CARCINOMAS OF THE LUNG

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Our first talk is a lecture on the Diagnosis and Treatment of Adenocarcinomas and Squamous Cell Carcinomas of the Lung. It’s my pleasure to introduce Dr. Millie Das of the Stanford School of Medicine and Ms. Alison Holmes Tisch of the Stanford Cancer Institute. Please give a round of applause. Thank you.

DR. DAS Hey. Thank you so much to the organizers for the invitation to speak today. Alison and I are going to be discussing the diagnosis and treatment of adenocarcinomas and squamous cell carcinomas of the lung.

These here are the learning objectives. First is to discuss the range of genetic variants and non-small cell lung cancer and how they’re used to select targeted agents for our patients. Second is to identify current diagnosis and treatment paradigms for patients with squamous cell lung cancer. And third is to identify and manage adverse events that occur with the use of immunotherapies across all subtypes of lung cancer. And I noted that there was a great talk yesterday that went into a lot more detail about this third point and so I’m just going to touch on that briefly towards the end of the presentation.

Alison and I have nothing to disclose. Here’s an outline for today’s talk. We’re going to first review how we stage and diagnose our patients with lung cancer and then discuss how we decide treatment for a patient based upon histology, as well as review a number of different targeted agents, particularly in patients who have an EGFR mutation, an ALK translocation, or ROS1 fusion. And, finally, we’ll end on reviewing the role of immunotherapy in lung cancer.
Let Alison speak first on staging and diagnosis of lung cancer.

ALISON   Hi. It’s really great to be here, and I thank so much the organizers for asking us to be here and for all of you deciding to come to our talk. I am a nurse practitioner in thoracic oncology, and I’m also the lead APP for our Thoracic Neuro and Neuro-Oncology Departments at Stanford.

I’m first going to be just briefly reviewing much of what we know about this very common disease. We know that it’s the second most commonly diagnosed cancer in both men and women in the U.S., but it’s by far the number one cause of cancer-related death among men and women, with more deaths than breast, colon, and prostate cancer combined. One of the most challenging parts of this disease is that the symptoms can be pretty vague at first and attributed to other illnesses. People present with local symptoms; with cough, dyspnea, hemoptysis, or maybe chest pain; general symptoms, constitutional symptoms, such as fatigue, weight loss, often finding them with symptoms related to distant metastasis such as brain metastasis, new neurologic symptoms, or bony pain, and occasionally with paraneoplastic syndrome, such as SIADH.

Our work-up for lung cancer is really, as with every disease, we start with a good history and physical exam, and initially the first imaging is often a chest x-ray and then routine labs. For our complete work-up, we’re going to do a chest CT, include the adrenals as that’s a common site for metastasis. We’re also going to do a PET to look for any distant metastasis, as well as a dedicated brain MRI.
When we’re thinking about making the diagnosis, it’s really key to ensure an adequate tissue sample and so most often our patients undergo a bronchoscopy, CT-guided biopsy, or thoracentesis, and really making sure that you’re getting a decent sized cell block, core biopsy ideally, because there is a lot of histological and molecular testing that needs to be done.

I’m not going to go into great detail over the staging; it can be complicated, particularly for the earlier stage disease. And most of our talk is really focusing on management of metastatic disease, and that’s either with localized metastatic disease, metastasis to the pleura or the pericardium, or nodules in the contralateral lung, or distant metastasis.

When you’re doing your biopsy, you’re hoping to establish your diagnosis, determine histology, and determine a molecular profile, and so like I mentioned, you really need to obtain adequate tissue. Bone biopsies tend to not give you adequate tissue for molecular diagnosis because the DNA is difficult to extract in that setting.

Our histologic subtyping -- what we’re really looking for in just a nonsquamous cancer is the squamous histology because that’s going to direct our chemotherapy selection. Primarily in every nonsquamous histology we’re looking for an EGFR mutation or ROS translocations initially. And now, actually, as we’ll talk about a little bit later on, with the new indication for pembrolizumab first-line treatment for high expressers of PD-L1, we will want to start doing PD-L1 testing on all of our patients at diagnosis.
At our center we are often looking at other mutations: KRAS, BRAF, HER2 RET, and others. If somebody has a KRAS mutation, they’re not going to have a targeted therapy that is available to them, but we understand what’s driving their cancer versus some of the others where there will be potentially second-line or off-label or clinical trial options for them in the future. There are a couple circumstances under which we would test in squamous cell, and we’ll talk about that in a bit.

For our patients particularly with mutations that are receiving targeted therapy, we really do recommend getting a re-biopsy at the time of disease progression because this helps in determining what is their mechanism of resistance and what next line treatment options are going to be recommended for that patient. And, fortunately, we’ve had the advent of these so-called liquid biopsies where they’re taking blood samples looking for circulating tumor DNA in the blood to identify these resistance mechanisms. And these are being increasingly used, and we’re helping our patients avoid a repeat biopsy.

DR. DAS  Okay. Here’s an overview of the different histologies among cancer. The major histologic classifications are listed here, so really the first distinction is whether a patient has small cell lung cancer or non-small cell. Small cell constitutes about 10 to 15% of all lung cancer cases, and non-small cell really constitutes the vast majority. So, 85 to 90% of cases of lung cancer are going to fall into this non-small cell category.

And within non-small cell we have a number of different histologies. So, there’s adenocarcinoma, which accounts for about 30 to 40% of all non-small cell
lung cancer; there's squamous cell carcinoma, which accounts for 20 to 25%; large cell carcinoma, which is 10 to 15%; and then there's other or mixed histology, which accounts for about 3 to 5%.

This is just a slide to depict some of the differences between adenocarcinoma and squamous cell carcinoma, which may already be familiar to many of you. Again, adenocarcinoma tends to occur more commonly; 30 to 40% of non-small cell lung cancer cases, squamous cell 25 to 35%. As far as age distribution, there is a bimodal age distribution for adenocarcinomas with a younger subset. Squamous histology tends to occur in older patients. There does seem to be more females diagnosed with adenocarcinoma compared to males, and the reverse is true for squamous histology; we're more frequently seeing this in men.

As far as location goes, adenocarcinomas tend to occur more peripherally, whereas squamous cell cancers tend to occur more centrally. Smoking status for adenocarcinoma -- there's definitely a never-smoker subset, and for squamous these cancers tend to be smoking related.

As far as therapies contraindicated, there are really no therapies contraindicated for adenocarcinoma, but we know for squamous histology we really don't use pemetrexed or bevacizumab. For biomarker-driven targeted therapy, this is more frequently done in patients with adenocarcinoma histology precisely because we're seeing more of the EGFR mutation–positive patients. The ALK, the ROS fusion -- we're seeing those more frequently in adenocarcinoma, not so much in the squamous histology. And as far as
improved survival, we are seeing better survival rates for patients with adenocarcinoma precisely because we’re seeing these higher rates of targetable mutations within this histology and, again, not so much in the squamous cell histology.

Over the last decade there’s been a lot of progress into the molecular classification of lung cancer. Back in 2004, the driving genetic alteration was actually unknown in the majority of lung cancer cases. But since 2013, we’ve made tremendous progress in identifying the driving genetic alterations. And the importance of discovering these new targets is really to be able to develop drugs that specifically work against the genetic alteration. And we’ve already been able to do that in the case of EGFR, ALK, and ROS, with more and more therapies that are being discovered and tested every day to help us continue to fill in this pie.

Moving on now to how we decide treatment options for our patients with lung cancer. There’s chemotherapy where the choice of chemotherapeutic agent is dependent upon histologic subtype. There are also now targeted options, particularly for those patients who are found to have EGFR, ALK, or ROS1. And now we also have immune checkpoint inhibitors, including anti-PD-1 antibodies, anti-PD-L1 antibodies, and anti-CTLA-4 antibodies.

Considerations for first-line therapy for advanced non-small cell lung cancer -- it’s always very important to consider a patient’s clinical features, obviously, a patient’s performance status, functional status, will play into our treatment recommendations; whether or not the patient’s continuing to smoke
and if they are, then offering smoking cessation counseling. Whether or not a patient presents with CNS metastases will also dictate how we’re going to proceed with their treatment. And, of course, also considering whether the patients received prior chemotherapy, either in the locally advanced or adjuvant setting, and the time to recurrence.

Of course, histology is very important, so really making that distinction between adenocarcinoma versus squamous versus large cell neuroendocrine carcinoma. Depending upon the histology, you’re going to probably come up with a different chemotherapeutic treatment recommendation, and then, of course, molecular testing, so looking for EGFR, ALK, ROS. And then there’s more and more interest in doing next-generation sequencing on tumors to look for other potential targets.

These are the guidelines for molecular testing in non-small cell lung cancer, and this is essentially taken from the NCCN guidelines. For adenocarcinoma, large cell, or non-small lung cancer not otherwise specified, the standard recommendation now is really to look for EGFR and ALK. And you can also be testing for EGFR and ALK as part of a broader molecular profiling, such as next-gen sequencing. It’s also recommended that you go ahead and look for ROS when EGFR and ALK are negative or unknown.

For squamous cell histology, you can consider EFGR and ALK testing in certain patients with a probability of finding an EGFR or an ALK in a squamous patient [that] is much lower, but should be considered in a squamous patient who has a never-smoking or a light-smoking history or has mixed histology.
Treatment based upon histology -- just some quick background on first-line stage IV non-small cell lung cancer treatment. The standard of care is a combination of two chemotherapy drugs, platinum-based. There are new strategies that are under development to really help us tailor our therapy for individual patients. And the standard generally is to give four cycles of chemotherapy up front, which is generally given over a 3-month period. And second-line therapy can start either immediately after first-line therapy as a maintenance strategy or at the time of disease progression.

This is the ECOG 1594 study, which looked at overall survival by treatment group. This was a study that compared four different platinum doublet chemotherapies. And what you can see here is that there is clear overlap of the curves, which really indicates that the choice of platinum doublet doesn't really matter. And since the carboplatin/paclitaxel regimen seemed to fair just as well as these other cisplatin-based regimens that are more difficult to tolerate, the standard for a long time in lung cancer was the carboplatin/paclitaxel regimen.

This is the Scagliotti study that really showed that histology matters. This was a phase III study looking at advanced-stage lung cancer patients who were previously untreated, randomizing them to receiving cisplatin/gemcitabine versus cisplatin/pemetrexed. And what you can see here is that in the nonsquamous patient population, those patients receiving cisplatin/pemetrexed actually did better compared to cisplatin/gemcitabine. So, 11.8 months survival for the cisplatin/pemetrexed arm, 10.4 months survival for the cisplatin/gemcitabine arm.
And this was statistically significant. This is really the study that led to the approval of pemetrexed in nonsquamous histology.

Next is the ECOG 4599 study. This is looking at carboplatin/paclitaxel plus or minus bevacizumab in nonsquamous, non-small cell lung cancer. Again, this was a phase III study confined to the nonsquamous lung cancer patients with no prior chemotherapy. Close to 900 patients were randomized to either standard carboplatin/paclitaxel or carboplatin/paclitaxel with the addition of bevacizumab, which is a monoclonal antibody that targets VEGF, or vascular endothelial growth factor.

And what you can see here is that the addition of bevacizumab led to a 2-month survival benefit. And this was actually pretty exciting when it came out; it was really the first study to show an improvement in overall survival with the addition of a targeted agent to chemotherapy. But, again, it’s important to point out this was really just in the nonsquamous subset of patients. When they looked at the use of bevacizumab in squamous patients, there was a much higher fatality rate related to pulmonary hemorrhage, and so we are not supposed to be using this drug in squamous histology.

This is looking at MAb-paclitaxel in non-small cell lung cancer. A phase III study was done; again, advanced lung cancer patients with good performance status, no prior chemotherapy. Over a thousand patients were randomized to either carboplatin/paclitaxel or carboplatin MAb-paclitaxel. In the overall study population, you can see here that with regard to progression-free and overall survival, the results were actually pretty similar between the carboplatin/paclitaxel...
and the carboplatin/MAb-paclitaxel arms. It did appear that the overall response rate seemed to favor those patients receiving MAb-paclitaxel over paclitaxel. When you look specifically at the squamous cell subset of patients, actually the difference in overall response rate seems to be more pronounced. Those patients receiving MAb-paclitaxel in the squamous subset had a response rate of about 41% versus 24% in the paclitaxel arm.

This is the SQUIRE study. This is looking at necitumumab in squamous lung cancer phase III, stage IV squamous patients with no prior chemo, performance status of 0, 1, or 2. Over a thousand patients were randomized to receive either cisplatin/gemcitabine or cisplatin/gemcitabine with the addition of necitumumab, which is a second-generation EGFR antibody. And what you can see from these curves here is that the addition of necitumumab led to a 1.6-month survival benefit, leading the FDA to approve this drug in November 2015.

I’ll let Alison discuss our first case.

ALISON Mr. K, he’s an 80-year-old man, 90 pack a year smoking history, presented to his primary care doctor after several months of having a cough back in August of last year. Had a chest x-ray, which showed a mass, and went on to get CT imaging, which showed a 5 x 7 cm mass in the left lower lobe extending into the chest wall, had prominent mediastinal lymph nodes, some other pulmonary nodules, and a 2 x 3 cm left adrenal mass.

He underwent CT-guided biopsy of that left lung mass, came back showing a squamous cell lung cancer. The immunohistochemistry was p63 positive, CK5/6 positive, which are classic markers for squamous cell, and TTF-1
negative, which is more commonly positive in adenocarcinomas. His final staging was a T4, N2, N1b squamous cell lung cancer. Based on his smoking history and the fact that he had a squamous cell cancer, we did not do molecular testing. He was a pretty fit 80-year-old guy; he was going to the gym 6 days a week, swimming regularly, had a really supportive family who was present with him, and we gave him standard first-line chemotherapy with carboplatin and paclitaxel, slight dose reduction on the carboplatin.

He received that every 3 weeks for four cycles, tolerated it beautifully, and actually ended up having a pretty nice initial response. You can see this left lower lobe mass here, smaller and significantly less hypermetabolic, and that was seen in his other sites of disease.

He went on to have just planned for surveillance imaging in about 3 months and unfortunately did have progression of disease on those next scans, both in the brain and body at this point. We treated the brain with stereotactic radiation, and he went on to have multiple cycles of chemotherapy, both immunotherapy and standard chemotherapy, which unfortunately he progressed right through, which is something we do see sometimes in squamous cells and is part of why it’s considered prognostically unfavorable. He had progression of his main mass with worsening pain in the left lower lobe, so he got some palliative radiation; however, [he] continued to progress and, based on his goals, started hospice.

DR. DAS  Moving on to maintenance chemotherapy options. There have now been a number of different studies really evaluating the role of
maintenance treatment after completion of first-line treatment. There’s this concept of continuation maintenance. Patients in first-line treatment are going to get a platinum doublet for four to six cycles, assuming they’ve had either a complete response, partial response, or stable disease after completion. You can go on and then give them one or two of the agents that they received in the frontline setting as a maintenance treatment.

For example, if they got carboplatin/pemetrexed frontline, you can continue the pemetrexed alone as maintenance treatment. If they received carboplatin/pemetrexed/bevacizumab, you can continue the pemetrexed/bevacizumab as maintenance. And so that’s the concept of continuation maintenance. There’s also switch maintenance; we have some data for pemetrexed/docetaxel in an erlotinib setting -- again, patients are going to get platinum doublet for four to six cycles. Assuming they have achieved at least stable disease at the end of that, you can actually do switch maintenance with pemetrexed assuming you didn’t use it in the frontline setting, docetaxel or erlotinib.

And then there’s this concept of early second-line therapy, which is really done in an attempt to delay disease progression and perhaps to be able to offer drugs that a patient may not have been able to receive when they actually developed disease progression due to poor functional status related to disease burden. And so that’s something that’s now being looked at and more commonly being done for certain patients; again, kind of having the conversation with the patient, discussing these different options. A lot of times our patients after they’re
done with first-line treatment don’t really want to be continuing on chemotherapy, and so this is an individual choice. You know, we have data to support it; it’s not really the right thing for everybody.

Speaking of second-line therapy, this is the REVEL study. This is looking at ramucirumab in non-small cell lung cancer; again, a phase III study, stage IV, non-small cell lung cancer patients who had progressed after first-line platinum chemo. Over 1,200 patients were randomized to receive docetaxel plus placebo or docetaxel with the addition of ramucirumab, which is an IgD antibody targeting the VEGF receptor 2. And results from this study actually indicated a 1.4-month survival benefit for those patients receiving ramucirumab, leading the FDA to approve this drug in December 2015.

Moving on now to targeted agents. Just a little bit of background on EGFR mutations. We know that EGFR mutations are found in 10 to 15% of all non-small cell lung cancers. They do predict responsiveness to EGFR tyrosine kinase inhibitors, namely erlotinib, gefitinib, or afatinib. EGFR mutations occur more commonly in never smokers, in patients with adenocarcinoma histology, in women, and in patients of Asian ethnicity. They’re predominantly located in EGFR exons 18 through 21, so 85% of EGFR mutations are either deletions in exon 19 or are a single point mutation in exon 21, which is the LA58 arm mutation.

The specific EGFR mutation identified is actually quite important because we know that there are sensitive mutations, there are primary resistance mutations, which are often in exon 20. And these are the patients you’re not
going to necessarily be wanting to offer any EGFR TKI to in the frontline setting. And then there are required resistance mutations, such as T790M.

This is the I-PASS study. This is really a landmark study when it was published in the *New England Journal of Medicine*. This was looking at first-line gefitinib versus carboplatin/paclitaxel. This study was a phase III and involved previously untreated patients with advanced lung cancer, all with adenocarcinoma and never or extra light smokers. They had a performance status of 0, 1, or 2; over 1,200 patients were randomized to receive either gefitinib 250 mg PO daily, or carboplatin and paclitaxel. And remember, again, gefitinib is an EGFR tyrosine kinase inhibitor.

And what you can see here, in the overall study population the survival curves clearly crossed, indicating really there didn’t seem to be any difference between the gefitinib and the carboplatin/paclitaxel arms. When you look in that second square, specifically in the EGFR mutation–positive patients, there is a clear difference here. Those patients receiving gefitinib clearly did better with progression-free survival compared to those who received carboplatin/paclitaxel. This was really practice changing; this led to us looking for EGFR mutations and offering the mutation-positive patients gefitinib up front as opposed to chemotherapy.

In the EGFR mutation–negative group, which is in the C category, progression-free survival actually favored those patients receiving the carboplatin/paclitaxel, again, really changing the way we practice in the negative
patients. We’re not going to be offering gefitinib or any EGFR TKI; these are the patients that should be getting platinum doublet chemotherapy up front.

So, afatinib is another EGFR tyrosine kinase inhibitor that was studied in the LUX-Lung 3 and LUX-Lung 6 studies in comparison to chemotherapy. And in these studies there appeared to be a clear benefit of afatinib compared to chemotherapy in the frontline setting in EGFR mutation–positive patients. And what was also really interesting here was that in those patients who specifically had an exon 19 deletion in EGFR, these patients had even more pronounced survival benefit with afatinib as compared to chemotherapy. We’re seeing 33.3 months survival in the LUX-Lung 3 study with afatinib compared to 21.1 months with chemotherapy; hazard ratio 0.54, so a really dramatic difference. Again, just adding to the data for EGFR TKI treatment for mutant-positive patients as frontline treatment.

I did also want to mention the toxicities. Although these drugs tend to be fairly well tolerated compared to traditional IV chemotherapy, they do have side effects that need to be managed. The most common toxicities are acneiform rash and diarrhea, and they tend to be mild to moderate in most cases and require therapeutic intervention in about 30% of cases. We know that proactive management can actually decrease severity and maximize treatment outcome.

And there’s been some studies that have shown that rash can predict responsiveness to treatment and may be associated with longer progression-free and overall survival. But I should mention here that although this may be true for many of our patients, not all patients who are responding are going to be
exhibiting a rash and not all patients who develop a rash will necessarily be responding to treatment. There’s a definitive caveat here.

Disease progression on an EGFR TKI -- this is an important concept. We know that EGFR TKIs, while they’re effective in EGFR mutation–positive patients, they’re really not considered to be cures because, unfortunately, most patients will develop resistance to these drugs after about a year on treatment and that varies. There are some patients who will develop resistance much sooner than a year, we have other patients who are on these treatments for years.

The standard now is to perform a biopsy either in the tissue, blood, or even urine to look specifically for T790M, which is found in about 60% of cases. And the reason that this is done is because we have a new oral chemotherapeutic drug that’s been found to be effective in those patients who have acquired a T790M mutation, which I’ll speak to in more detail in a few slides.

First, here is the IMPRESS study that looked at whether there’s benefit to continuing an EGFR TKI beyond disease progression. In this study, phase III, stage IV, EGFR mutation–positive patients who had prior disease control with first-line gefitinib and recent disease progression, 265 patients were randomized to receive second-line treatment with cisplatin/pemetrexed plus placebo, or cisplatin/pemetrexed with the continuation of gefitinib beyond disease progression. And what you can see here, there’s clear overlap between the curves, which really shows that there’s no benefit to continuing the EGFR TKI
beyond disease progression. It’s not something that we’re commonly practicing these days.

This is the drug that I had mentioned to you earlier, osimertinib, which is a third-generation EGFR TKI. This is a waterfall plot that was published just recently in the *New England Journal of Medicine*. And what you can see here and what’s striking is the responses that we’re seeing with this drug, particularly in those patients who have an EGFR T790M mutation. Response is 61% in that patient population. The response rate is much lower, 21%, in the EGFR T790M-negative patient population. The FDA ended up approving this drug about a year ago in November 2015, specifically for those patients who have known T790M.

Alison will discuss our second case.

ALISON  This is Mrs. G, 46-year-old Asian woman who initially presented with worsening back pain back in October of 2013. At that time she had a left hilar mass, mediastinal lymph nodes, multiple bony metastases, and a brain MRI revealed a 2.3 cm left parietal metastasis. She initially underwent bronchoscopy and L4 biopsy, which revealed adenocarcinoma, TTF-1 positive. And there is an association with EGFR mutations, [they] do typically tend to be found in TTF-1-positive histology, and so it helps you predict, if somebody is negative, that maybe they’re not going to have an EGFR mutation, you still do the testing.

She did not actually have enough tissue from those biopsies to do the testing, but there was resection of her left parietal mass, and ultimately molecular testing did reveal an exon 19 deletion and EGFR. She went on to have standard
first-line therapy with erlotinib at 150 mg. And you may consider selecting afatinib in this setting, and it’s really a discussion with the patient because the side effects are sometimes more severe or challenging to manage with afatinib.

And for her socially, really important to her was her appearance. She did develop rash, which was not terrible to manage, but we weren’t able to manage it sufficiently and so we ended up dose-reducing her to 100 mg daily knowing that that would decrease those side effects and that even in much lower doses these exon 19 deletions and exon 21 point mutations tend to be very sensitive to these drugs.

She stayed on therapy for about 13 months, ultimately developed new progression in the brain; multiple teeny, tiny brain metastases. And, you know, we were faced with the question of, do we treat her with whole-brain radiation at that point? And oftentimes for our patients who do have a targetable mutation, going straight to whole brain isn’t always the right answer because these people might live for a very long time and ultimately end up developing some long-term sequelae from the whole-brain radiation. So, whenever it is appropriate, we do try to put that off for as long as possible.

For her, we started pulsed-dose erlotinib; there are several different schedules out there. And we actually did a very low-dose pulse for her, but, still, that rash came back up and that wasn’t tolerable for her. So we switched her to what is considered our standard type second-line treatment at that point, but our first-line treatment in people that don’t have these mutations, carboplatin/pemetrexed and bevacizumab, knowing that pemetrexed and
bevacizumab both have good CNS penetration, we might achieve control in the brain by choosing these drugs, and continued her on maintenance. Ultimately, she was able to stay on this therapy for 10 months with good disease control, good quality of life, until she developed further progression in the brain and the body in November of last year.

At that point, she did develop question of leptomeningeal carcinomatosis, and we were again faced with this question, do we do whole-brain radiation now or not? And at that point, our institution had an investigational systemic therapy that had good CNS penetration, actually had a cohort for leptomeningeal carcinomatosis, so we gave that a try. But, unfortunately, she progressed through that, had significant clinical decline in that period of time with worsening of her leptomeningeal disease, worsening mental status, balance issues, and really developed intractable nausea, vomiting, and severe headaches.

In this interval, the osimertinib hadn’t become available, so we did a blood biopsy looking for the T790M mutation, and she was found to be negative. So knowing that there is still a chance of response, but that chance of response was much less, we couldn’t rely on osimertinib, which also has great penetration into the brain. To control her disease or possibly improve her disease at that point, we did go ahead with whole-brain radiation and started osimertinib with the hope that she’d be one of those 20% of people that might respond with a negative mutation, negative T790M. And fortunately she did; she had a great response in the body. We see her lung mass has significantly decreased here. And we also saw a good response in the brain.
I want to take a minute and talk to you guys a little bit about leptomeningeal carcinomatosis, or LM disease, because it is something that we really are seeing more frequently in our patients who are on targeted therapies for prolonged periods of time. This is a space that tends to be a safe haven for cancer that the doses of medication don't get into as well and in as high a concentration. And so we are seeing this kind of rare side of metastasis much more frequently in this patient population.

When you’re looking at a scan and you’re trying to identify this, it’s best to be in the T1 axial post contrast series; you’re most likely to see it there. And it often ends up looking like this kind of fuzzy linear pattern of growth along the folds of the brain. If you have high enough clinical suspicion and it’s not caught on a brain MRI you’ve ordered, I would recommend calling the radiologist and asking them to take a closer look if you haven’t specifically written that in your order because it is a subtle finding. It can be confused with blood vessels, and it’s a very difficult diagnosis to make oftentimes. One is based on your clinical suspicion: are they having global cognitive changes? Are they having new symptoms that might be related to pressure issues? Are they having isolated cranial nerve deficits? Things like this might specifically alert you to have this on your differential.

You would consider a lumbar puncture. These are on the first pass 50 to 60% false-negative rate. So you're going to determine if you think a second lumbar puncture is worthwhile, or are you just going to base your decision making on a high clinical suspicion?
There is the option to treat -- people with lung cancer, with leptomeningeal disease, many of the intrathecal chemotherapies aren’t really specific and are not often very helpful. So, we think about doing things like pulsed-dosing their targeted therapy if that’s a safe option, or think about what systemic therapies could we treat them with, or treat with whole-brain radiation, depending on their performance status.

DR. DAS Moving on now to ALK rearrangements, just a little bit of background: ALK rearrangements are found in 4 to 5% of non-small cell adenocarcinoma patients. They do tend to occur more frequently in younger patients who are light or never smokers. There seems to be a slight male to female predominance, and ALK rearrangements predominantly involve a fusion of ALK with the EML4 partner oncogene and they are felt to occur mutually exclusive of EGFR mutations. If you get an EGFR mutation that comes back positive for a patient, you’re not going to generally be testing for ALK or other mutations. These mutations do tend to occur mutually exclusive of one another.

This is a waterfall plot showing dramatic activity of the ALK inhibitor crizotinib in ALK-positive patients. This was a phase I study which led to this phase III study on this next slide, the PROFILE 1014 study, which compared crizotinib versus pemetrexed platinum in advanced ALK-positive lung cancer. Before crizotinib we were generally using IV chemotherapy with pemetrexed-containing regimens in our patients with ALK-positive disease. This study really wanted to ask whether there was some benefit in giving the targeted drug up front compared to chemotherapy.
What we’re seeing here is a clear progression-free survival benefit for those patients receiving crizotinib over chemotherapy as frontline treatments in patients harboring an ALK translocation. And this is really, again, practice changing [and] got a lot of us to start offering the ALK inhibit up front for our patients with ALK rearrangements.

Ceritinib is a novel ALK inhibitor with greater potency compared to crizotinib. This was also looked at in a phase I study; again, the waterfall plot shown here and, again, dramatic responses. What we’re seeing here is that the anti-tumor activity was actually independent of prior ALK inhibitor therapy -- great option for patients who you’ve treated with crizotinib up front who’ve developed resistance. You now have this other drug that can still work as an oral targeted option. Ceritinib was FDA approved back in April of 2014 based upon this data.

Alectinib is yet another ALK inhibitor that was more recently approved by the FDA in December 2015. This drug showed similar high levels of response in ALK-positive patients who were previously treated with crizotinib. And what’s particularly interesting about this drug is its activity in the CNS, where we’re seeing much higher rates of response than what was seen previously with crizotinib or even with ceritinib. Although the current approval of this drug is really in the crizotinib-refractory setting, there’s a lot of interest in using this drug frontline, particularly in those patients with significant CNS metastases.

I’ll also mention here that the FDA recently approved crizotinib for a new indication in March of this year, specifically for those patients who have a ROS1 fusion based upon this data that was published in the New England Journal of
Medicine. We’re seeing a 72% overall response rate for ROS1 fusion patients who are treated with crizotinib. In this study, 64% of patients were having ongoing responses; median duration of response was 17.6 months, median progression-free survival, 19.2 months.

I’ll also mention now that we’re now seeing other genetic targets that are mutated in lung cancer with targeted treatment options. And this is really what provides the rationale for obtaining next-generation sequencing on tumor specimens. As you know, BRAF is more commonly mutated in melanoma, but we’re seeing this gene mutated in a small subset of lung cancer patients who have a good response to treatment with BRAF inhibitors. Other examples are RET and MET for which we have the drug cabozantinib, which has shown some promising activity.

Summary of the targeted therapies -- recently the FDA has approved a number of different targeted therapies for the treatment of advanced non-small cell lung cancer, including osimertinib, ceritinib, alectinib, and a new indication for crizotinib in ROS1-positive patients.

EGFR TKI therapy is appropriate for first-line treatment for patients with known EGFR-activating mutations. ALK-targeted therapy is appropriate first-line therapy for patients with known EMF or ALK fusion protein. And there are additional agents with activity and EGFR resistance and ALK resistance that are under clinical development. And so with every day that passes, we’re finding more and more targets and companies are working on developing active drugs against a lot of these targets.
Moving on to the last section of the talk -- immunotherapy in non-small cell lung cancer. This has really been the hot, new topic in oncology. It was highlighted at this year’s ASCO meeting as being an exciting new treatment option across various malignancies, including lung cancer.

This is a slide depicting the role of PD-1 and PD-L1 in immune system activation. And this may be familiar to a lot of you, but I’m just going to review it quickly. Normally this is the way in which the immune system reacts to foreign antigens. PD-1 is expressed on a patient’s T cells and binds to PD-L1, which is expressed on a tumor cell. And this leads to an inhibitory effect on the immune system, and this is what normally happens.

The development of inhibitors to PD-1 and PD-L1 actually inhibits this interaction from taking place, which basically puts a stop on this inhibitory effect and allows the immune system to recognize the tumor cells as foreign and to kill the tumor cells. Again, really exciting; you’re getting your harnessing in your immune system to kill the tumor.

One of the immune checkpoint inhibitors that’s gotten a lot of attention is nivolumab. This is the CheckMate 017 study looking at nivolumab in squamous cell lung cancer. This was a study involving patients with advanced squamous cell disease with one prior platinum doublet-based chemotherapy good performance status. These patients were randomized to either nivolumab 3 mg/kg IV every 2 weeks versus docetaxel 75 mg/m² IV every 3 weeks.

The primary endpoint here was overall survival, but the investigators also had some secondary endpoints, including objective response rate, progression-
free survival, efficacy by PD-L1 expression level, and disease-related symptom improvement by week 12. And the results from this study really showed clear benefit in those patients receiving nivolumab over docetaxel, so you're seeing 9.2 months versus 6 months overall survival. This led the FDA to approve nivolumab in March 2015 for squamous cell lung cancer.

When the investigators looked to see whether PD-L1 expression predicted response to nivolumab in these squamous patients, what we see here is that the responses to nivolumab were seen regardless of the degree of PD-L1 expression.

The next study was the CheckMate 057 study, which looked at nivolumab in nonsquamous patients. Again, very similar study design that I’m not going to repeat here. Just looking specifically at the nonsquamous patient population, results again here indicated a survival benefit in those patients receiving nivolumab over docetaxel. The probability of being alive at 1 year was 51% in those patients receiving nivolumab versus 39% in those patients receiving docetaxel. The FDA expanded approval of nivolumab in October of 2015 to include nonsquamous, non-small cell lung cancer.

I will also mention here that the FDA recently made the recommendation for a fixed dosing schedule of nivolumab, so we're no longer really using the 3 mg/kg dosing, the fixed dose is now 240 mg IV every 2 weeks.

Again, the investigators looked at whether degree of PD-L1 expression predicted response to nivolumab, and in the case of nonsquamous histology, it actually did. Patients with higher levels of PD-L1 expression tended to do better
with nivolumab, whereas those with low or no expression, they tended to do better when they got docetaxel.

The other immunotherapy drug that’s gotten a lot of attention in lung cancer is pembrolizumab, which is another PD-1 inhibitor. This drug was approved in lung cancer in October 2015, specifically in patients who had progressed on prior platinum doublet therapy based upon the results of this KEYNOTE-001 study. We see here survival based upon PD-L1 expression, and here the tumor specimens with greater than 50% PD-L1 standing had a much higher survival with pembrolizumab compared to those with lower or no PD-L1 expression, leading the FDA to initially approve this drug specifically in lung cancer patients who have greater than 50% PD-L1 expression.

Although, I’ll mention, again, just last week the FDA changed the label to allow use of pembrolizumab in patients who have greater than 1% PD-L1 expression in those patients who have received prior platinum doublet therapy. This is an evolving field.

I also wanted to include here the late-breaking KEYNOTE-024 study. We included this after submission of our slides only because it was just published recently in the New England Journal of Medicine on October 9. This is a phase III study of 305 patients previously untreated with greater than 50% PD-L1 expression with no EGFR ALK, randomizing these patients to getting frontline pembrolizumab versus platinum doublet chemotherapy. These results were pretty exciting; median progression-free survival 10.3 months in the pembro arm versus 6 months in the platinum doublet chemo arm; hazard ratio 0.50
statistically significant. Overall survival at 6 months 80.2% in the pembrolizumab arm versus 72.4% in the platinum doublet chemo arm; again, hazard ratio 0.60. Response rates were also higher in those patients receiving pembrolizumab; 44.8% versus 27.8% in the platinum doublet chemo arm.

A few weeks ago, October 24, 2016, the FDA approved pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer in the frontline setting with over 50% PD-L1 expressions. This was the first FDA approval of a checkpoint inhibitor for a first-line treatment of lung cancer -- really exciting.

Although these new immunotherapy drugs tend to be very well tolerated without most of the traditional side effects of IV chemotherapy, such as myelosuppression or nausea/vomiting, these drugs have a unique side effect profile related to autoimmune phenomenon, as shown here. Patients can develop thyroiditis, adrenal insufficiency, enterocolitis, dermatitis, hepatitis. So it’s really important to be aware of these possibilities when you’re treating patients with these immune checkpoint inhibitors.

The onset of immune adverse events typically occurs 6 to 12 weeks after initiation of therapy, but can occur within days of the first dose or after several months of treatment or even after discontinuation of therapy. So it’s important to keep it in the back of your mind when you’re seeing these patients. Patient complaints should be really considered autoimmune or drug-related until proven otherwise. It’s always important to rule out infections or metabolic causes or tumor effects, but the key here is early recognition, evaluation, and treatment.
These are the general principles of immune-mediated toxicities. But for patients with grade 1 toxicities, you’re generally going to offer support care, consider withholding the drug. And patients with grade 2 toxicity, you’ll go ahead and withhold the drug, consider re-dosing if the toxicity resolves to less than or equal to grade 1, and then consider starting low-dose steroids if the patient’s symptoms don’t improve within a week.

For grade 3 toxicities, you’re going to discontinue the drug. You’re in a position where you’re going to probably have to start high-dose steroids tapered over a month or longer once the toxicity resolves to less than or equal to grade 1.

Moving on to our third case.

ALISON This is Mr. J, a 68-year-old man who initially presented in May 2015, worsening low back pain radiating down his right leg and urinary incontinence over the course of a month. CT imaging revealed a large mass in the sacrum and ileum 7 x 5 cm extending in the spinal canal with associated pathologic fracture. He also had a right lower lobe mass, other pulmonology nodules, and intra-abdominal metastasis. Biopsy was performed on the right lower lobe mass, as well as he had a partial (indiscernible). Pathology was consistent with non-small cell favoring adeno. It was CTF1 positive, but mutational testing was negative despite being a never smoker. He had a stage IV T2a, N2, M1b, among adenocarcinoma.

We treated him initially with palliative radiation to alleviate his pain and started first-line therapy with carboplatin/pemetrexed. He was pretty debilitated at
this point, but initially saw perhaps a mixed response after two cycles and went on to give him four cycles, which showed clear progression.

We started second-line therapy with nivolumab at that point. We didn’t do PD-L1 testing; nivolumab doesn’t have a diagnostic test associated with it. And we did give him some additional radiation because he has progressive pain. His course with nivolumab was actually initially complicated by anemia related to a GI bleed requiring very frequent transfusion, and then [he] developed a small bowel obstruction requiring two admissions. And so we were initially quite concerned that maybe he was just progressing through this or potentially, you know, it’s a pseudoprogression, he was having some worsening symptoms from his intra-abdominal disease initially.

Luckily for us he actually ended up having a slight response in his main mass and a clear response in his small bowel mass, which eventually his symptoms did resolve and improve and we weren’t facing that decision of, is this pseudoprogression or progressive disease when we ultimately saw his imaging. And he’s done actually remarkably well since that time. He’s been on treatment now for 14 months and is enjoying a pretty good quality of life considering how debilitated he was when we met him.

DR. DAS Summary of immunotherapies and nivolumab -- the PD-1 inhibitor has been approved for the treatment of both squamous and nonsquamous non-small cell lung cancer. Pembrolizumab, another PD-1 inhibitor, has been approved for the treatment of squamous and nonsquamous non-small cell lung center in both the frontline setting and in the relapse setting.
There is a companion diagnostic looking at level of PD-L1 expressions, so in the frontline setting, patients are required to have over 50% PD-L1 expression and are to be able to receive this drug. In the relapse setting, the threshold has now been dropped to greater than 1%.

Tumor PD-L1 expression may be a useful biomarker, especially in the nonsquamous patients, and there are other biomarkers that are now being explored, including resistance mechanisms. And a number of other immune checkpoint inhibitors are being studied, including atezolizumab, which is a PD-L1 inhibitor in lung cancer, with promising results. And I’ll go ahead and mention here that atezolizumab was also just recently approved by the FDA on October 18, 2016 in a second-line and beyond setting based upon encouraging phase III data, which I didn’t review in detail here only in the interest of time.

This is clearly a very, very exciting time in the treatment of lung cancer with many recent drug approvals. We really need to now sort out the various platforms that are available for PD-L1 testing to determine appropriate cutoffs for the various immune checkpoint inhibitors that are available. And, ultimately, the goal is going to be to individualize treatment for our patients based upon specific biomarkers or genetic alterations, leading to greater efficacy of or treatments, which will correspond hopefully to improve survival.

Overall conclusions from today’s talk -- for the vast majority of patients, histology still guides therapeutic choice. For patients with stage IV lung cancer and adenocarcinoma, component molecular testing is the standard of care. It’s always important to factor in a patient’s age and performance status when
determining a treatment plan and to become familiar with how to manage the treatment-related adverse events, whether you’re dealing with IV chemotherapy, the oral-targeted agents, or the immune checkpoint inhibitors.

And there have been a number of new FDA approvals for the treatment of metastatic non-small cell lung cancer. Again, I had to update this last week with so many of these new approvals in October. Ramucirumab has been approved, nivolumab, pembrolizumab now in the frontline setting, osimertinib, necitumumab, alectinib, crizotinib with this new indication in ROS1-positive patients, and finally, atezolizumab.

And that’s it. I’ll take any questions now.

FEMALE Thank you for this presentation. Do you mind walking us through the steps in terms of therapy that you would offer? For example, the patient comes in who was diagnosed with metastatic adenocarcinoma and has PD mutation. You did all the testing, and there is a PD mutation present. The patient has good performance status, no autoimmune disease -- what would push you for the patient to start pembro versus doublet chemotherapy?

ALISON I think it really depends on what is their level of expression of PD-L1. If it’s over 50%, that indication is now there and you can do pembrolizumab as first-line therapy.

FEMALE If it is more than 50%, would you consider then pembro versus chemotherapy?

ALISON Yeah.
DR. DAS I think if you’re going to offer patients the option of pembrolizumab or IV platinum doublet, those patients are going to choose the immunotherapy option. So the question now becomes what if you get somebody with 42% PD-L1 expression? What would you do with that patient?

And this is where I don’t think we have the answers yet. I think a lot of us would still want to, perhaps, give pembrolizumab in the frontline setting even though the FDA label is really specifically for patients over 50%. And so sometimes, again, depending on a patient’s performance status, you can make an argument that they may not be able to tolerate IV chemo, and so you can make a case to the insurance company to authorize the pembrolizumab. I think it’s a work in progress. I think that 50% right now, that’s what it is, and this cutoff may change. Other questions?

FEMALE I just wanted to ask, it’s my understanding that a PD-L1 expression greater than 50% is still a fairly small percentage of these lung cancer patients, which is unfortunate. But I think it’s 20 or 25% --

DR. DAS Correct.

FEMALE -- possibly. And there’s still less and they’re not even doing the PD-L1 testing, especially in the community.

DR. DAS I think that’s a great point. Although this is really exciting, it does really affect a small percentage. So you’re right, 20 to 25% of patients are showing that level of over 50% PD-L1 expression.

ALISON I think the level of PD-L1 expression helps guide you in where do you place this treatment option in these multiple lines of therapy, and
you have to consider what is their targetable mutation, what’s their PD-L1 expression level, what’s their performance status, and how are you going to order these? For somebody that maybe has one of those more medium levels PD-L1 expression, 30%, maybe you’re in more of a gray area of offering that chemotherapy first. And insurance may force your hand on that, but it may help you to say, “Well, let’s try that second-line because that indication is there too.”

[END]