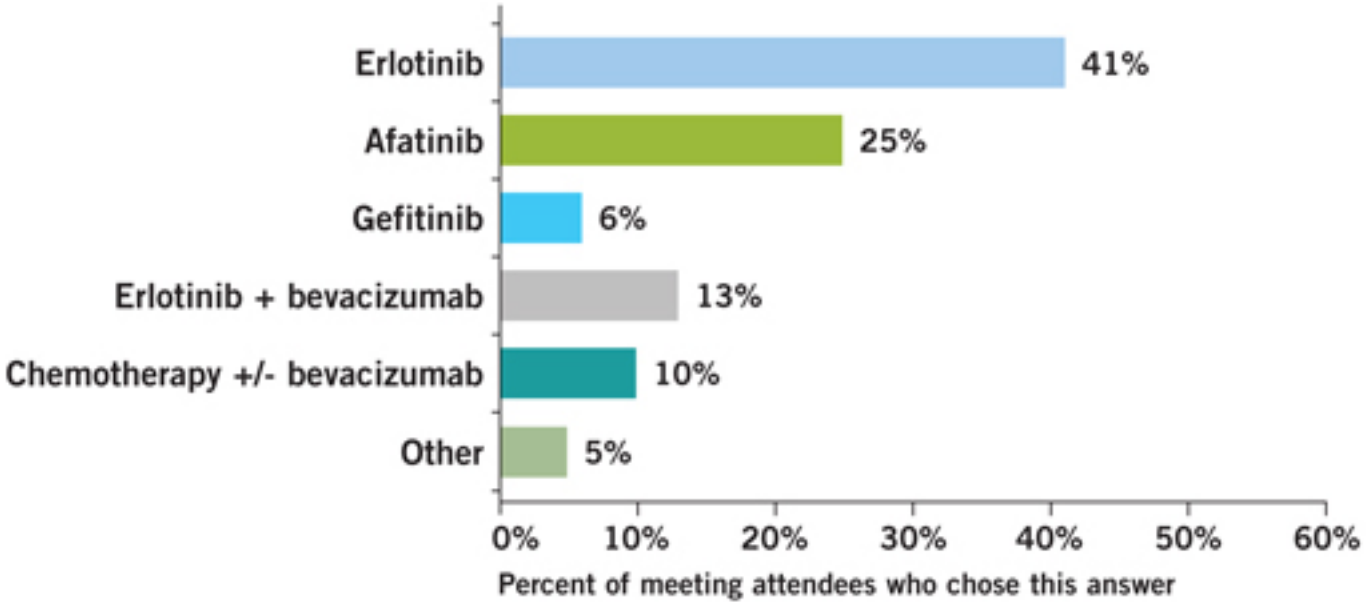
Year in Review

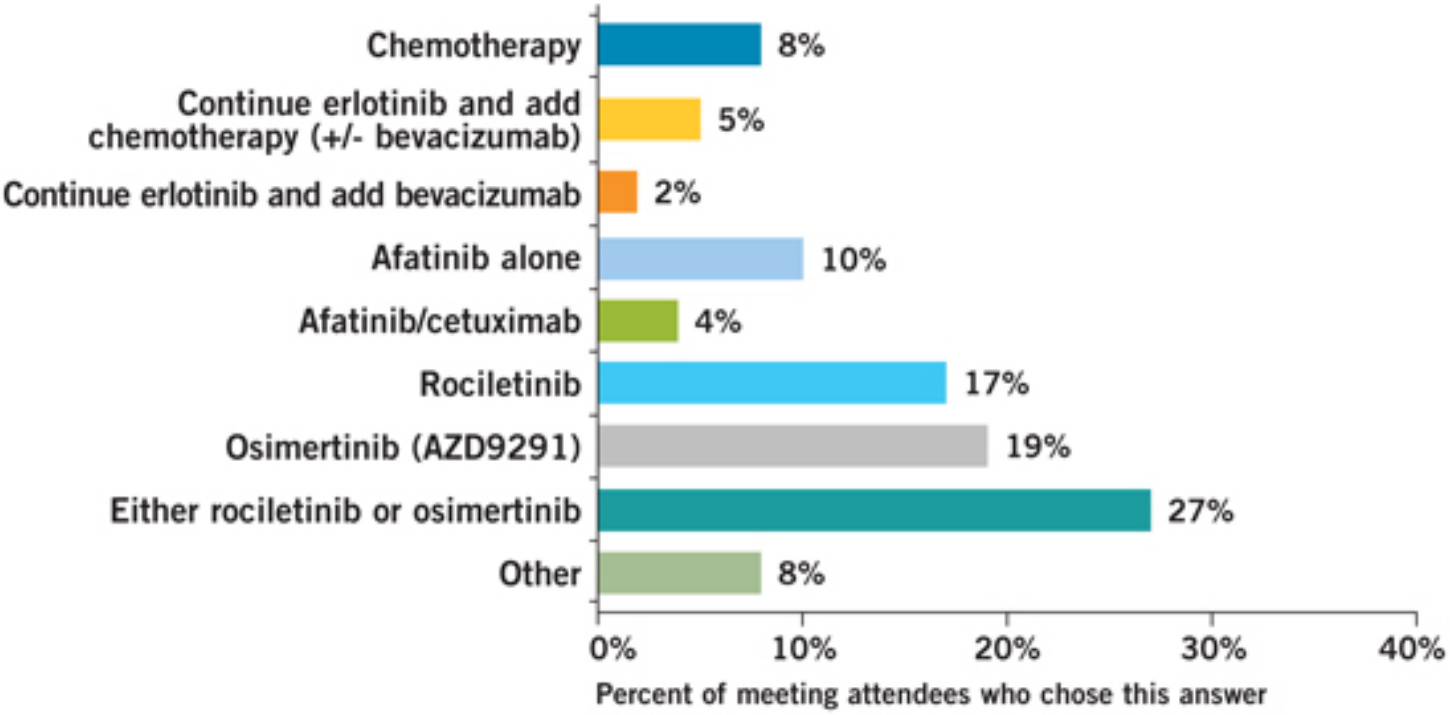
Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Management of Mutation-Positive NSCLC (EGFR, ALK, RET, BRAF) — Roy S Herbst, MD, PhD

Which systemic therapy would you generally recommend for an otherwise healthy patient who has newly diagnosed metastatic adenocarcinoma of the lung and an EGFR del(19) mutation?



A 56-year-old man, a never smoker, with widespread metastatic adenocarcinoma of the lung and an EGFR mutation experiences disease progression on imaging after 11 months on erlotinib. What would be your most likely treatment approach if the patient underwent rebiopsy that revealed a T790M mutation? (Assume rociletinib is available.)



DR LOVE: We've been talking for years about the very common situation of the patient who gets an EGFR TKI with a mutation. They respond and then they progress. What do you do? Do you keep the TKI going and start chemotherapy? We were talking about afatinib and cetuximab, and then, boom, all of the sudden, we woke up one day and there were a couple of third-generation agents. These are the two agents, rociletinib and osimertinib, which used to be called AZD9291. It looks like the audience is kind of split, yet, Corey, when we asked investigators, "What would you do in a T790-mutant situation," we see more people going with osimertinib. How do you think that one through, or how are you going to think it through?

DR LANGER: Number one, I agree with the audience. I think the preferred agents here are the new generation of T790 inhibitors. This patient's T790 mutant-positive — a whole different paradigm for T790-negative. Of the two agents, osi is probably less toxic. This is based on personal experience. Rociletinib generates quite a bit of hyperglycemia. This isn't just a paper toxicity with high blood sugars. This is symptomatic hyperglycemia with fatigue, malaise, appetite loss. It requires a whole level of management and monitoring that, frankly, I don't have the time to do — I doubt many in the audience have that time to do. We've grown quite adept at managing rash and diarrhea.

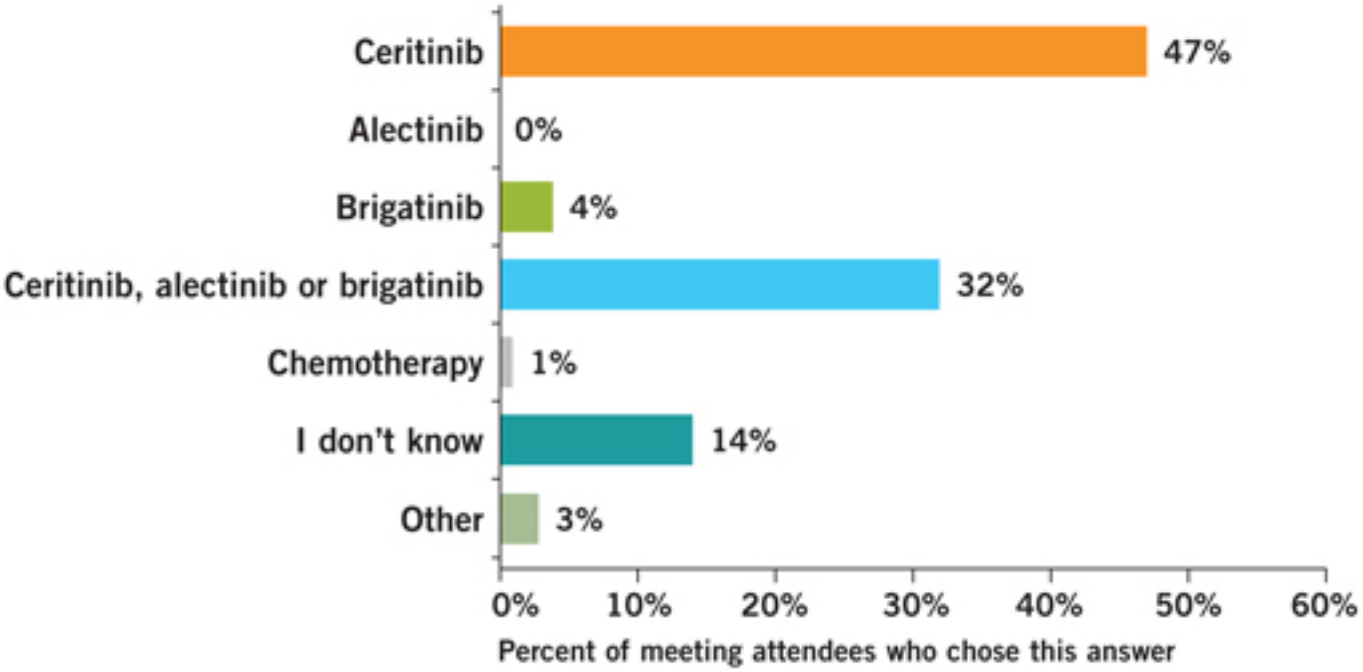
Osimertinib does retain some activity against wild type, so you do see some levels of diarrhea and rash, but not really at the level of the first generation. So I think from the standpoint of toxicity, osi wins. From the standpoint of efficacy, they're probably equivalent. Again, neither is yet FDA approved. That time's coming, I'm sure. Coin flip may be the best answer.

DR LOVE: One of the themes that's gone through this day, Roy, is just how close, experimentally, a trial therapy now is to practice — that there's so many situations where you know what the best therapy is and you can't get it except on a trial. I think this maybe is one of them. Also, there's an implied issue here about biopsy in this situation, the question being: If you have a patient who's on a first-line TKI, they have progression, is biopsy standard? And what about, quote, liquid biopsies, Roy? Where are we heading in that regard?

DR HERBST: Yes to both. I think you do want to know if the patient has T790M as their mechanism of resistance because both of these drugs are designed exactly for that criterion. So, yes, I think you would want to get a biopsy.

I think the liquid biopsy is certainly good. If you're positive on the liquid biopsy for T790M, I think you can move forward and treat. I think the data support that. But if you're negative, it's still more sensitive to go to the tissue. But, clearly, for each of these drugs, I would want to know. Certainly now, as we're using these drugs in trials, we are getting biopsies in all these patients.

What would be your most likely choice of second-line therapy for a patient with ALK-rearranged metastatic adenocarcinoma of the lung who experiences disease progression on crizotinib (assume all agents are approved and available)?



DR LOVE: We were curious where people are in terms of ALK disease. One issue in particular is the patient who has already had crizotinib and now you're talking about second-line therapy. Of course, we have an approved agent, ceritinib, so we made up this question to see whether, if alectinib became approved, people would approve that. And Corey came in and said, "Well, you've got to add brigatinib," which I wasn't even that familiar with, "to this list, because that's my answer." But, in any event, I'm curious. Let's start with Roy. Assuming all these agents were approved, what would you like to use in a patient progressing on ceritinib, Roy?

DR HERBST: I would have done the coin flip. I think both these next-generation agents — ceritinib, alectinib — the data are quite compelling, not only because they work in the patients who are ALK resistant but also because of the effects in the brain. I'm not too familiar with brigatinib, so I'll have to ask Corey about that. I know it's part of the trial, a master protocol that's been talked about. I've seen it bandied about.

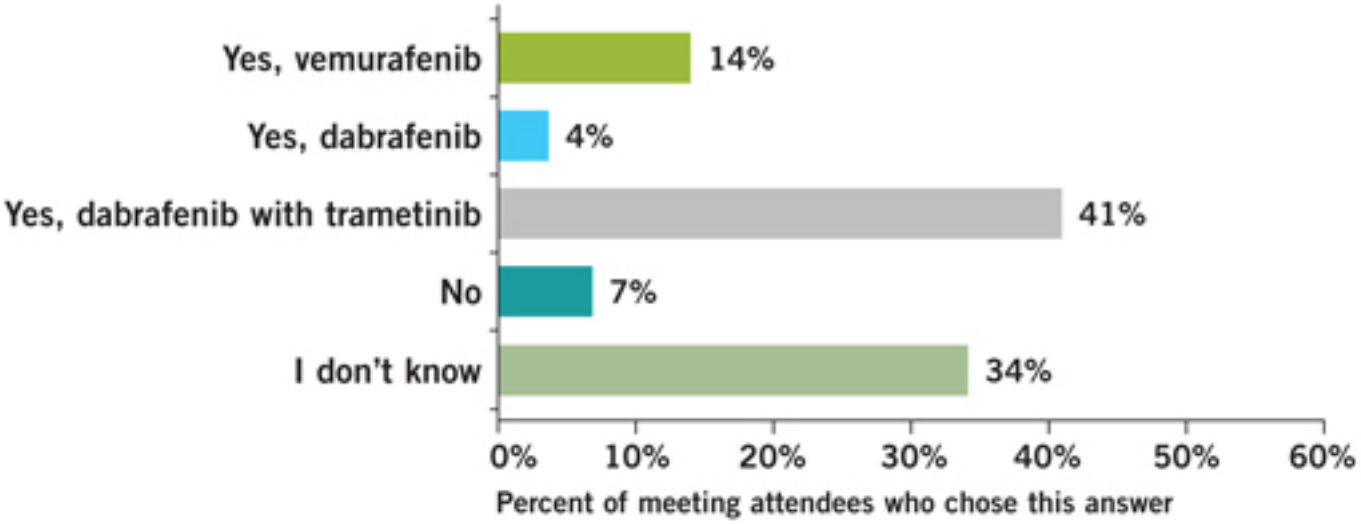
DR LOVE: Also the issue of ceritinib, because we've heard challenges with using the drug, particularly in terms of GI toxicity. I haven't heard that same story with alectinib and brigatinib.

DR LANGER: Because that story doesn't exist. The other two agents have far less GI toxicity compared to ceritinib. I've had a devil of a time managing some of the upper GI side effects. At least one patient, I felt like, was the second coming of platinum. It is not the easiest drug to give. Some people do fine. Many patients do not. I frequently have to dose reduce it. It's the only approved drug currently, but I suspect alectinib, for sure, possibly brigatinib, may garner approvals. They're both on fast track. My answer would have been a coin flip, probably between alectinib and brigatinib.

The response rates and progression-free survival for all these compounds look virtually identical, maybe favoring the two newer-generation drugs. The only answer here that I think is wrong is chemo.

DR HERBST: It is interesting, Neil. As the new kinases are made, they're getting even more specific. It's incredible to me that we keep seeing more and more specific kinase inhibitors, meaning that we are seeing less toxicities.

Cost and reimbursement issues aside, would you recommend a BRAF inhibitor, either alone or in combination with a MEK inhibitor, as either first- or later-line treatment for a patient with metastatic nonsquamous cell lung cancer and a BRAF V600E tumor mutation?



DR LOVE: The final issue that came out, that really was interesting, is the issue of BRAF. We were curious how people are thinking this through. Are they going to use a BRAF inhibitor? This audience, Roy, would use a BRAF inhibitor in lung cancer. The most common choice would be the combination, although a fair number of people would use single agent. Roy, do you use a BRAF inhibitor? Do you use it first line, later line or you combine it?

DR HERBST: It's quite a rare event, but if you can find the V600E patient, which now you're going to find because we're doing these next-gen panels and we have profiles at all of our centers, yes, these patients should get a BRAF inhibitor. I guess you could make a case for front line, though I would probably use it second line. And there are data now for the trametinib combination. That looked quite compelling.