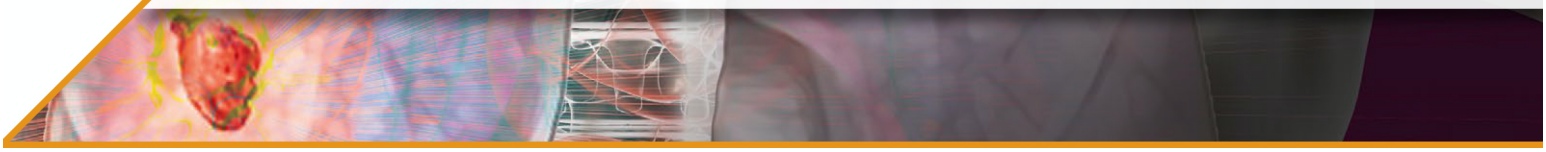
Optimizing Patient Outcomes in Advanced NSCLC in a Rapidly Evolving Treatment Era



Karen Reckamp, MS, MD: This is first-line treatment for advanced non–small cell lung cancer without targetable activating mutations. We are going to focus on nonsquamous non–small cell lung cancer with some of the data in squamous cell. And we'll talk about single-agent checkpoint inhibition, checkpoint inhibition with chemotherapy, and then dual checkpoint inhibition with or without chemotherapy.

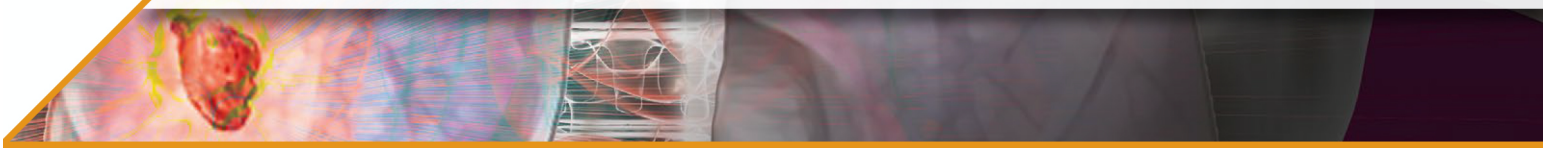
And here are our approved options, FDA-approved options for first-line therapy for these patients without actionable mutations. And it's pretty impressive here, and we'll be talking about each of these specifically. But this is just to show you that there are a lot of options, all of which are FDA approved and potentially reasonable options for these patients.

The NCCN Guidelines do help us some. Again, for patients who have high programmed cell death ligand 1 (PD-L1) expression, greater than 50%, pembrolizumab and atezolizumab as single agents are preferred options but also the combination of platinum/pemetrexed/pembrolizumab. Other recommended are the combinations of carboplatin/paclitaxel/bevacizumab/atezolizumab, carboplatin/albumin-bound paclitaxel/atezolizumab, and then the nivolumab/ipilimumab/pemetrexed/platinum, or the nivolumab/ipilimumab combination in certain patients.

For those that are 1% to 49%, generally we steer away from single-agent immune checkpoint inhibition. And so, the preferred here, again, for nonsquamous, is platinum/pemetrexed, but we also do have the other combinations, including bevacizumab, the atezolizumab combination, and the nivolumab/ipilimumab/chemo, or nivolumab/ipilimumab alone.

The single-agent data started with the KEYNOTE-024 study, which was a first-line trial, untreated patients, *EGFR*/*ALK* wild type, and patients had to have PD-L1 expression of greater than 50%. This was both in squamous and nonsquamous histologies. Patients received pembrolizumab for up to 35 cycles, or platinum-based doubled chemotherapy with the use of maintenance therapy as per investigator. The primary endpoint was progression-free survival (PFS); overall survival was the secondary endpoint.

The overall survival has been updated, and significantly favors the pembrolizumab arm over the chemotherapy arm, 30.0 months to 14.2 months. PFS also significantly better, 10 months versus 6 months. The response rates



still are not spectacular. They're still about 45% of patients. In looking at responses, if a patient needs a more dramatic response, then immunotherapy alone might not be the right option. But this was the first study to show us that immunotherapy alone could be reasonable in patients, at least with high PD-L1 expression.

Adverse events are what we are going to see for most of these studies, that there are serious adverse events in both groups, generally less in the immunotherapy arms. But events tend to be slightly different. Cytopenias and nausea for patients receiving chemotherapy, with more immune-related toxicities, as you see at the bottom row. 30% of these were immune-related toxicities for the pembrolizumab arm.

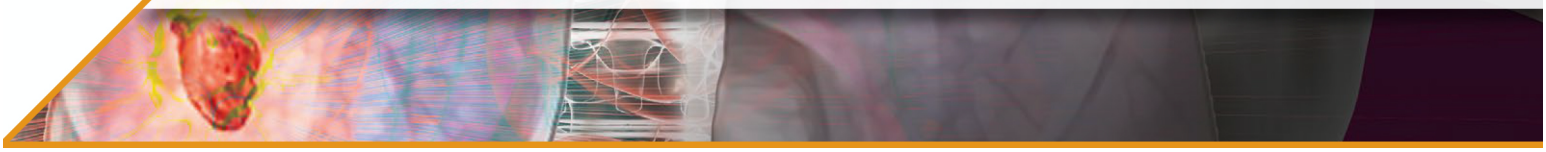
KEYNOTE-042 took a look at patients with PD-L1 expression greater than or equal to 1%. And it was a similar trial, looking at pembrolizumab versus chemotherapy. And they had overall survival endpoints in those with tumor proportion scores over 50%, 20%, and 1%. And each group included the group in front of us. They were stratified by their region, ECOG performance, histology, and PD-L1 status.

Early on there is crossover of the trials. This is looking specifically at the 50% or more, which was more than half of the population. But there was an improvement in median overall survival in this population, 20 months versus 12.0 months.

When we looked at the 20% or more, then we had about 18 months versus 13 months, so the curves are narrowing. When we looked at 1% or more, there was still a survival benefit, 16.7 versus 12.0 months, but the curves again continuing to narrow.

However, in this population, in whom we were most interested in are these 1% to 49%, knowing that the 50% or more, have a benefit, and those are all included in these subsets of the primary analysis. So, in the 1% to 49% group, there was not a statistically significant difference, and the curves cross over each other in the middle. Overall, there was a 13-month versus 12-month overall survival benefit in this group. This was not part of the statistical evaluation of the study.

The PFS was not significantly different in patients with tumor proportion scores >1. It was 5.0 months for the pembrolizumab, and 6.5 months for the chemo. And based on this, there was an FDA approval. Toxicities were similar to what we see



with most of these immunotherapy alone trials. A very small number of patients had pneumonitis and about 28% had immune-related adverse events.

So that led to an FDA approval. However, for most patients with 1% to 49%, we prefer to give more active regimens that include some chemotherapy.

IMpower110 was the single-agent atezolizumab trial compared to chemotherapy. And these were patients with PD-L1 high expression, tumor content or immune cell content three. Patients received atezolizumab or chemotherapy depending on histology; the primary endpoint was overall survival in the wild-type population.

This is another study that in these tumor cell or immune cell three cohort had a significant improvement in overall survival, 20 months versus 13 months. This led to an FDA approval.

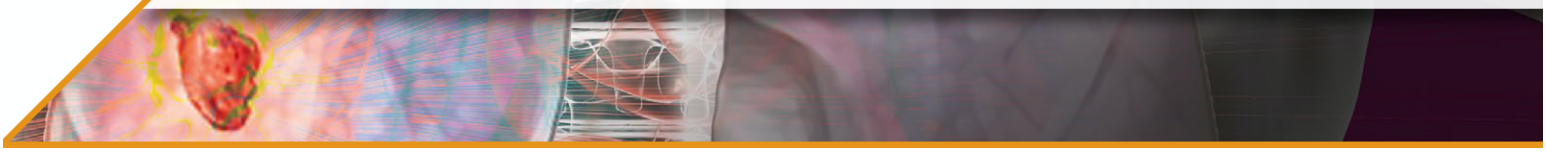
Grade 3 to 4 toxicities were significantly higher with chemotherapy, which is similar to what we see with other single-agent immunotherapy drugs. The majority of toxicities with atezolizumab are immune related.

If immune therapy, immune checkpoint inhibition by itself is good for some patients, how about adding it to chemotherapy? The thought is that the chemotherapy can help to release tumor-associated antigens and enhance the antigen presentation as we improve the T-cell response.

In the KEYNOTE-189 trial, these were patients with metastatic, nonsquamous, non–small cell lung cancer, *EGFR*/*ALK* wild type, and they were randomized to chemotherapy plus pembrolizumab, or chemotherapy with platinum/pemetrexed on its own. The primary endpoints were overall survival and PFS.

The overall survival, was significantly improved in patients with the combination. The median was not reached, versus 11 months in the chemotherapy-alone arm; the hazard ratio was 0.49.

Looking at PD-L1 status, what I think is important here is that regardless of PD-L1 status, there's significant benefit in median overall survival. They do get wider as PD-L1 expression increases. So, patients with high PD-L1 definitely benefit, and they benefit even more significantly with the combination of chemo and immunotherapy.



The hazard ratios based on PD-L1 status were significant across all PD-L1 statuses.

Most patients have some adverse events, with about two-thirds of patients having grade 3 to 5. Both groups had similar adverse events that led to death, about 6%. Discontinuation was slightly higher in the pembrolizumab arm. Immune-related adverse events were significantly higher in pembrolizumab arm, about 23%. Only 9% were grade 3 to 5, and very few led to death. Overall, the therapy was well tolerated, and is one of our go-to regimens for nonsquamous, non–small cell lung cancer.

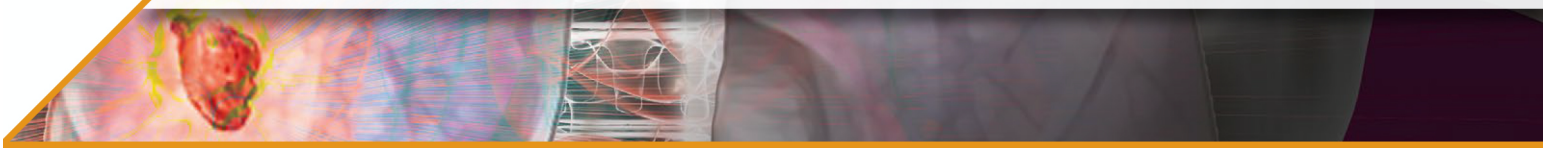
Moving to the squamous arena, the KEYNOTE-407 involved metastatic non–small cell lung cancer without prior therapy with squamous cell histology. These patients received carboplatin with either paclitaxel or nab-paclitaxel with pembrolizumab, or placebo. The primary endpoints were overall survival and PFS.

Here we see again the significant improvement in median overall survival, about 16 months versus 11 months. This is one of the most significant benefits we've seen for patients with squamous cell alone.

Looking again at the PD-L1 tumor proportion score, we see significant improvement in overall survival across all PD-L1 statuses. Here, there was less difference based on PD-L1 status. So, all patients are benefitting significantly.

As far as adverse events are concerned, we see most patients have some adverse events. Those leading to discontinuation slightly higher for pembrolizumab, but those leading to death or attributed to the trial regimen were low, and similar in both arms. There were more immune-related adverse events, in the range of about 30%, in pembrolizumab arm.

So, if 3 drugs are good, maybe 4 drugs would be better. The IMpower150 trial looked at carboplatin, paclitaxel, atezolizumab, and bevacizumab, and various combinations of these 4 drugs. In one of the arms was the chemotherapy plus bevacizumab alone. One had chemotherapy plus atezolizumab alone. And the other had chemotherapy plus both atezolizumab and bevacizumab. The primary endpoint was PFS followed by overall survival.



PFS was significantly better in the combination atezolizumab/bevacizumab plus chemotherapy over the chemotherapy plus bevacizumab arm, which was the reference arm, 8.0 months versus about 6.8 months.

This combination was allowed for patients who had *EGFR* and *ALK* alterations, if they had received prior therapy for those alterations. This was one of the first trials that allowed these patients.

Patients in all cohorts had a benefit. This was one of the first studies to show any benefit with an immune checkpoint inhibitor therapy in *EGFR* and *ALK* non–small cell lung cancer. There was also significant benefit for patients with liver metastases. However, these numbers are small and more hypothesis-generating.

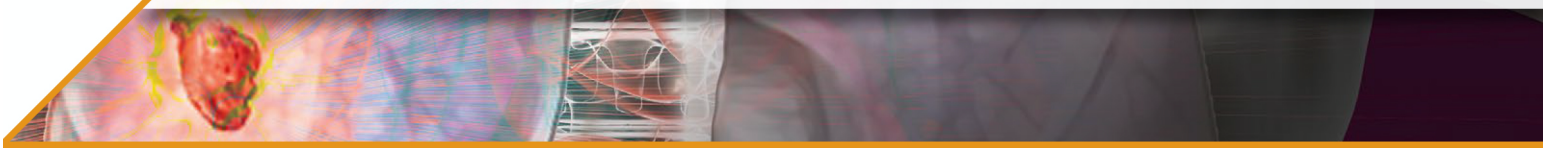
The majority of patients had some adverse events, about 60% with grade 3 and 4, treatment related, about 20% to 25%, immune related, much significantly higher in the 4-drug combination. And double the patients had withdrawal from some of their treatment, about 30% versus 15%. However, the number of treatment-related deaths was low and not significantly different. That was a regimen that is approved for patients without activating mutations. It was not approved for patients with *ALK* or *EGFR* alterations.

Another regimen for all comers for nonsquamous non–small cell lung cancer is the IMpower130 with carboplatin, nab-paclitaxel, and atezolizumab. This was for nonsquamous non–small cell lung cancer patients that received the chemotherapy plus atezolizumab versus placebo, followed by maintenance atezolizumab or best supportive care, or pemetrexed was allowed for these patients. Overall survival and PFS were coprimary endpoints, looking at the wild-type population.

We see significant improvement in overall survival, 18.6 versus 13.9 months in the chemotherapy arm.

Toxicity is very similar to what we've seen before.

If we can use chemotherapy with immunotherapy, and we can use immunotherapy alone, what about getting rid of the chemotherapy and using dual checkpoint inhibition?



This is based on data that first came out of melanoma, looking at CTLA-4 and PD-1 or PD-L1 inhibitors, going both to the antigen-presenting phase, and enhancing the tumor antigen presentation and T-cell effector phase, and improving the T-cell effectors and tumor cell depth from the inhibition of the PD-L1 blockade.

Using both together has worked very well for melanoma. And there have been multiple studies in lung cancer, but the most definitive is probably CheckMate 227. This study has, as you can see here, 3 arms in 2 separate cohorts. And so, there was a specific cohort of PD-L1 expression greater than or equal to 1%, which is where the statistical significance, where the primary analysis was formed. And then, the PD-L1 of less than 1%.

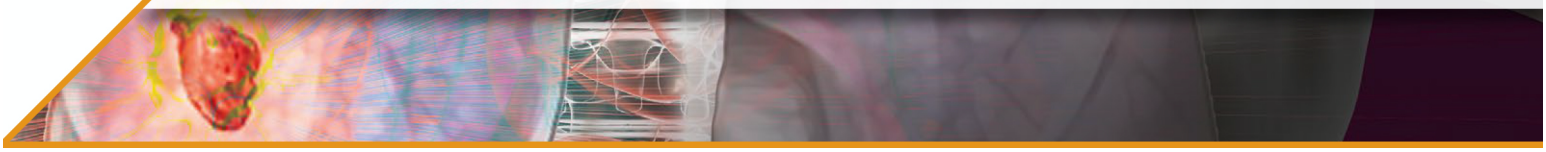
In these combinations, they looked at ipilimumab/nivolumab as a combination. They looked at chemotherapy without immunotherapy as a combination. And then, in the PD-L1 ≥1%, they had a nivolumab-alone arm. And in the PD-L1 < 1%, they had a nivolumab plus chemotherapy arm. In these, they were comparing to the chemotherapy-alone arm. They looked at PD-L1 as their primary biomarker. They also had a secondary coprimary endpoint of PFS in the tumor mutation burden-selected population.

The first analysis with TMB was published in *The New England Journal of Medicine* and showed a benefit based on high TMB, although TMB was not statistically significant in their final analysis. So, the final analysis is really based on the PD-L1 analysis.

In the PD-L1 ≥1%, there was a significant improvement in overall survival for patients who received ipilimumab/nivolumab over chemotherapy. When you looked at the 1% to 49%, there was not a significant difference. Those patients with > 50% had a highly significant difference, which is where possibly more of the benefit is coming from.

Interestingly, there was also a significant difference in those with PD-L1 <1%, although this was not a part of their initial primary analysis. Again, here looking at <1%, 17 months versus 12 months. The FDA approval is based on the PD-L1 of ≥1%.

These patients have more immune-related toxicities in the nivolumab/ipilimumab arm than in the nivolumab alone arm. Overall, there are higher levels of grade 3



to 4 toxicities, and any grade toxicities, but still relatively low grade 3 to 4 toxicities. The highest was about 8% with hepatic toxicity.

If using 4 cycles of chemotherapy with immunotherapy is good, what if you could decrease the amount of chemotherapy that you're giving a patient? The CheckMate 9LA study, which was presented this year at ASCO, and some of the newest data that we have, looked at ipilimumab/nivolumab plus chemotherapy for 2 cycles, versus chemotherapy alone for 4 cycles, with the option of pemetrexed maintenance. The primary endpoint was overall survival.

We see significant improvement in overall survival, 15.6 versus 10.9 months for the nivolumab/ipilimumab plus chemotherapy arm.

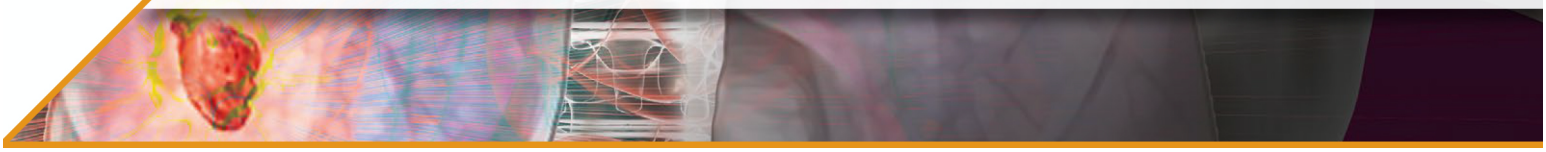
Toxicities are more significant with the nivolumab/ipilimumab/chemotherapy arm, and those leading to discontinuation and serious toxicities are also much more frequent, although treatment-related deaths were similar in both arms. This led to an FDA approval of combination ipilimumab/nivolumab, and 2 cycles of frontline chemotherapy.

Moving on to selection of therapy for these patients without targetable activating mutations, once they progress on platinum-based first-line therapy, assuming again, most of these patients have progressed on immunotherapy also.

For about a decade, we had platinum-based doublet plus or minus bevacizumab, and this was our preferred first-line approach. We generally used a platinum-based doublet, based on toxicities we thought were compatible with a patient's underlying comorbidities, but we didn't have a lot of good options for patients.

But now, almost all patients will receive immunotherapy in the first line. So how do we treat these patients if they didn't receive immunotherapy in the first line? Maybe some of them began prior to the approvals, or for some reason didn't get it but could be eligible. How do we treat patients who progress on chemoimmunotherapy? Are there patients who may benefit less from immunotherapy?

Looking again at the NCCN Guidelines and subsequent therapy for patients with non–small cell lung cancer without activating mutations, we have the 3 immunotherapies that were approved based on the second-line setting, all category 1, nivolumab/pembrolizumab for PD-L1 ≥1%, and atezolizumab. Most of



these patients now are starting on immune checkpoint inhibitors, and so those are not going to be preferred for most patients. Now we're back to what we had 20 years ago, docetaxel pemetrexed if not used in the front line, gemcitabine, and then the combination of ramucirumab and docetaxel.

This is looking back at the original data when all of the drugs we're looking at, immunotherapy, checkpoint inhibitor versus docetaxel. Nivolumab was looked at in both squamous cell and nonsquamous cell separately. Pembrolizumab was assessed specifically in patients with PD-L1 ≥1%, and atezolizumab in all comers.

All of them were set up in similar ways, even though they all had discrete populations. And patients had disease progression on a prior platinum-based therapy.

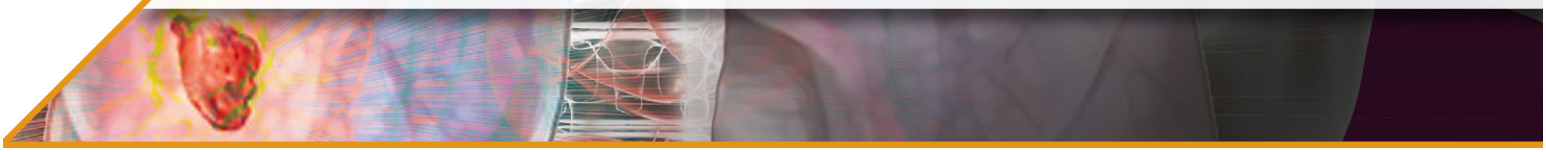
This is looking at the overall survival curves for all of these. Despite the fact that not all showed improvement in PFS, or showed significant benefit in response rates, overall survival was improved across the board. The top left is nivolumab in the squamous cell population, followed by the top right, which is pembrolizumab, and that's looking at multiple PD-L1 statuses. And then the OAK trial with atezolizumab on the bottom left. And then CheckMate 057 with nivolumab on the bottom right, with the nonsquamous population.

They all showed an improvement in overall survival, with very modest response rates across the board. And they all were approved.

This is showing the key elements as we discussed, that pembrolizumab required PD-L1 ≥1%, nivolumab separated by histology, and atezolizumab did not restrict on PD-L1 or histology.

We do have some longer-term survival results in these patients. Despite the fact that response rates were not spectacular, and that in some cases, PFS was minimally improved, there are some patients who have significant overall survival. For the previously treated, it's about 10% to 20%, highest in the PD-L1 ≥50%.

Most of our patients are going to have had immune checkpoint inhibitors as frontline therapy, so we really need to look at something that will benefit a patient post-immune checkpoint inhibitor therapy. And so, one addition is ramucirumab,



which was approved, in 2014, in combination with docetaxel, for disease that progressed after platinum-based therapy.

This is second-line therapy. They received the combination of ramucirumab and docetaxel or placebo plus docetaxel. And the primary endpoint was overall survival.

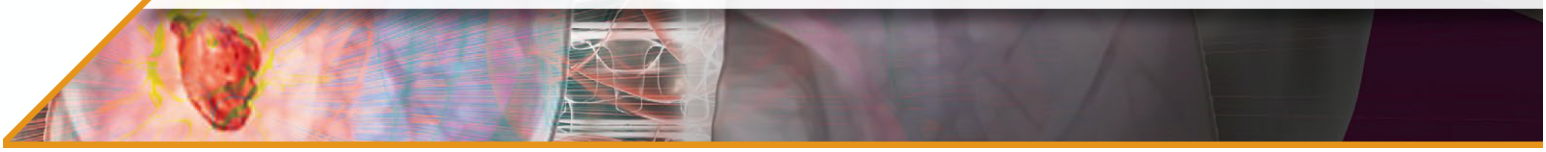
There was a 10.5-month median overall survival versus 9.0 months, which was statistically significant and remained true across the time period.

So, there is a statistically significant improvement in overall survival. I think what we also see is that the response rate goes up to almost 25% versus about 15% for patients on docetaxel alone. There is a longer PFS, 4.5 versus 3.0 months, a longer overall survival, and improvement in the response rate. So, for patients who can tolerate the conservative therapy, definitely something to be thinking about.

As you might expect, we do see more toxicities, but any grade and greater than grade 3 were very similar across the board. There were more patients with cytopenias and febrile neutropenia, and then things like hypertension that you see, and proteinuria that you see with the VEGF inhibitors.

Heather Wakelee, MD: When we first found the EGFR TKIs, gefitinib was first being developed. We didn't know about *EGFR* mutations at that time. We just knew that certain groups of patients seemed to be having better responses, and they tended to be people who developed lung cancer as never-smokers, more often were women, and often tended to be Asian, either in Asia, or of Asian ancestry.

So, the IPASS trial was launched, looking at gefitinib, the first EGFR TKI that was developed, versus standard chemotherapy. If you look at the bottom of the slide, in panel A, you see that PFS for all comers, these curves were crossing, and it was a little bit confusing. As this trial was being conducted, it was discovered that about 10% of all patients with non–small cell lung cancer have an activating mutation in *EGFR*. Those percentages are much higher in people who are non-smokers, especially if you're a never-smoking Asian woman with newly



diagnosed lung cancer, you have about a 60% chance of it being an *EGFR*-mutant lung cancer.

So, when they went back and analyzed this trial, and divided the tumors into those that had the *EGFR* mutations, and it was about 60% of patients on trial, versus those who did not, that's panels B and C. So, if there was a mutation that gefitinib was clearly better than chemo, that's panel B. And panel C, if you did not have the mutation and you got an EGFR TKI, you did very poorly; there was rapid progression.

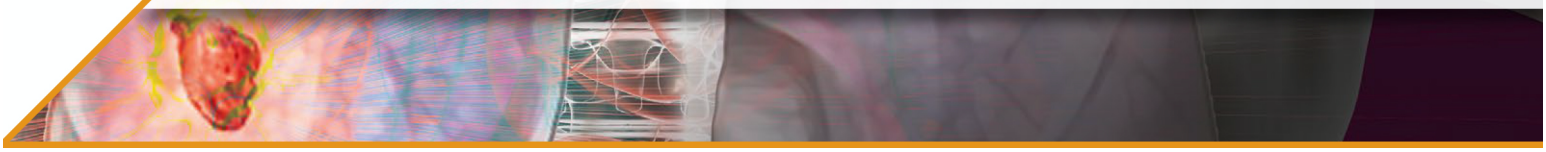
This really totally changed our paradigm of how we treat newly diagnosed non–small cell lung cancer, with the idea that we've got to look for those *EGFR* mutations. We've now expanded that, so we've got to look for about 10 different mutations to make sure that we're giving patients the right treatment because this was the first study to show that when there is a targetable mutation, the targeted agent is better than chemo. We've seen that over and over again. As far as we can tell from the data that exist, that also holds true for when we're giving immunotherapy, which is not going to be as good as giving targeted therapy.

Why don't we just start with the chemo and immunotherapy, and then if they have a mutation in their tumor, we can switch to the targeted therapy? The danger with that is that once you've given immunotherapy with a PD-1 or PD-L1 checkpoint inhibitor, that stays around in the system for a number of months. Many of the TKIs interact very poorly with the immune checkpoint inhibitors, whether it's concurrently, or whether the immune checkpoint is still in the system.

With osimertinib, there's a very high rate of pneumonitis. With some of the other drugs, high rates of hepatitis. So, it's actually potentially harmful to just give a patient an immune checkpoint inhibitor while you're waiting for those molecular results. Much better to just hold on another week or 2, get your results, and then you know how to move forward.

The IPASS trial showed that targeted therapy was better than chemo when you identify a target, especially EGFR. That's now been shown in multiple other trials that were TKI versus chemo in the setting of EGFR, and every one of these responses and PFS are markedly better.

Then the question becomes which TKI should we be giving? Is there a better one? For the NCCN Guidelines, you can see that osimertinib is the category 1



preferred. That's from the FLAURA trial, which I'll go through. But we still have these other options—erlotinib, afatinib, dacomitinib, gefitinib, and erlotinib plus ramucirumab. And these are the first- and second-generation drugs, or first-generation plus VEGF or TKI, and then there's some other choices too.

One of the trials that was looking at which TKI is best compared gefitinib, the first EGFR TKI, a first-generation drug, versus dacomitinib, a second-generation drug. This was the ARCHER 1050 study. You'll notice that this trial did not include patients with brain metastases. They were looking particularly at PFS.

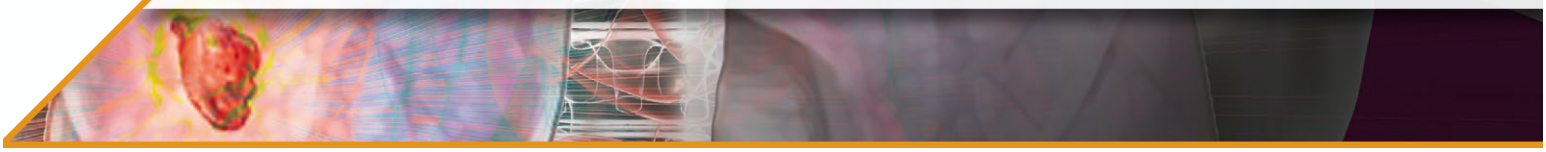
Dacomitinib clearly was superior to gefitinib for PFS. And it actually had an overall survival benefit as well. And people are thinking, well, why don't we hear more about dacomitinib? Part of it was timing. These results came out after we had already heard about osimertinib in the first-line setting from the FLAURA trial.

The other challenge is that with the second-generation drugs, afatinib and dacomitinib, there is more toxicity in regard to rash and diarrhea, and you can see that here on this slide. A lot more issues with diarrhea, paronychia, different rashes, acneiform rashes, some stomatitis, and as well as the only thing where gefitinib looked a little bit worse was with some of the transaminitis.

These are the FLAURA data. The ARCHER 1050 was second-generation dacomitinib versus first-generation gefitinib. The FLAURA trial was third-generation osimertinib versus first-generation either erlotinib or gefitinib. As shown on this slide, there was a very striking PFS benefit, over 8 months improvement, hazard ratio of 0.46. And this was true across all of the subsets.

And when we look at overall survival, there was actually a statistically significant improvement in overall survival. There's still a debate about why not start with a first- or second-generation drug. And then at the time of progression, switch over to osimertinib. Because we know that when you use a first- or second-generation drug, around 60% of the time, the resistance will be the T790M mutation, which osimertinib can target.

So, you can get activity with osimertinib if you start with a first- or second-generation drug, and the resistance pathway is T790M. And if in all cases, T790M was the resistance pathway and you could switch over to osimertinib, that would make sense. The challenge we face is that many patients, ≥40% have



other resistance pathways. Or at the time of progression, things happen where they never get to osimertinib. And so, that's where we get this overall survival benefit from starting with osimertinib. And it was this data that led to practice patterns in the United States.

Now, there are a lot of reimbursement issues and other questions that led to different practices around the world. But this is sort of the rationale for why the US data is to start with the osimertinib.

The drug is also overall generally better tolerated, with much less rash, much less diarrhea. But we do need to be mindful of certain toxicities. There is pneumonitis with all of these drugs at low levels. With osimertinib, we do have some cardiac toxicities we need to be mindful of, such as QTc prolongation, and also a very low risk for cardiomyopathy.

So, it's important that patients starting osimertinib have ECGs done very regularly when they're first getting started. And then, also getting echocardiograms. We also sometimes see drops in white blood cell counts as well as thrombocytopenia, so it's important to monitor for those. Those are toxicities we don't always think about with the other TKIs.

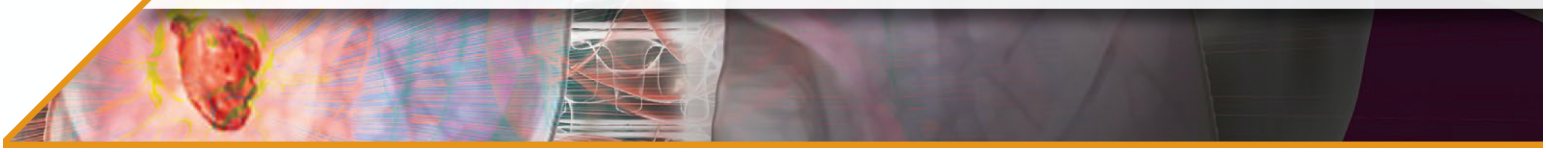
Another point of FLAURA is that it has superior activity in the brain. These charts are showing higher PFS for brain activity, and lower risk for development of brain metastases for patients started on first-line osimertinib.

Here we have that overall survival data showing a statistically significant hazard ratio improvement, and overall survival ratio of 0.8. And so again, in the United States, this is our standard. But there is a lot of variability still as to why one might think about other drugs.

So, we need to think about tolerability, efficacy, and cost.

CNS activity is another factor that we often will think about as well, as that can be quite symptomatic for patients.

This was a phase 2 trial of erlotinib versus erlotinib plus bevacizumab. And this was one of the first studies to look at this combination of EGFR plus VEGF combination in the setting of *EGFR* mutation. If you go back, before we knew about *EGFR* mutations, but we had EGFR therapy, we were looking at combining



with VEGF therapy then, which was pretty exciting. But it never went anywhere because we then started to realize that EGFR therapy really works best when you have the *EGFR* mutation.

This was a study in patients with *EGFR* mutations, erlotinib plus or minus bevacizumab. The PFS was strikingly in favor of the combination. However, when overall survival was looked at, there was no overall survival benefit. So, there was a significant PFS benefit with erlotinib/bevacizumab, and no overall survival benefit.

This is another phase 3 of erlotinib plus or minus bevacizumab, again showing a striking PFS benefit, but we don't have the overall survival yet.

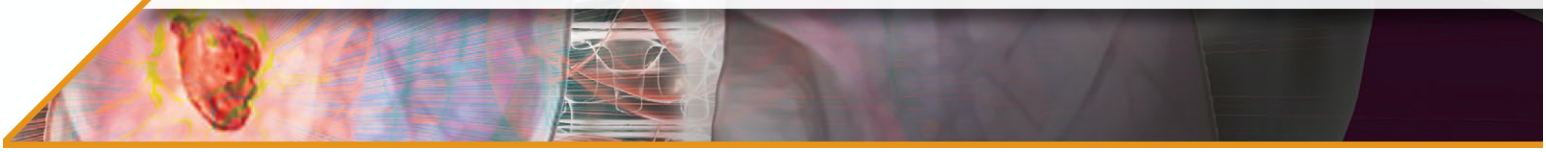
When you combine any 2 drugs, you're obviously going to have more toxicity than with 1 drug. When you add an anti-VEGF agent, bevacizumab in this study, you of course increase toxicities. There was more neutropenia, some hepatic dysfunction, some hypertension, those sorts of things seen as well. But no treatment-related deaths in this study.

The next big trial that was looking at a combination of VEGF agent with erlotinib was the RELAY trial, and that's with ramucirumab. Bevacizumab, of course, is the VEGF antibody. Ramucirumab is the VEGF receptor antibody, which we have approved in combination with docetaxel in the US.

This was looking at ramucirumab with erlotinib in patients with activating *EGFR* mutations in the first line. It did exclude patients with brain metastases, as well as those who had been previously treated. The brain metastases exclusion was based more on theoretical concerns about toxicity, as opposed to lack of efficacy. I'm pretty comfortable giving VEGF agents like bevacizumab in patients with brain metastases.

And this was the schema. It is an every-2-week infusion. So, that's a hassle for patients. They have erlotinib and then ramucirumab or placebo every 2 weeks, and then were followed with the primary endpoint being PFS, which was definitely met.

You can see this striking separation of the curves. Strong PFS benefit, hazard ratio 0.59. We do not have overall survival benefit yet from this trial. Because the PFS was the primary endpoint, it did get FDA approval in May of this year, so it



did make it on the NCCN Guidelines. It is an option. But as Dr. Reckamp talked about with the bevacizumab trials where we didn't end up with that overall survival benefit, here we're seeing this big PFS benefit with ramucirumab. We don't know if that's going to translate into overall survival benefit, and I think that's one of the questions that still remains.

When the RELAY trial was looked at based on whether the patient had an exon 19, or L858R, that didn't seem to matter at all.

When we talk about toxicity, if you add another drug, you're going to add more toxicity. First, you have to think about the toxicity to the patient of having to come in every 2 weeks versus just taking an oral medication. You are also increasing the potential for infections. Of course, hypertension, stomatitis, proteinuria, some alopecia and other issues as well.

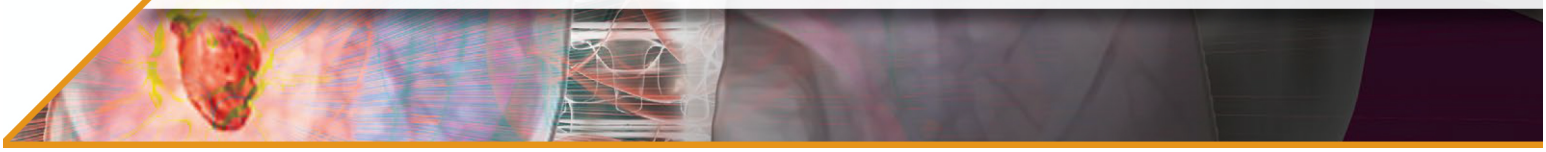
And then some laboratory abnormalities that were increased, as expected to. But generally, this is a pretty well-tolerated combination.

And the next step, of course, is then looking at, well, what about adding VEGF inhibition to osimertinib. If we're using more osimertinib first line, we should see what that does with bevacizumab or ramucirumab. And so, there are ongoing trials looking at that.

For those of you who are puzzled by our discussion of chemo plus EGFR/TKI, we've had a lot of data coming out on that in the past few years. Again, if you go back in time to when we first started looking at EGFR therapy, before we knew about the mutations, there were a lot of studies of EGFR combination with chemo. But those trials were completely negative. That was before we knew about the mutations. And because the trials in the distant past that were just all comers getting chemo and EGFR therapy were negative, we didn't really go back and look at that question for over a decade.

But then this trial came out. This was the NEJ009 study conducted in Japan. And they took patients with known activating *EGFR* mutations, and they either received gefitinib alone or gefitinib plus chemo. And the chemo in this case was carboplatin/pemetrexed.

If they were receiving all 3 drugs together, they went on maintenance of gefitinib and pemetrexed. If they only received gefitinib alone at the time of progression,



they then went on to get the chemo. So it was an everything concurrently or a sequential approach. It was a very well-designed study.

If you looked at progression one, which was progression on gefitinib alone versus progression on the combination, the combination looked much better. But if you looked at the endpoint of the 3 drugs versus the sequential where everyone received gefitinib and then they received their chemo, if you looked at the PFS, which was the timepoint where everybody had had gefitinib, and everybody had chemotherapy, those curves actually came together. But despite that, there was a clear overall survival benefit.

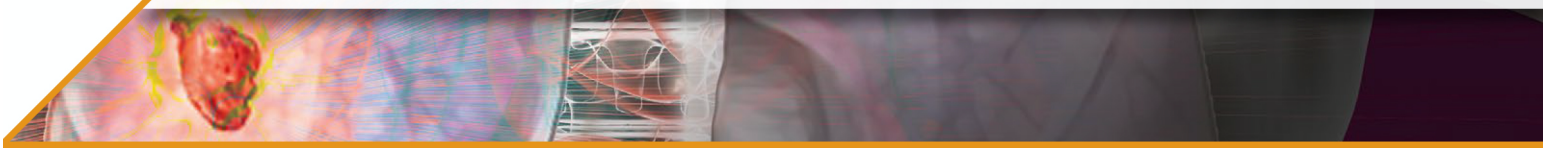
For some reason, even though the PFS was the same if you received sequential gefitinib and then chemo versus all of it together, there was still an overall survival benefit of getting all of them together. This was very intriguing and led to further studies and questions.

There was a study done in India where patients received gefitinib alone, or the combination of carboplatin, pemetrexed, and gefitinib. This study was a little bit different because the people receiving gefitinib alone did not necessarily go on to get that chemotherapy at the time of progression, just based on resources and differences. It was a different design to the study. But this also showed a clear PFS benefit with the combination. And in this case, also a clear overall survival benefit.

This has really got people thinking, should we be starting with chemo plus an EGFR/TKI, as opposed to just an EGFR/TKI alone? There are a lot of questions, of course, around the toxicity and cost. This is not yet being widely adopted, but definitely being widely studied.

I'm going to talk a little bit about immune therapy in the setting of *EGFR* mutation-positive lung cancer. Dr. Reckamp and I talked about the toxicity here. The first data that we had, the immune therapy, the checkpoint inhibitors (PD-1, PD-L1) that might not be so good in EGFR, came from the first checkpoint inhibitor trials in lung cancer, all of which were docetaxel versus a single-agent checkpoint inhibitor in the second line. So, you have to think back.

In the trials of docetaxel versus checkpoint inhibitor, every single subset had an overall survival benefit with the checkpoint inhibitors versus docetaxel except patients with *EGFR* mutations. That was the only group. And for that reason,



most of our trials that have looked at checkpoint inhibitors alone in first line, or in combination with chemotherapy first line, have excluded patients with *EGFR* mutations.

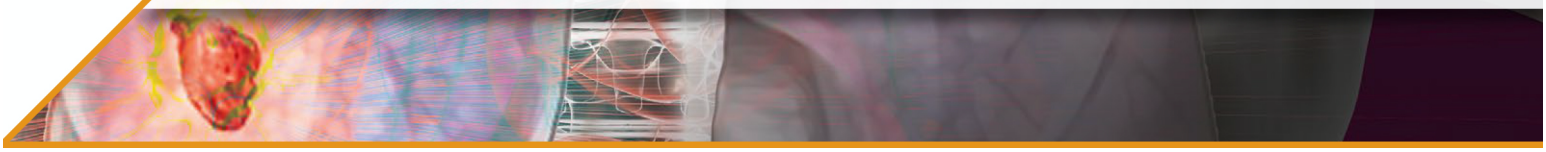
In the ATLANTIC trial, patients who had an *EGFR* mutation, who had PD-L1 expression of at least 25%, had a response rate to single-agent checkpoint inhibitors of around 12%, which is lower than we would expect for high PD-L1 expression, single-agent checkpoint inhibitor in other patients. So, it's not zero, but it's pretty low.

But if they had no or low PD-L1 expression, they had almost no response. So, when you're using checkpoint inhibitors in patients with *EGFR* mutations, keep in mind that if they have low PD-L1 expression, the response rates are very low. If they have high PD-L1 expressions, the response rates are still pretty low. They're not terribly low, but they're not great.

We really don't know much about the combination of chemo plus checkpoint inhibitors in patients with EGFR. The only exception was the IMpower150 trial.

There were 2 first-line trials, Impower130 and IMpower150, that had chemotherapy plus or minus atezolizumab, and included patients with *EGFR* mutations. IMpower150 also included bevacizumab. So, it had chemo, bevacizumab plus or minus atezolizumab. And this study actually showed a progression-free and overall survival benefit for the 4-drug mutation in patients with *EGFR* mutations. But this was a randomized phase 2 study. We have to be very cautious not to over-interpret this data. There's been a lot of discussion around it, but again, we need to be very, very careful that this was a small study.

This is some other data looking at responses to patients with *EGFR* mutations, who had received checkpoint inhibitors. This is a pretty complicated slide, but it's essentially showing that patients who have *EGFR* mutations don't tend to do well. This was a study that was done for patients newly diagnosed with *EGFR*-mutant lung cancer, who had high PD-L1 expression, and they were randomized to get pembrolizumab first line. They did very poorly. There was only one responder. It turned out they didn't actually have an *EGFR* mutation, and there was a lot of toxicity on this study. So, this is just another study reinforcing approach checkpoint inhibitors cautiously in patients with *EGFR* mutations, and approach first-line immune therapy cautiously in patients who might have an *EGFR* mutation. So, you've got to make sure you know what's going on.



We talked a lot about *EGFR* because the general themes that we have when we think about *EGFR* also carry over to the other driver mutations such as *ALK*.

So, just like looking for *EGFR* at the beginning when someone's newly diagnosed, especially in a non-smoker, we also need to be thinking about *ALK*, *ROS*, *RET*, *MET*, *BRAF*, and *NTRK*. There are a large number of these driver mutations where we now have targeted drugs that we know would be better when we find them.

With *ALK*, when *ALK* was first discovered, crizotinib was already in development and was found to be better than chemotherapy for patients who had *ALK*, crizotinib being one of our ALK-targeted drugs. There are newer, more potent ALK drugs, alectinib and brigatinib. And at the IASLC World Conference on Lung Cancer, we also heard about ensartinib being superior to crizotinib so there are many choices.

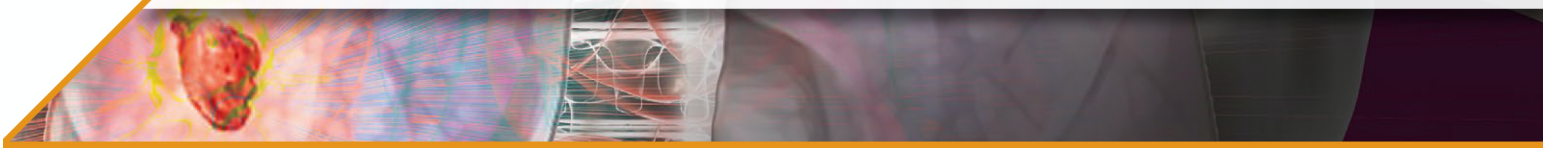
These data show that crizotinib is superior to chemotherapy for PFS. It did not reach its statistical significance for overall survival because of crossover, but it did have a strong PFS benefit.

This was alectinib versus crizotinib in Japan, the J-ALEX trial, which was the first study we saw of alectinib versus crizotinib; it showed a strong PFS benefit.

This was the global ALEX trial, which also showed very strong PFS improvement and hazard ratio of 0.47. And overall survival maybe is going to end up being there. It's not yet statistically significant but look at how long those curves are going out. It's really striking how long our patients with *ALK* mutations are living with their disease, especially when they're on these potent drugs, which are very well tolerated.

One of benefits that we saw again with the newer-generation drugs is improved brain activity. So just like we saw with the third-generation versus first-generation EGFR study, same story here with ALK. The later-generation ALK drugs are more potent in the brain than the first-generation drug, crizotinib.

Brigatinib is also highly active compared to crizotinib, with strongly improved PFS. It also has better brain activity.

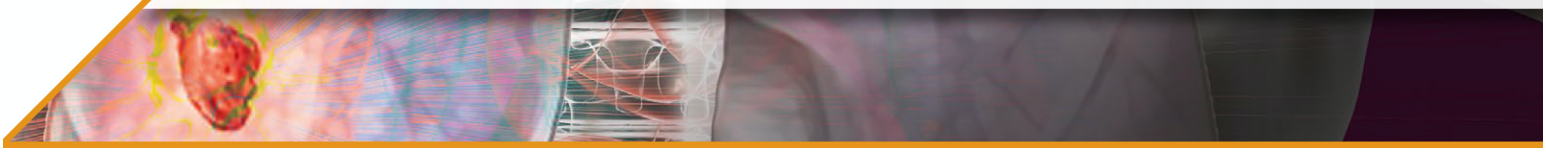


When we look at the NCCN Guidelines for ALK, alectinib is the preferred category 1. But we also have brigatinib, and we have ceritinib. Possibly ensartinib will eventually end up there. Crizotinib is also something to consider in some cases. If a patient progresses on crizotinib, we have alectinib, brigatinib, lorlatinib, and ceritinib all approved. If they progress on alectinib, we have lorlatinib. So, we also have 5 ALK drugs approved—a lot to keep track of.

Here again, these same themes like we talked about with EGFR. You have to look for driver mutations, or you won't find them. If they're there and you don't know about them, you're not giving the patient the best possible care.

If you find *ALK*, you have 5 drugs to choose from. Alectinib is preferred in the United States, and crizotinib is also a reasonable option. There are a lot of drugs with activity after crizotinib. And the brain activity is better with those later-generation drugs.

There's a lot of discussion around looking at VEGF inhibition with ALK, chemo in combination with ALK, TKIs, but those are still all trial questions. We do know that ALK often has high PD-L1 and really does not respond well to checkpoint inhibitors. So again, you have to really look.



References

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123-135.

Camidge R, Kim HR, Ahn, MJ, et al. Brigatinib versus crizotinib in *ALK*-positive non–small-cell lung cancer. *N Engl J Med*. 2018;379:2027-2039.

Camidge R, Kim HR, Ahn M, et al. Brigatinib vs crizotinib in patients with ALK inhibitor-naive advanced ALK+ NSCLC: Updated results from the phase III ALTA-1L trial. ESMO Asia Congress 2019.

ClinicalTrials.gov. NCT03909334. Study of osimertinib with and without ramucirumab in locally advanced or metastatic non-small cell lung cancer (NSCLC). https://clinicaltrials.gov/ct2/show/NCT03909334.

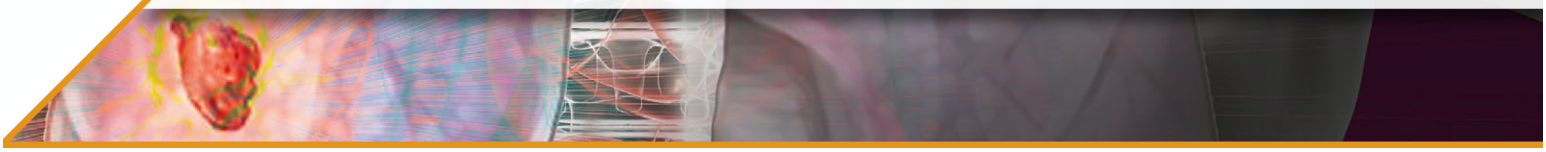
Cross DAE, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov.* 2014;4:1046-1061.

Ettinger DS, Wood DE, Aisner DL, et al. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 6.2020. © 2020 National Comprehensive Cancer Network, Inc. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

FDA News Release. December 12, 2014. Ramucirumab (Cyramza). http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm426735.htm.

FDA News Release. March 4, 2015. Nivolumab (Opdivo). http://wayback.archive-it.org/7993/20170111231639/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm436566.htm.

FDA News Release. October 2, 2015. Pembrolizumab injection. http://wayback.archive-it.org/7993/20170111231626/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm465650.htm.



FDA News Release. October 9, 2015. Nivolumab injection. http://wayback.archive-it.org/7993/20170111231625/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm466576.htm.

FDA News Release. October 18, 2016. Atezolizumab (Tecentriq). http://wayback.archive-it.org/7993/20170111231550/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm525780.htm.

FDA News Release. October 24, 2016. Pembrolizumab (Keytruda) checkpoint inhibitor. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526430.htm.

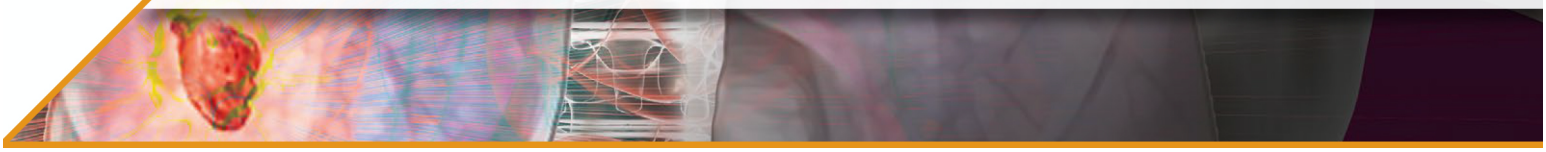
FDA News Release. May 10, 2017. Pembrolizumab (Keytruda). https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm558048.htm.

FDA News Release. August 20, 2018. FDA grants regular approval for pembrolizumab in combination with chemotherapy for first-line treatment of metastatic nonsquamous NSCLC. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617471.htm?utm_campaign=Oncology%20Pembrolizumab%208%2F20%2F2018%20&utm_medium=email&utm_source=Eloqua&elqTrackId=863601bda2b24a2b8502899dc6cdb179&elq=bccbf54bd0334203886812c8676b5c66&elqaid=4707&elqat=1&elqCampaignId=3746.

FDA News Release. October 30, 2018. FDA approves pembrolizumab in combination with chemotherapy for first-line treatment of metastatic squamous NSCLC. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm624659.htm.

FDA News Release. December 6, 2018. FDA approves atezolizumab with chemotherapy and bevacizumab for first-line treatment of metastatic non-squamous NSCLC. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm627874.htm.

FDA News Release. April 11, 2019. FDA expands pembrolizumab indication for first-line treatment of NSCLC (TPS ≥1%). https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm635857.htm.



FDA News Release. December 3, 2019. FDA approves atezolizumab with nab-paclitaxel and carboplatin for metastatic NSCLC without *EGFR*/*ALK* aberrations. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-nab-paclitaxel-and-carboplatin-metastatic-nsclc-without-egfralk.

FDA News Release. May 15, 2020. FDA approves nivolumab plus ipilimumab for first-line mNSCLC (PD-L1 tumor expression ≥1%). https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-ipilimumab-first-line-mnsclc-pd-l1-tumor-expression-1.

FDA News Release. May 18, 2020. FDA approves atezolizumab for first-line treatment of metastatic NSCLC with high PD-L1 expression. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-first-line-treatment-metastatic-nsclc-high-pd-l1-expression.

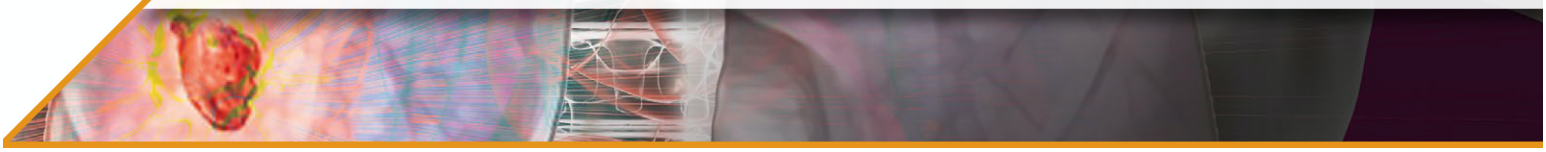
FDA News Release. May 26, 2020. FDA approves nivolumab plus ipilimumab and chemotherapy for first-line treatment of metastatic NSCLC. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-ipilimumab-and-chemotherapy-first-line-treatment-metastatic-nsclc.

FDA News Release. May 29, 2020. FDA approves ramucirumab plus erlotinib for first-line metastatic NSCLC. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-ramucirumab-plus-erlotinib-first-line-metastatic-nsclc.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicenter, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837-1846.

Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non–small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol*. 2018;4:1543-1552.

Finlay MR, Anderton M, Ashton S, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem*. 2014;57:8249-8267.



Furuya N, Fukuhara T, Saito H, et al. Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating EGFR mutations: NEJ026. *J Clin Oncol*. 2018;36:9006.

Gadgeel SM, Garassino MC, Esteban E, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. *J Clin Oncol*. 2019;37: abstract 9013.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.

Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028.

Garon EB, Hellman MD, Costa EC, et al. Five-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab: results from KEYNOTE-001. *J Clin Oncol* 2019;37: abstract LBA9015.

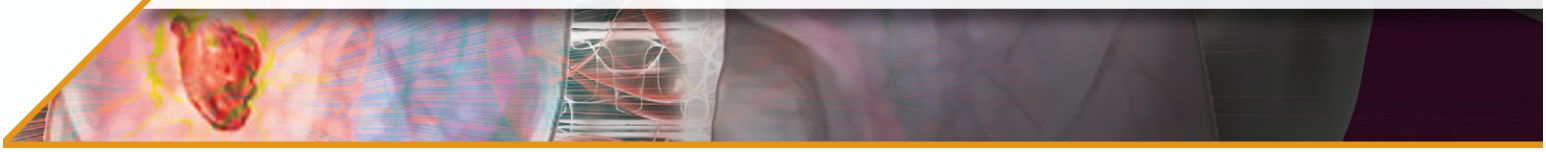
Garon EB, Clyleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014;384:665-673.

Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden**.** *N Engl J Med*. 2018;378:2093-2104.

Hellmann MD, Paz-Ares L, Caro RB, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.

Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-1550.

Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017;390:29-39.



Hosomi Y, Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non–small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. *J Clin Oncol*. 2020;38:115-123.

Kato T, Seto T, Nishio M, et al. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation–positive nonsquamous non-small cell lung cancer (NSCLC): An open-label randomized trial. *J Clin Oncol*. 2014;32:8005.

Lee JS, Park K, Kim SW. A randomized phase III study of gefitinib versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the lung. Abstract PRS.4. Presented at the 13th World Conference on Lung Cancer; July 31-August 4, 2009; San Francisco, California.

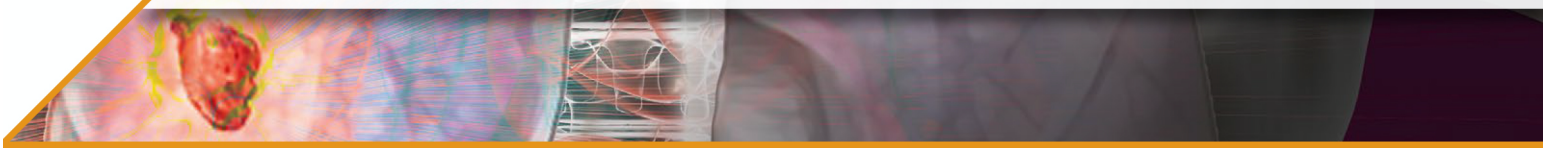
Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non–small cell lung carcinoma. *JAMA Oncol*. 2018;4:210-216.

Leonardi GC, Gainor JF, Altam M, et al. Safety of programmed death–1 pathway inhibitors among patients with non–small-cell lung cancer and preexisting autoimmune disorders. *J Clin Oncol*. 2018;36:1905-1912.

Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. *J Thorac Oncol*. 2018;13:1138-1145.

Lopes G, Wu Y-L, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: open-label, phase 3 KEYNOTE-042 study. *J Clin Oncol*. 2018;36: abstract LBA4.

Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362:2380-2388.



Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121-128.

Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;3939:1819-1830.

Mok TS, Wu Y-L, Thongpresert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.

Mok T, Cheng Y, Zhou X, et al. Dacomitinib (daco) versus gefitinib (gef) for first-line treatment of advanced NSCLC (ARCHER 1050): final overall survival (OS) analysis. *J Clin Oncol*. 2018;36:9004.

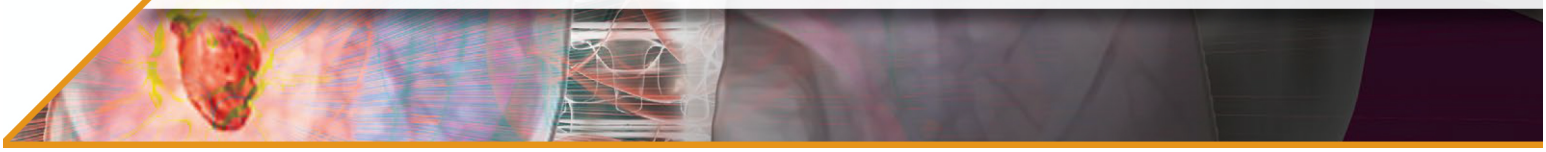
Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum pemetrexed in EGFR T790M positive lung cancer. *N Engl J Med*. 2017;376:629-640.

Nakagawa K, Garon EB, Seto T, et al. RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2019;37:9000.

Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1655-1669.

Nakamura A, Inoue A, Morita S, et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). *J Clin Oncol*. 2018;36:9005.

Noronha V, Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in *EGFR*-mutated lung cancer. *J Clin Oncol*. 2020;38:124-136.



Paz-Ares L, Luft. A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.

Peters S, Ramalingam SS, Paz-Ares L, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced non-small cell lung cancer (NSCLC): CheckMate 227 Part 1 final. *Ann Oncol*. 2019;30:v851-v934.

Peters S, Camidge Dr, Shaw AT, et al. Alectinib versus crizotinib in untreated *ALK*-positive non–small-cell lung cancer. *N Engl J Med*. 2017;377:829-838.

Planchard D, Yu HA, Yang JC-H, et al. Efficacy and safety results of ramucirumab in combination with osimertinib in advanced T790M-positive *EGFR*-mutant NSCLC. *J Clin Oncol*. 2018;36:9053.

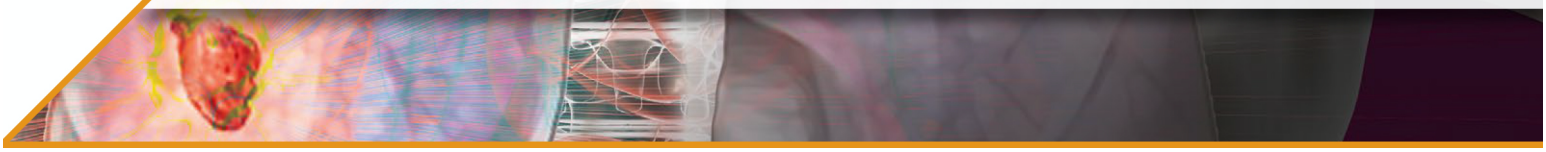
Ramalingam S, Reungwetwattana T, Chewaskulyong B, et al. Osimertinib vs standard of care (SOC) EGFR-TKI as first-line therapy in patients (pts) with EGFRm advanced NSCLC: FLAURA. *Ann Oncol.* 2017;28:v635.

Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41-50.

Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.

Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol.* 2019;27:537-546.

Reck M, Ciuleanu TE, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. *J Clin Oncol*. 2020;38: abstract 9501.



Reck M, Paz-Ares LG, Bidoli P, et al. Exploratory subgroup analysis of patients (Pts) refractory to first-line (1L) chemotherapy from REVEL, a randomized phase III study of docetaxel (DOC) with ramucirumab (RAM) or placebo (PBO) for second-line (2L) treatment of stage IV non-small-cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34: abstract 9079.

Reck M, Paz-Ares, Bidoli P, et al. Outcomes in patients with aggressive or refractory disease from REVEL: a randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer. *Lung Cancer* 2017;112:181-187.

Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated *EGFR*-mutated advanced non–small-cell lung cancer. *J Clin Oncol.* 2018;36:3290-3297.

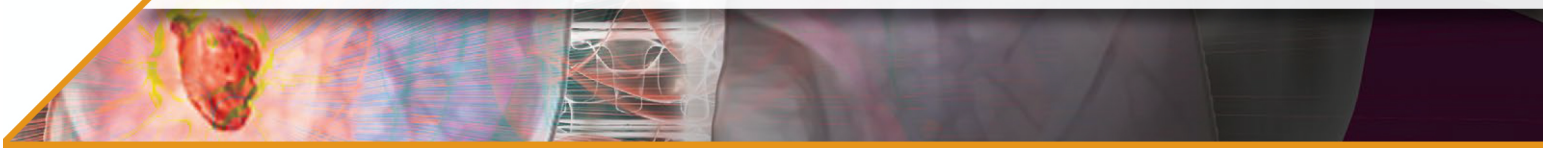
Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012;366:2517-2519.

Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255-265.

Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial. *J Clin Oncol*. 2011;29(suppl): abstract 7503.

Saito J, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2019;20:625-635.

Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol*. 2014;15:1236-1244.



Socinski MA, Jotte RM, Cappuzzo F. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.

Socinski MA, Jotte RM, Cappuzzo F. Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. *J Clin Oncol.* 2018;36: abstract 9002.

Spigel D, de Marinis F, Giaccone G, et al. IMpower110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. *Ann Oncol*. 2019;30:v851-v934.

Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177.

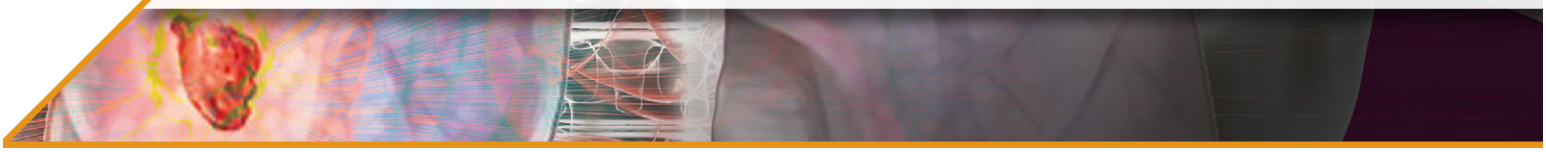
Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.

West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924-937.

Westover D, Zugazagoitia J, Cho BC, et al. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol*. 2018;29(suppl_1):i10-i19.

Wu YL, Zhou C, Hu C, et al. LUX-Lung 6: a randomized, open-label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. *J Clin Oncol*. 2013;31(suppl): abstract 8016.

Wu Y-L, Ahn M-J, Garassino MC, et al. CNS efficacy of osimertinib in patients with T790M-positive advanced non–small-cell lung cancer: data from a randomized phase III trial (AURA3). *J Clin Oncol*. 2018;36:2702-2709.



Wu Y-L, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454-1466.

Yamamoto N, Seto T, Nishio M, et al. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation–positive non-squamous non–small-cell lung cancer (NSCLC): Survival follow-up results of JO25567. *J Clin Oncol*. 2018;36(15):9007-9007.

Yang J C-H, Schuler MH, Yamamoto N, et al. LUX-Lung 3: A randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. *J Clin Oncol*. 2012;30(suppl):LBA7500.

Zhou C, Wu Y-L, Chen G et al. Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin (CBDCA) plus gemcitabine (GEM), in Chinese advanced non-small-cell lung cancer (NSCLC) patients (PTS) with EGFR activating mutations. *Ann Oncol.* 2010;21(suppl 8):LBA13.