable response.
   c. Immunotherapy is only effective in those who exhibit high levels of PD-L1 expression (> 75%)
   d. Immune-related adverse effects occur in a large percentage of patients.

6. Which of the following is becoming the outcome standard for clinical trials in molecular subsets of lung cancer?
   a. Overall response rate (ORR)
   b. Overall survival (OS)
   c. Duration of response (DOR)
   d. Progression free survival (PFS)

7. Which of the following tyrosine kinase inhibitors (TKI), approved for use in NSCLC with EGFR mutation, has the highest EGFR-related adverse effects?
   a. Afatinib b. Gefitinib c. Erlotinib d.Sunitinib

8. Which of the following is the most common form of acquired resistance to EGFR TKI?
   a. Met amplification
   b. Conversion to small cell
   c. T790M mutation
   d. Unknown

9. Which of the following is next line therapy for those with ALK positive disease who progressed on crizotinib which would likely be better tolerated (i.e., fewer adverse effects)?
   a. Ceritinib b. Alectinib c. Necitumumab d. Erlotinib

10. Which of the following is a rare genetic mutation found in some NSCLC tumors for which crizotinib is effective?
    a. ROS1 b. EGFR c. KRAS d. MET

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented I am better able to:

   Review the mechanisms of action, safety and efficacy of current and emerging treatments in the management of advanced NSCLC.

   4 3 2 1

   Analyze recent clinical data and pathological evidence on novel treatments for patients with metastatic squamous NSCLC.

   4 3 2 1

   Describe current data relating histology and biomarkers to treatment decisions and sub-typing in advanced NSCLC.

   4 3 2 1

   Evaluate new treatment options for patients who have metastatic NSCLC with disease progression.

   4 3 2 1

   Examine patient and clinical factors used to guide first-line and maintenance therapy selection in NSCLC.

   4 3 2 1

   Discuss whether switching treatment or continued use of the same treatment is most appropriate in maintenance or progressive settings of advanced NCSLC.

   4 3 2 1

2. The activity met my expectations. 4 3 2 1
3. The activity and presenter were free of bias. 4 3 2 1
4. The activity was applicable to my position. 4 3 2 1
5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

   4 3 2 1

6. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

7. What other topics interest you? _____
8. My goal of participating in this activity was: _____

   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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Introduction

It is estimated that there will be 244,390 new cases of lung cancer in the United States (U.S.) in 2016 and 158,080 deaths from this disease.[1] Lung cancer is the second most common cancer for both men and women but the number one cause of death from cancer for either gender.[1] With declines in smoking rates, the incidence of lung cancer and death rates has been declining in both genders.[1]

Overall, the five-year relative survival rate for lung cancer in the U.S. is 18 percent; survival rates however depend on the type of lung cancer and the stage at diagnosis.[2] Race affects survival, but the data have been somewhat conflicting. Some studies have shown that Asian populations do better, but this may be because of higher rates of certain mutations which can be targeted with therapy (epidermal growth factor receptor mutation positivity of ~40%) and that many are never smokers (a positive prognostic factor). African Americans have worse five-year survival than Caucasians (16% vs 19%), but it is unknown if this is a biology issue or health care access issue.[1] African Americans tend to present with more advanced disease.

Smoking is the major risk factor for lung cancer. Men and women who smoke are about 25 times more likely to develop lung cancer than nonsmokers, but nonsmokers do develop lung cancer.[1] Exposure to radon gas is estimated to be the second-leading cause of lung cancer in the U.S.[1] Other risk factors include exposure to secondhand smoke, asbestos (particularly among smokers), certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution, and diesel exhaust.[1]

Lung cancer can be divided histologically into small cell (13%) and non-small cell types (83%).[1] The non-small cell lung cancer (NSCLC) group can be further subdivided into adenocarcinoma and squamous cell. Adenocarcinomas account for the largest percentage of all lung cancers and of NSCLC. Because squamous cell carcinomas are associated with smoking history, the percentages of tumors with this histologic type will vary by the smoking rate in a particular population.

Based on type and stage of cancer, as well as specific molecular characteristics of cancer cells, treatments can include surgery, radiation therapy, chemotherapy, and/or targeted therapies. The National Comprehensive Cancer Network (NCCN) evidence-based guidelines, which are updated annually, are available and detail treatment of lung cancer by type and stage. This monograph focuses on the treatment of NSCLC. [3]

For early stage NSCLC, surgery is usually the treatment of choice; chemotherapy, sometimes in combination with radiation therapy, may also be given. Advanced-stage NSCLC patients are usually treated with chemotherapy, targeted therapy, a combination of the two, or immunotherapy. Identifying the histologic subset of NSCLC is important to treatment selection. The other important issue in selecting therapy are the genetic mutations found in the tumor for which there are specific targeted therapies.

First-line Treatments for Advanced Non-squamous (mutation negative) NSCLC

At the time of diagnosis, patients with advanced non-squamous tumors are now routinely tested for certain activating genetic mutations which drive cancer growth including endothelial growth factor receptor (EGFR), echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase (EML4-ALK) rearrangement, and ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) because targeted therapy is available for these mutations. Tumors with these mutations are unique and really should be considered separate diseases. Treatment with targeted therapy is discussed later.

In patients with advanced non-squamous NSCLC who do not have any identified activating genetic mutation, treatment is still chemotherapy with or without the addition of a vascular endothelial growth factor (VEGF) inhibitor [bevacizumab (Avastin®)]. This agent stops angiogenesis, which is vital to tumor growth.

In a pivotal trial of bevacizumab, that still influences therapy selection, patients with both squamous and non-squamous disease were given the agent, but those with squamous disease had significant pulmonary hemorrhage.[4] Because of this finding, bevacizumab is only used in those with non-squamous disease. The addition of bevacizumab to a standard chemotherapy regimen combination for non-squamous NSCLC (paclitaxel and carboplatin) resulted in a statistically higher overall response rate (ORR, 35% vs 15% for paclitaxel/carboplatin), longer median progression-free survival (PFS, difference of 1.7 months), and longer median overall survival (OS, 2 months).[5] This was a signficant advance in improving overall survival in NSCLC.

For chemotherapy, OS is considered the benchmark for determining if therapy is effective and has clinical impact. There are three commonly used platinum-based doublet regimens with or without bevacizumab; carboplatin/pemetrexed, carboplatin/paclitaxel/bevacizumab, and carboplatin/pemetrexed/bevacizaumab are the current first-line treatments for advanced non-squamous NSCLC without driving mutations. Each of these regimens has been shown to improve OS compared with earlier regimens.

First-line Treatments for Advanced Squamous NSCLC

Squamous NSCLC is more associated with tobacco use and tends to be a more difficult to treat disease compared with adenocarcinoma. These patients have smoking history, more underlying cardiopulmonary disease, are older, and tend to be sicker in general. The first-line chemotherapy treatment for advanced squamous NSCLC is a platinum-based doublet; some of the options include cisplatin with gemcitabine, docetaxel, etoposide, or paclitaxel and carboplatin with one of the previously listed agents.[3]

Several clinical trials have influenced the prescribing patterns of first-line therapy in squamous NSCLC. In a trial of carboplatin and paclitaxel compared with nanoparticle albumin- bound (nab) carboplatin and paclitaxel in chemotherapy naïve NSCLC patients, there was a higher response rate in those with squamous disease with nab carboplatin/paclitaxel but no statistically significant improvement in PFS or OS.[6] This trial was designed before trials split subjects into histologic classes of squamous and non-squamous. The benefit in squamous disease was shown in a post-hoc analysis. This trial led to discussions on whether a treatment combination that has been shown to produce a tumor reduction response but not a significant change in PFS or OS, which have been traditional endpoints in lung cancer, should be used. This regimen may be of use in patients who are frail where the weekly regimen allows the oncologist more control of the situation or the patient is very symptomatic and the oncologist thinks a good tumor response in a timely manner would be beneficial.

Necitumumab (Portrazza®) is the first FDA-approved biologic for the first-line treatment of patients with metastatic squamous NSCLC in combination with cisplatin and gemcitabine. It is a fully humanized monoclonal antibody against the EGFR protein on the outside of the tumor cell and was FDA approved in 2015. EGFR activation leads to tumor growth and spread, induction of angiogenesis

and inhibition of cell death. Blocking the activation of EGFR, reverses the effect of activation.

In combination with cisplatin and gemcitabine, median OS was increased statistically by the addition of necitumumab (11.5 vs 9.9 months).[7] In this trial, necitumumab was continued as a maintenance treatment after the active treatment phase. This agent has been somewhat controversial because of its price during a time when value-based assessments are getting more scrutiny in terms of magnitude of benefit. Its place in therapy is still being discussed and determined. In the current NCCN guidelines, the combination of cisplatin/gemcitabine/necitumumab is a category 3 recommendation versus category 1 for the regimen without necitumumab.

Maintenance Therapy

It is well known that after patients receive four cycles of platinum-based chemotherapy, which is the standard of care in metastatic NSCLC, their disease will progress within a median of two to three months after the end of therapy. Researchers and clinicians have looked for a way to continue a tolerable therapy which would suppress tumor growth (maintenance therapy). Metastatic lung cancer treatment is largely a palliative setting with modest survival thus the maintenance therapy chosen needs to be tolerable, in addition to effective, for a good patient quality of life.

The trial that established the concept of maintenance therapy in lung cancer compared pemetrexed with placebo in patients who had received four cycles of gemcitabine, docetaxel, or paclitaxel in combination with cisplatin or carboplatin, with complete or partial response or stable disease.[8] This trial included both those with non-squamous and squamous disease. Those with non-squamous disease had a more robust improvement in median OS (5.2 months) than those with squamous who had the same or worse survival with placebo or pemetrexed. Thus, pemetrexed is not an effective maintenance agent in those with squamous histology and should not be used in them. It is effective maintenance for those with non-squamous disease and is frequently used for this purpose because of a favorable toxicity profile with pemetrexed.

A trial that was ongoing at the same time as the pemetrexed trial used a different design and maintenance agent, erlotinib, an EGFR tyrosine kinase inhibitor (TKI). This trial gave erlotinib or placebo to the advanced NSCLC patients who had no progression after four cycles of cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, cisplatin/vinorelbine, carboplatin/gemcitabine, carboplatin/docetaxel, or carboplatin/paclitaxel. Only about 45 percent of the patients screened for this trial made it to the randomization to erlotinib or placebo because they progressed on chemotherapy. Clinicians now know that EGFR mutation status is the marker for whether erlotinib will work but at the time of this trial design this was not known. There was a modest improvement in median OS of one month shown in all patients.[9] The survival benefit was better in those with an EGFR mutation. Currently, patients with an EGFR mutation will get a TKI in the first-line setting. Based on this trial, there is some question now about the value of TKIs in those without an EGFR mutation (EGFR wild type tumor).

One of the challenges with maintenance therapy is that pemetrexed is frequently used as first-line therapy. In the past, clinicians did not know if the benefit of pemetrexed maintenance therapy still occurred in those who got upfront pemetrexed. A trial examined this issue by giving pemetrexed or placebo maintenance to patients who had a response to four cycles of pemetrexed/cisplatin. The trial met its endpoint of improvement in PFS but also showed improved median OS (2.9 months).[10] Using pemetrexed for maintenance after pemetrexed as initial therapy is sometimes referred to as continuation therapy.

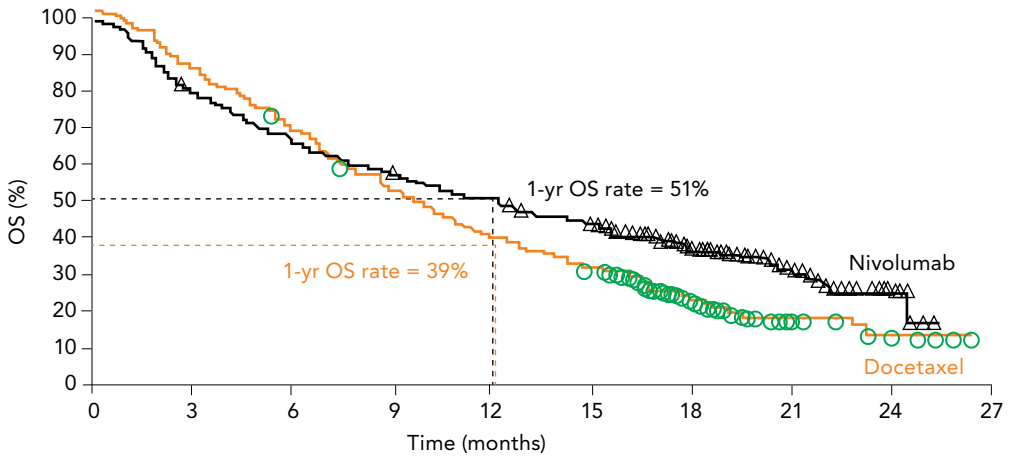
In selecting maintenance therapy, several patient factors are taken into account. Performance status of the patient is very important. The Eastern Cooperative Oncology Group (ECOG) criteria are commonly used to measure performance status.[11] This scale grades performance status from 0 (fully active, able to carry on all pre-disease performance without restriction) to 4 (completely disabled; cannot carry on any self-care; totally confined to bed or chair. There is a grade 5, which is death. Those with a 0 to 1 performance status are those who have shown to benefit from maintenance. Treatment-related toxicities from their earlier treatment, such as anemia, nausea, or fatigue, can impact whether to continue giving a particular agent for maintenance. Patients can be educated on the options and then allowed to choose whether to continue with maintenance therapy. Many patients will be worried that if they stop therapy the cancer will grow. Others may feel therapy has been a hassle and want to stop it.

Second-line Immunotherapy

Once a patient with advanced NSCLC progresses on first-line therapy, immunotherapy is given. Initially, there was some skepticism whether lung cancer would ever be amenable to immunotherapy. Trials with newer agents have shown that it is an immune-responsive disease, thus immunotherapy has become the dominant second-line therapy.

Nivolumab (Opdivo®) is a programmed death

Exhibit 1: One Year Overall Survival with Nivolumamb Compared to Docetaxel[12]



Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations

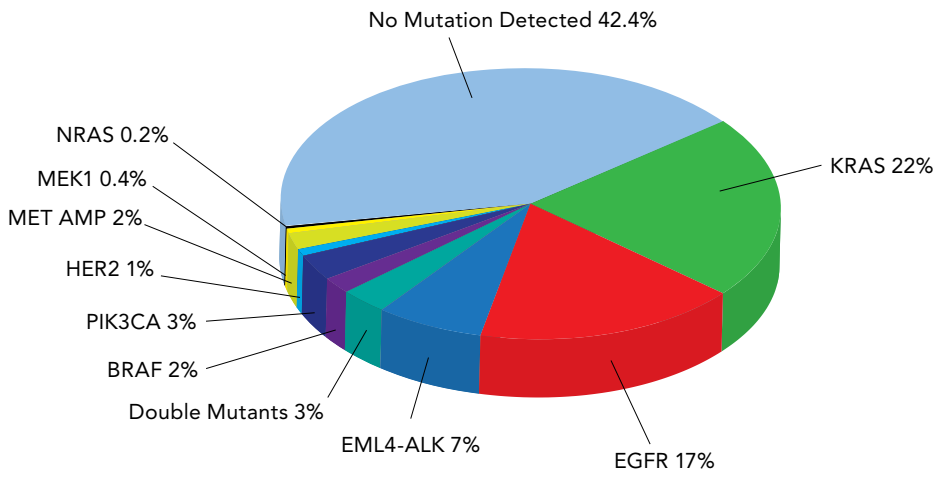
receptor one (PD-1) blocking antibody. Blocking PD-1 leads to cell death. Nivolumab is indicated for NSCLC which has progressed on or after platinum-based chemotherapy. In a trial of nivolumab compared to docetaxel in patients with squamous NSCLC who had received at least one prior platinum doublet-based chemotherapy regimen, there was a dramatic improvement in OS with nivolumab that led to the trial being stopped early.[12] The difference in median OS was 3.2 months, but the real difference was in one-year OS. The one-year OS was 42 percent in the nivolumab group and 24 percent in the docetaxel group (Exhibit 1).[12] The ORR was 20 percent in the nivolumab group compared with 9 percent in docetaxel arm. Some patients appear to hit a plateau on this agent and do not progress for a long period of time. At the time of publication, the median duration of response for those receiving nivolumab had not yet been reached in this trial. Historically, response with chemotherapy in the second-line setting only lasts for one to two months and progression occurs. The fact that one in five patients will have a very durable response to immunotherapy is challenging the previous paradigms and thinking about lung cancer.

Nivolumab has also been studied in patients with non-squamous disease who had failed on at least one prior platinum doublet and prior maintenance therapy was allowed. Also prior TKI therapy was allowed for known responsive mutations. Again a similar effect on median OS (difference of 2.8 months) and one-year OS (51% vs 39%) was seen.[13] There appears to be a group of patients whose disease worsens at the beginning, and there appears to be a plateau effect in this type of patients also. Nineteen percent of patients responded to nivolumab and 12 percent to docetaxel. The median duration of response was 17.2 months and 5.6 months, respectively. Those who respond to nivolumab appear to have good disease control for a long period of time.

The other thing that is attractive about immunotherapy compared with chemotherapy is the rate of adverse effects. The rate of serious (grade 3-4) events is much lower with immunotherapy.[12,13] The most common adverse events with nivolumab are fatigue, decreased appetite, and asthenia compared with traditional chemotherapy adverse effects of neutropenia. [12,13] Immunotherapy is not without serious adverse events. It can cause immune-related hepatitis, pneumonitis, and colitis in about 1 percent of patients.

The second immunotherapy agent to enter the arena was pembrolizumab (Keytruda), another PD-1 blocking antibody. It is approved for metastatic NSCLC tumors that express programmed death ligand (PD-L1). It was initially approved for those with test results of greater than or equal to 50 percent (i.e., 50% of cells tested had PD-L1). A re-

Exhibit 2: Rate of Mutations in NSCLC-Adenocarcinoma[15]



cently published trial led to wider use and a change in the FDA approval that just requires expression. This trial compared pembrolizumab at two doses (2 mg/kg and 10 mg/kg) and docetaxel every three weeks. The primary endpoints were PFS and OS and secondary endpoints were ORR, duration of response (DOR), and safety. Data on response were separated out by PD-L1 greater than or equal to 50 percent and PD-L1 greater than or equal to 1 percent treatment groups. About a third of the patients had PD-L1 greater than 50 percent. The results in this group were improved median OS (14.9 months for 2 mg/kg, 17.3 for 10 mg/kg, and 8.9 months for docetaxel).[14] There was still an improvement in OS in the overall study population (irrespective of PD-L1 levels). Thirty percent of those with PD-L1 greater than 50 percent responded to the agent, whereas 18 percent responded in the overall study population. Eight to 9 percent of patients responded to docetaxel. This trial provided evidence of benefit for using anti-PD-1 therapy in patients who have at least 1 percent PD-L1 levels. Like with nivolumab, there was a lower rate of serious adverse effects with pembrolizumab compared with docetaxel.

The differences between nivolumab and pembrolizumab are the dosing intervals and FDA approved indication. Nivolumab is given every two weeks and pembrolizumab every three weeks. FDA approval of pembrolizumab requires PD-L1 expression before it should be prescribed.

With immunotherapy, response rates and duration of response are the preferred parameters for determining efficacy. Clinicians really would like to figure out why one in five patients have a durable response with immunotherapy and the others do not. Expression of PD-L1 is one biomarker used to predict response to PD-1 antibodies but there are many issues with whether this is the best marker, what level of PD-L1 expression is needed to indicate likelihood of response, and whether it should be required to prescribe anti PD-1 agents. At this point, PD-L1 testing is not routinely done on all patients.

Molecular Subsets of NSCLC

As shown in Exhibit 2, there are multiple oncogenic mutations found in adenocarcinoma NSCLC, the most common subset.[15] Testing for these mutations are recommended without regard for age, gender, or smoking status. For patients with metastatic adenocarcinoma, their tumors will be tested for EGFR and EMLA4/ALK mutations and possibly ROS1. Similar mutations are also found in squamous tumors but at lower rates; the guidelines recommend considering mutation testing in those with squamous disease who are never smokers or have mixed histology. The NCCN guidelines advocate for broader molecular profiling with the goal of identifying rare driver mutations for which effective therapy may be available but not necessarily approved for NSCLC.[3]

EGFR-Mutated NSCLC

There have been a number of trials in the EGFR mutation-positive population that have compared targeted therapy with TKIs (erlotinib, gefitinib, afatinib) with platinum doublets. If EGFR mutation is present, there is a consistently higher ORR and PFS

Exhibit 3: Platinum-Based Therapy versus EGFR TKI[16-23]

Trial	Comparison	ORR	PFS (HR)	OS
IPASS* (n = 261)	Gefitinib vs Carboplatin/paclitaxel	71.2% vs 47.3% P < .001	0.48, P < 0.001 9.5 vs 6.3 mos	MST 21.6 vs 21.9 mos HR 1.00, P = 0.990
NEJSG (n = 200)	Gefitinib vs Carboplatin/paclitaxel	73.7% vs 30.7% P < .001	0.30, P < 0.001 10.8 vs 5.4 mos	MST 30.5 vs 23.6 mos P = 0.31
WJTOG (n = 172)	Gefitinib vs Cisplatin/docetaxel	62.1% vs 32.2% P < .0001	0.489, P < 0.0001 9.2 vs 6.3 mos	MST 36 vs 39 mos HR = 1.10
CTONG (n = 165)	Erlotinib vs Carboplatin/gemcitabine	83.0% vs 36.0% P < .0001	0.16, P < 0.001 13.1 vs 4.6 mos	MST 22.8 vs 27.2 mos HR = 1.10, P = 0.2663
First-signal* (n = 42)	Gefitinib vs Cisplatin/gemcitabine	84.6% vs 37.5% P = .002	0.613, P = 0.084 8.4 vs 6.7 mos	30.6 vs 26.5 mos HR = 0.823, P = .648
EURTAC (n = 174)	ERlotinib vs Various platinum doublets	58% vs 15% P < 0.0001	0.37, P < 0.0001 9.7 vs 5.2 mos	MST 19.3 vs 19.5 P = 0.87
LUX-Lung3* (n = 307)	Afatinib vs Cisplatin/pemetrexed	60.8% vs 22.1% P = 0.0150	0.47, P = 0.001 13.6 vs 6.9 mos	MST 31.6 vs 28.2 HR = 0.78, P = 0.11
LUX-Lung6* (n = 324)	Afatinib vs Cisplatin/gemcitabine	66.9% vs 23.0% P < 0.0001	0.28, P , 0.0001 11.0 vs 5.6 mos	MST 23.6 vs 23.5 HR = 0.83, P = 0.18

*Number represent EGFR mutation exon 19 and 21 subsets

ORR = overall response rate
PFS = progression free survival
HR = hazard ratio
OS = overall survival
MST = median survival time
mos = months

to targeted therapy than to chemotherapy (Exhibit 3).[16-23] None of the trials have shown a statistically significant OS benefit; this may be because many of the subjects in the trials were switched from the chemotherapy arm to the TKI arm, creating a confounding variable. PFS, rather than OS, is becoming the outcome standard for the clinical trials in molecular subsets of lung cancer.

There are some differences in toxicity among the TKIs. Gefitinib tends to cause a lower rate of rash and diarrhea, which are EGFR blockade specific toxicities, compared with the other two. These lower rates are likely due to the fact that it is dosed at 250 mg daily, which is half the maximum tolerated dose. Rates with erlotinib are in the middle. Afatinib is an irreversible binder, so it causes higher rates of EGFR associated toxicities. Any one of the three TKIs are options for first-line therapy in those with known EGFR mutations.

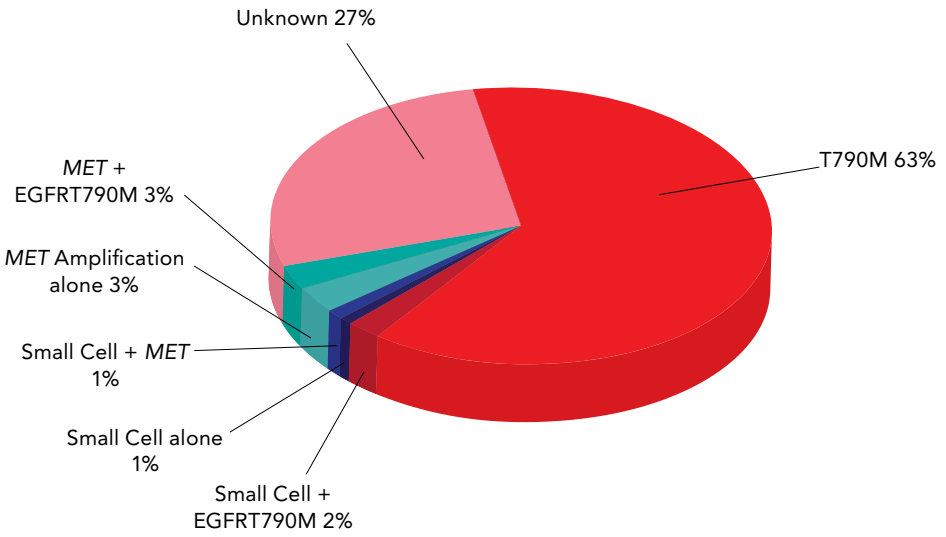
Unfortunately, resistance to TKI therapy develops within 10 to 14 months of starting therapy. There are many different identified mechanisms of resistance (Exhibit 4).[24] The most common form of acquired resistance is the development of the T790M mutation. Interestingly, some patients will convert to small cell lung cancer.

The next step in drug development for EGFR mutation-positive NSCLC was the development of osimertinib (Tagrisso®), a designer EGFR-TKI targeting the T790M mutation. It has been studied in patients with acquired resistance to EGFR-TKIs and is only approved for those with T790M-positive tumors and have progressed on or after another TKI. In the approval trial of osimertinib, the T790M-positive group had a median ORR of 66 percent.[25] Overall, 90 percent of T790M-positive patients had disease control (complete, partial, or stable disease response) and the median PFS was 9.6 months. The median PFS in patients without the mutation was only 2.8 months, so this agent really should not be used in those without the mutation. Diarrhea, rash, and decreased appetite are the most common adverse effects of osimertinib, but they are much lower than with the first-generation TKIs. Interstitial pneumonitis has been reported with this agent.

Therapies for EML4/ALK Rearranged NSCLC

Another common mutation in NSCLC is EML4/ALK rearrangement. There is increasing research interest in this group of patients. Crizotinib (Xalko-

Exhibit 4: Mechanisms of Acquired Resistance in EGFR-Mutated Lung Cancer[24]



ri®), an ALK and ROS1 protein kinase inhibitor, is the first-line treatment in those with this mutation. Compared with pemetrexed-based chemotherapy, crizotinib treatment led to longer PFS (10.9 months vs 7.0) and greater ORR (74% vs 45%).[26]

Like with EGFR-positive disease, those with ALK rearrangement will also progress on or after therapy. Several agents have been developed for second-line therapy. Ceritinib (Zykadia®) was the second targeted agent for ALK rearrangement. In Phase I trials, an ORR of 56 percent in those who had received a prior ALK therapy and 62 percent in those who were ALK naïve was seen in one trial.[27] There is some interest in moving ceritinib into first line because of durable responses in the treatment naïve groups in some trials. The challenge with this agent is that 60 percent of patients will need a dose reduction because of adverse effects (gastrointestinal toxicities, increased liver function tests) at the standard 750 mg dose.

Alectinib (Alecensa®) is approved for those with ALK-positive disease who progressed on crizotinib. Many patients on crizotinib will have progression on therapy which appears in the brain because of this agent's relatively poor penetration into the central nervous system. Alectinib produced a 50 percent ORR and median PFS of 8.9 months in a crizotinib-resistant population.[28] The promise with this agent is lower rates of moderate to severe adverse effects. Constipation, fatigue, peripheral edema, and myalgia were the most common adverse effects.[28] It appears to be better tolerated than ceritinib for the second-line setting.

There has been a trial conducted in Japan, which so far has only been presented at an ASCO meeting, that compared crizotinib and alectinib which found a longer PFS with alectinib (median not reached vs 10.2 months).[29] There is also much interest in whether this agent will move to the front-line setting for ALK-positive patients.

There is a rare ROS1 rearrangement found in about 1 percent of all lung cancer patients. There is similarity between ROS1 and ALK rearrangements. In a trial of 50 patients, crizotinib treatment produced an ORR of 72 percent, median PFS of 19.5 months.[30] Crizotinib was FDA approved for ROS1 rearrangement positive disease based on this small single arm trial. It was recognized that it would be very difficult, if not impossible, to do a comparative trial in this rare population.

Conclusion

The treatment of NSCLC continues to change rapidly with the discovery of numerous genetic mutations driving tumor growth and subsequent development of therapy targeted at these growth factors. Multiple new agents have come to market and more are under study. First-line therapy for advanced non-squamous (mutation negative) and squamous NSCLC continues to be platinum-based chemotherapy. Maintenance therapy can be continuation of bevacizumab or pemetrexed (non-squamous),

a switch to pemetrexed (non-squamous) or erlotinib (without regard to histology). Second-line therapy is immunotherapy with nivolumab and pembrolizumab. For molecularly defined NSCLC, the first-line treatments are different. EGFR mutant NSCLC is treated with erlotinib, gefitinib, or afatinib. Second-line treatment for EGFR mutation with a T790M mutation is osimertinib. ALK-rearranged NSCLC is treated with crizotinib first and then ceritinib or alectinib in the second line. ROS1 mutation is targeted with crizotinib.

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