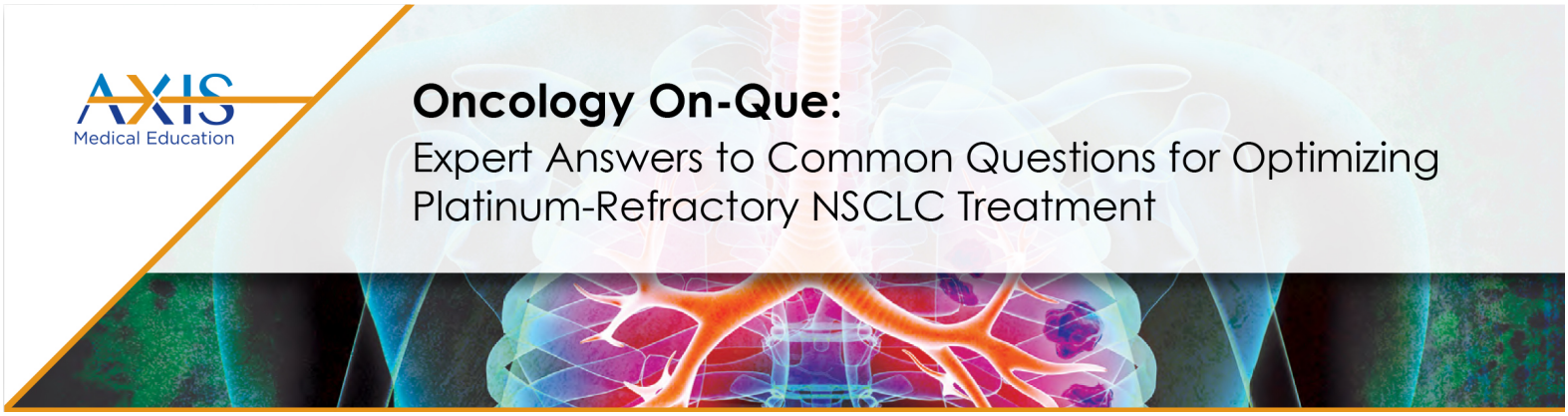


Joshua Bauml, MD: Hello, and welcome to this educational activity entitled *Oncology On-Que: Expert Answers to Common Questions for Optimizing Platinum-Refractory Non–Small Cell Lung Cancer Treatment.*

I'm Dr. Joshua Bauml. I'm an Assistant Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, Pennsylvania. This activity will provide my perspective on participant questions from a recent AXIS Grand Rounds series on platinum-refractory non–small cell lung cancer.

Here is a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.

Here's my financial disclosure information.

Here are the learning objectives for this activity.

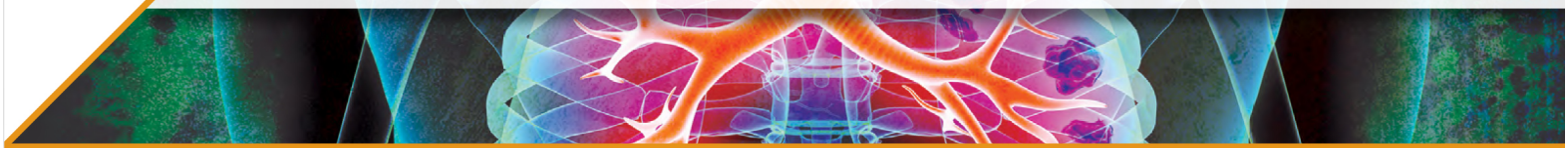
So, today we're going to focus on three main topics that came up in the lecture series. First, we're going to talk about molecular testing; next we'll talk about biomarkers in immunotherapy; and then we'll talk about the treatment of rapidly progressing disease on first-line treatment.

We have a 50-year-old woman who presents with adenocarcinoma of the lung, metastatic to bone and liver. Her tumor has both an *EGFR* exon 19 deletion and PD-L1 overexpression with 90% tumor staining on the DAKO 22C3 assay.

Your first-line treatment should be: (a) osimertinib, (b) pembrolizumab, (c) carboplatin/pemetrexed/pembrolizumab, (d) carboplatin/pemetrexed, or (e) unsure.

In this case, the correct answer would be (a) osimertinib.

In this pie chart, what you can see is that non–small cell lung cancer is becoming a more and more heterogeneous disease. This is looking at molecular drivers of cancerous behavior among adenocarcinoma of the lung. What I'd like to call your attention to here are, first of all, that the most common mutation, *KRAS*, unfortunately does not have a targeted therapy. However, if you look at *EGFR*, there are many targeted therapies that are currently FDA approved.



On the right side of this slide, there is a large blue section indicating “Unknown.” This does not mean that those tumors do not have a mutation that makes them behave like a tumor. It just means we haven’t seen what that is yet. As we see these ever-shrinking pieces of the pie on the left side of the pie chart, what I’m reminded of is that it’s quite likely that you may find a patient who comes in with a result on a next-generation sequencing assay that you’ve never seen before. And it’s important to seek out the appropriate treatment for such patients.

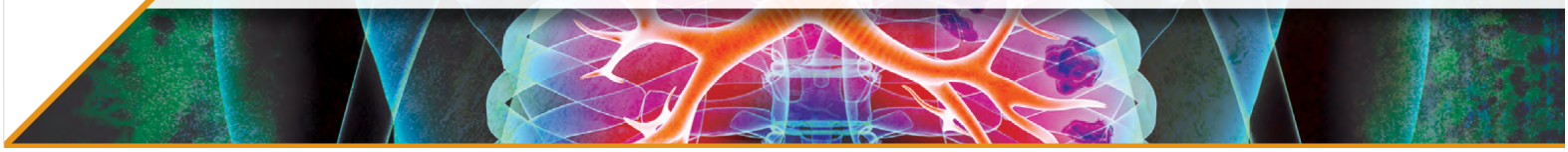
So, why should we do that? This is from a very important study published by Dr. Kris, in *JAMA,* in 2014. They took patients who had non–small cell lung cancer, adenocarcinoma in particular, and did a rather limited next-generation sequencing assay on those tumors. And what they found was that, for those patients who had a targetable alteration and received a targeted therapy, their median overall survival was more than 1 year longer than those patients who had only an oncologic driver and did not receive a targeted therapy.

And here this is important, because when we think about patients with *EGFR* mutations, or *ALK* translocations, they tend to be young, never-smokers who would, overall, tend to have a better prognosis anyway. But what we can see in this study is that we really are changing outcomes for these patients with the addition of a tyrosine kinase inhibitor (TKI).

So, EURTAC was the first study that evaluated a TKI versus a chemotherapy in established *EGFR* mutation–positive non–small cell lung cancer. Patients were randomized to erlotinib 150 mg daily or a platinum doublet.

And what you can see here is that the progression-free survival was much better for those patients receiving erlotinib. And we can also see that the toxicity profile was different with erlotinib as opposed to chemotherapy, of course, with a higher rate of rash and diarrhea for erlotinib, and a higher rate of cytopenias for cytotoxic chemotherapy.

But what you can see, when think about this, is that when you look at the progression-free survival and the response rate—and this is from multiple trials comparing a TKI to chemotherapy—the response rate and progression-free survival are much higher for the TKI than they are for chemo. But if you look at overall survival, you see that there is not a significant improvement in overall survival in these studies. And one of the reasons for this was that there was significant crossover from a chemotherapy to a TKI in these studies. And that likely would diminish any survival benefit that we would see.



Taking a look at osimertinib, this was originally developed as a TKI to be used for patients refractory to a first- or second-generation TKI that had developed the T790M mutation, the most common resistance mutation, to a first- or second-generation TKI. In this waterfall plot, we see a remarkable response rate for the drug.

This led to the FLAURA study, which evaluated osimertinib as the first-line treatment as compared to erlotinib or gefitinib at investigator's discretion, for patients with *EGFR* mutation–positive non–small cell lung cancer.

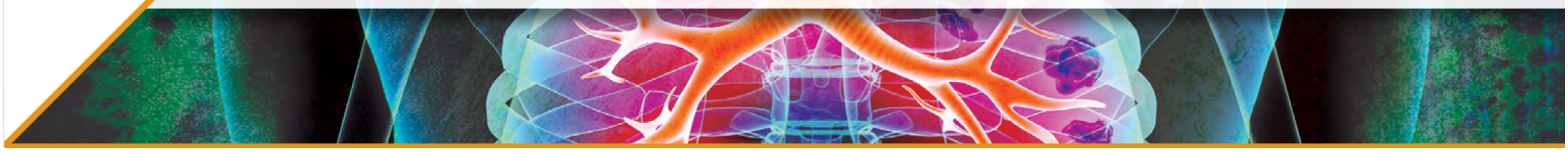
And what we saw—and it has subsequently been published—is that osimertinib was associated with a marked increase in progression-free survival. And osimertinib also had an improved safety profile, with a lower rate of rash as compared to standard of care. There was a slightly higher rate of stomatitis and diarrhea, but these were not a large difference between the groups.

So, in the case study that we presented at the beginning of this discussion, I noted that the patient had a PD-L1 expression of greater than 50%. And some may have thought to give the patient immunotherapy. It's important to remember that most studies that evaluated immunotherapy in non–small cell lung cancer excluded patients with *EGFR* mutations, and the reason for that is seen on this slide.

What you can see here is that, if you look at patients with *EGFR* wild-type, it's clear that PD-1 and PD-L1 inhibitors are superior to docetaxel in this second-line study. However, if you look below at the *EGFR*-mutation–positive non–small cell lung cancer, there is no incremental benefit to the addition of immunotherapy for such patients over docetaxel. It just doesn't seem to work as well in this patient population.

So what about first-line immunotherapy trials? As I mentioned, most of them excluded patients with *EGFR* mutation or *ALK* translocation. KEYNOTE-024, which led to the approval of first-line pembrolizumab monotherapy, as well as KEYNOTE-021G, the combination of carboplatin/pemetrexed/pembrolizumab, both of these studies excluded patients with *EGFR* mutation. And so, it would not be appropriate to use either of these regimens as first-line therapy for a patient with *EGFR* mutation.

The IMpower150 study, which evaluated carboplatin, a taxane, bevacizumab, and atezolizumab did allow patients who had *EGFR* mutations or *ALK* translocations, but they needed to have



failed a prior TKI. So, it's important to remember that, for patients with a targetable aberration, we should give them the targeted therapy.

In summary, if there is a target, we should use it. Osimertinib led to improved progression-free survival as compared to gefitinib or erlotinib in the FLAURA study. And immunotherapy may have reduced efficacy among patients with *EGFR* mutations.

Here we have a 65-year-old man who presents with widely metastatic adenocarcinoma of the lung. He is relatively asymptomatic. His tumor is found to have overexpression of PD-L1, staining 60% of the tumor on the DAKO 22C3 assay. His next-generation sequencing assay does not reveal any targetable aberration.

So, what should his first-line treatment be? (a) Carboplatin/pemetrexed/pembrolizumab, (b) pembrolizumab, (c) carboplatin/gemcitabine, (d) either A or B, or (e) unsure.

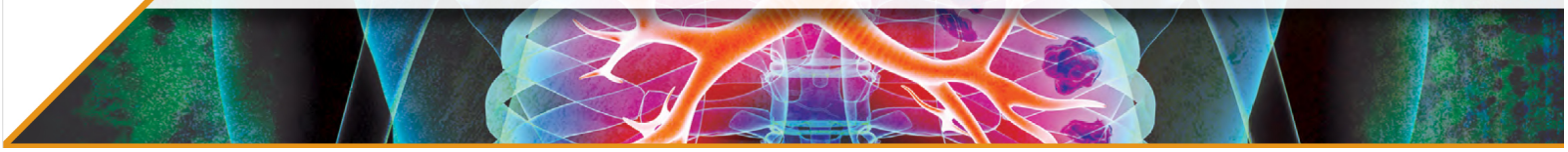
In this case, the correct answer would be (d) either A or B. Let's talk a little bit about why that is.

The first study that established that the choice of chemotherapy may be important, based upon histology, was led by Dr. Scagliotti, where patients with advanced non–small cell lung cancer were randomized to either cisplatin/pemetrexed or cisplatin/gemcitabine.

And what they found was that, while on the intention-to-treat analysis there was no difference between the two arms, when we look at patients with nonsquamous non–small cell lung cancer, cisplatin/pemetrexed was associated with improved overall survival. It's on this basis, that in the case we described, the use of a gemcitabine-based approach would be less than optimal.

But how about the incorporation of immunotherapy? Remember, we said that this patient had a PD-L1 staining of 60%.

KEYNOTE-024 looked at patients with greater than 50% staining for PD-L1 and randomized them to either pembrolizumab monotherapy or a platinum doublet of the investigator's choosing. As I mentioned before, patients with *EGFR* mutations or *ALK* translocations were not allowed to enroll.



What we can see on the toxicity profile is that pembrolizumab was much better tolerated than cytotoxic chemotherapy. The incidence of grade 3 to 5 immune-related adverse events was 9.7% with pembrolizumab, and obviously would not be seen as much with cytotoxic chemotherapy. The rate of grade 3 to 5 pneumonitis was 2.6%.

But if we take a look at all treatment-related adverse events, it's 26.6% for grades greater than 3 for pembrolizumab, and 53.3% for cytotoxic chemotherapy. That's a significant difference that we're seeing here.

You can see that both the overall and progression-free survivals favored the use of pembrolizumab. Based on these data, pembrolizumab monotherapy became the standard of care for patients with PD-L1–overexpressing non–small cell lung cancer.

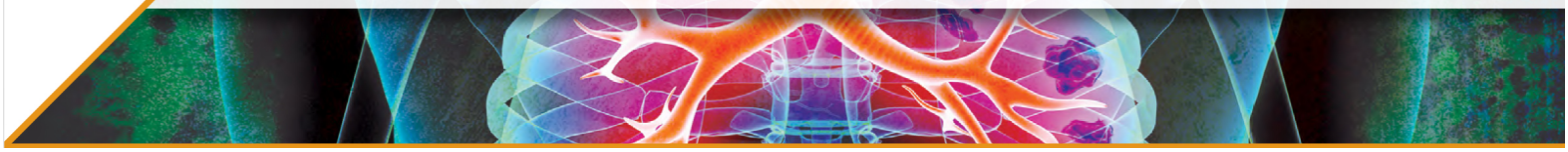
These results were presented in updated fashion at last year's World Conference on Lung Cancer, in Japan. And Dr. Brahmer showed that we did finally reach the median overall survival for patients receiving pembrolizumab at 30 months. This is more than double what was seen for cytotoxic chemotherapy.

KEYNOTE-189 was a phase 3 study that evaluated whether we could improve outcomes over chemotherapy in a different way. So instead of comparing chemotherapy to pembrolizumab alone, this compared carboplatin/pemetrexed/placebo to carboplatin/pemetrexed and pembrolizumab. This was following up on a positive phase 2 study, the KEYNOTE-021G trial.

What we can see in terms of toxicity was that the addition of pembrolizumab to cytotoxic chemotherapy did not substantially alter the toxicity profile. There was a slightly higher rate of events leading to discontinuation—about 20% versus 10.9%. But it was generally a well-tolerated combination.

In the intention-to-treat analysis, both the overall and progression-free survivals favored the triplet of carboplatin/pemetrexed/pembrolizumab over carboplatin/pemetrexed with placebo.

If we break the overall survival down by PD-L1, what you can see is that there an improvement in overall survival at all levels of PD-L1 staining. This is important, because prior to this study being reported, many were worried that the positivity seen in KEYNOTE-021G was driven entirely by those with >50% PD-L1–positive disease. Although those with >50% PD-L1–positive disease has the largest difference between the triplet and the placebo arm, there was still an



improvement in overall survival that reached statistical significance in patients with PD-L1–negative disease.

In summary, we know that pemetrexed is associated with a better overall survival than gemcitabine as a platinum partner for nonsquamous non–small cell lung cancer. But if we go back to the case, a patient with PD-L1–overexpressing non–small cell lung cancer, it would be reasonable to give them either pembrolizumab, which has been associated with improved overall and progression-free survivals over platinum doublet in non–small cell lung cancer. Or carboplatin/pemetrexed and pembrolizumab, which has also been associated with improved overall and progression-free survivals over a platinum doublet in nonsquamous lung cancer.

I'd like to move on to topic 3. This is the treatment of rapidly progressive disease.

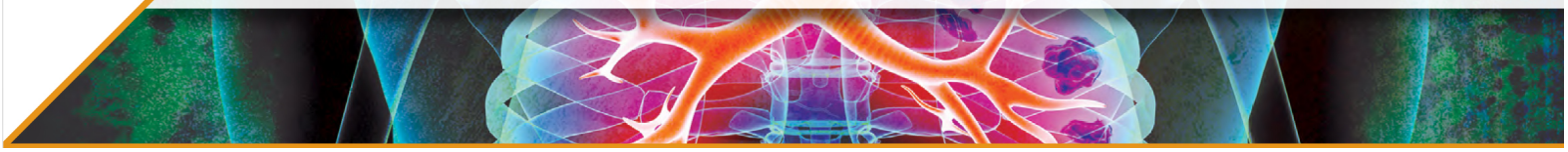
We described this patient earlier, who is started on carboplatin/pemetrexed and pembrolizumab. After 2 cycles, he was found to have rapidly progressive disease, with a new pleural effusion. He was feeling short of breath. He was losing weight.

Which of the following is the most appropriate next step? (a) Continue carboplatin/pemetrexed/pembrolizumab, as this is likely pseudoprogression; (b) switch to nivolumab, (c) switch to docetaxel/ramucirumab, (d) switch to afatinib, or (e) unsure.

In this case, I would say that the best answer of these choices is (c) switch to docetaxel/ramucirumab. Let's explore the data to figure out why.

So first let's talk a little bit about pseudoprogression. When we gave someone cytotoxic chemotherapy or targeted therapy in the past, if we did a scan, and the tumor was growing, we would stop the treatment. However, in immunotherapy, there is this experience that has been reported where the tumor can get bigger, followed by regression. And clinically, we have no way to distinguish this from true progressive disease.

This was the origin of the IR-RECIST measurement. But it's important to remember that for it to be even considered pseudoprogression, the patient must be asymptomatic. We need to get a second scan at least 4 weeks after the first to confirm or refute progressive disease. But it's difficult to know what to do if that second scan shows no further growth. By technicality it would be progressive disease, but it feels uncomfortable to stop a drug when the cancer is no longer growing.



So how often does this happen? An FDA series was done looking at 503 patients on phase 3 PD-1 inhibitor studies, where treatment past progression was allowed. And what you can see is that of patients who received treatment past progression—121 of them—only 10 of them went on to have a subsequent partial response. So this is relatively rare, which is important to remember when we're talking about immunotherapy. Most of the time, when a patient has radiographic progression of disease on immunotherapy, they are truly experiencing disease progression.

The REVEL study evaluated the addition of ramucirumab to docetaxel in the second-line management of patients with platinum-refractory non–small cell lung cancer. Patients were randomized—over 1,000 patients were randomized—to docetaxel/ramucirumab or docetaxel with placebo.

And what we can see here is that the addition of ramucirumab was associated with a statistically significant improvement in progression-free survival.

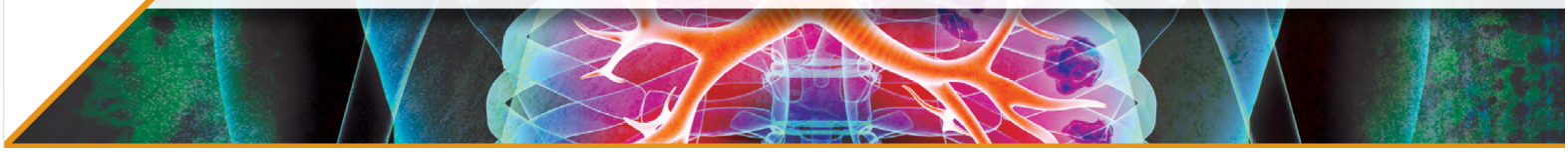
With the addition of ramucirumab, the toxicity was not that much worse than what we expect to see with docetaxel alone, as you can see on this slide.

Looking at the overall survival, we also see that there is a statistically significant improvement in overall survival with the addition of ramucirumab.

If we look at an exploratory subgroup analysis looking at patients who are truly refractory to first-line chemotherapy, we can see that these patients who do poorly with first-line chemotherapy have a more substantial benefit from the addition of ramucirumab, with an overall response rate of 23% as opposed to 13%. This could identify a subgroup of patients who may benefit from this combination.

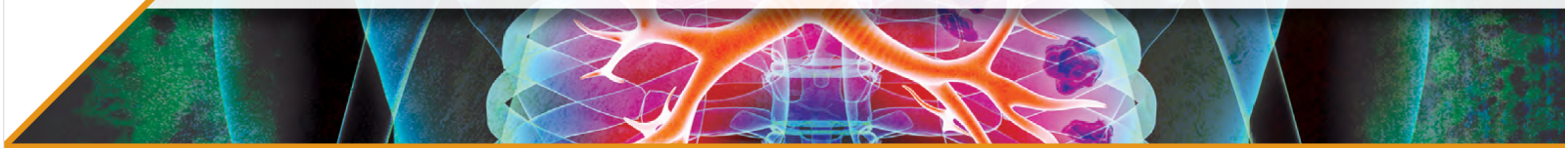
In summary, pseudoprogression is relatively rare in immunotherapy for non–small cell lung cancer. The addition of ramucirumab to docetaxel did improve progression-free survival, overall survival, and overall response rate, but this benefit may be amplified among patients with rapid disease progression.

The key takeaways from this exercise is that when a patient is a candidate for an FDA-approved targeted therapy for non–small cell lung cancer, it really should be used first line. For patients with PD-L1 levels >50% without a targetable aberration, first-line therapy can be either pembrolizumab monotherapy or carboplatin/pemetrexed/pembrolizumab. My current practice



has been that, for patients who are doing well and are not in extremis, I tend to use pembrolizumab monotherapy, reserving platinum doublets for next line or using a clinical trial. The third point is that docetaxel/ramucirumab is a reasonable option for patients with platinum-refractory non–small cell lung cancer, particularly those with rapidly progressive disease.

Thank you for participating in this activity and have a great day.



REFERENCES

Brahmer JR, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab vs platinum-based chemotherapy for advanced NSCLC with PD-L1 TPS ≥50%. *J Thorac Oncol*. 2017;12:S1793-S1794.

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, Ciuleanu TE, 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.

Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012;30:1122-1128.

Janne PA, Yang JC-H, Kim D-W, et al. AZD9291 in EGFR inhibitor–resistant non–small-cell lung cancer. *N Engl J Med*. 2015;372:1689-1699.

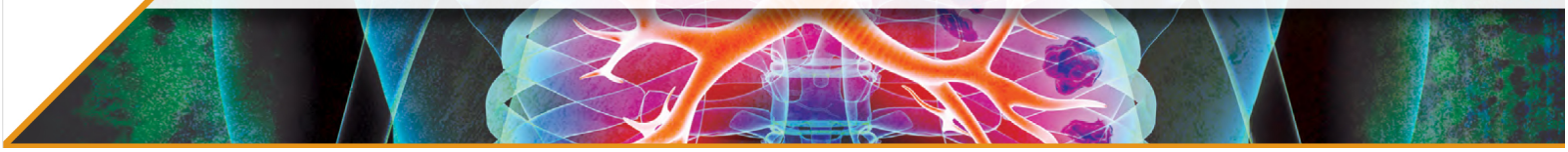
Kazandjian DG, Blumenthal GM, Khozin S, et al. Characterization of patients treated with a programmed cell death protein 1 inhibitor (anti-PD-1) past RECIST progression from a metastatic non-small cell lung cancer (mNSCLC) trial. *J Clin Oncol*. 2016;34:3000.

Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* 2014;311:1998-2006.

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: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:210-216.

Lovly CM, Horn L, Pao W. 2016. Molecular profiling of lung cancer. https://www.mycancergenome.org/content/disease/lung-cancer/.

Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib and chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med.* 2010;262:2380-2388.



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, randomized, phase 3 trial. *Lancet Oncol.* 2010;11:121-128.

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

Ramalingam S, Reungwetwattana R, 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:v605-v649.

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.

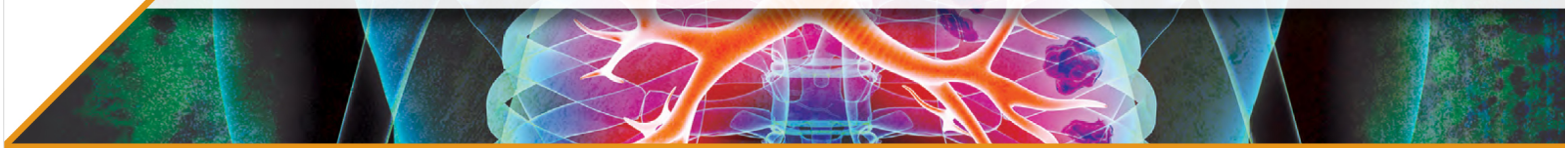
Reck M, Rodriquez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.

Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239-246.

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543-3551.

Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327-3334.

Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:213-222.



Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2011;12:735-742.