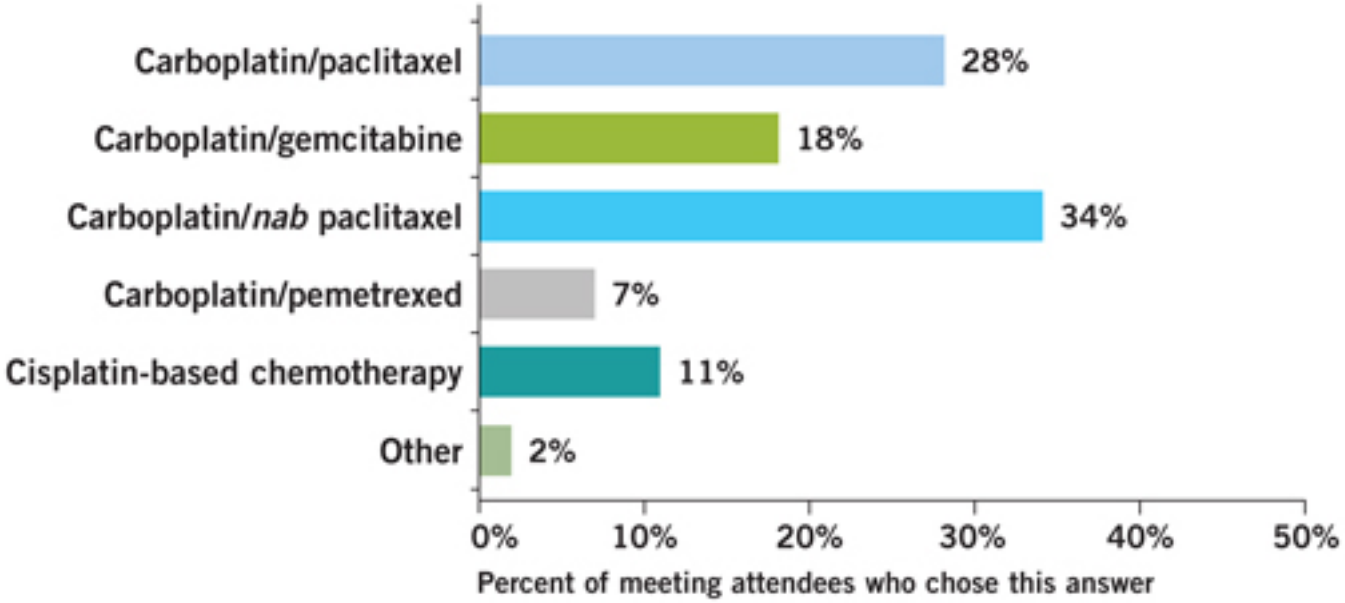
Year in Review

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

Chemotherapeutic and Immunotherapeutic Approaches to Wild-Type NSCLC — Corey J Langer, MD

In general, what first-line chemotherapy regimen would you most likely recommend for an otherwise healthy 65-year-old patient (PS = 0) with metastatic squamous cell cancer (mSCC) of the lung?



DR LOVE: Corey, we're talking about a 65-year-old patient with metastatic squamous cell, likely first-line therapy. We typically see this kind of a split between these choices, a little more *nab* in this group. How do you think this one through, Corey? What's your usual first-line therapy?

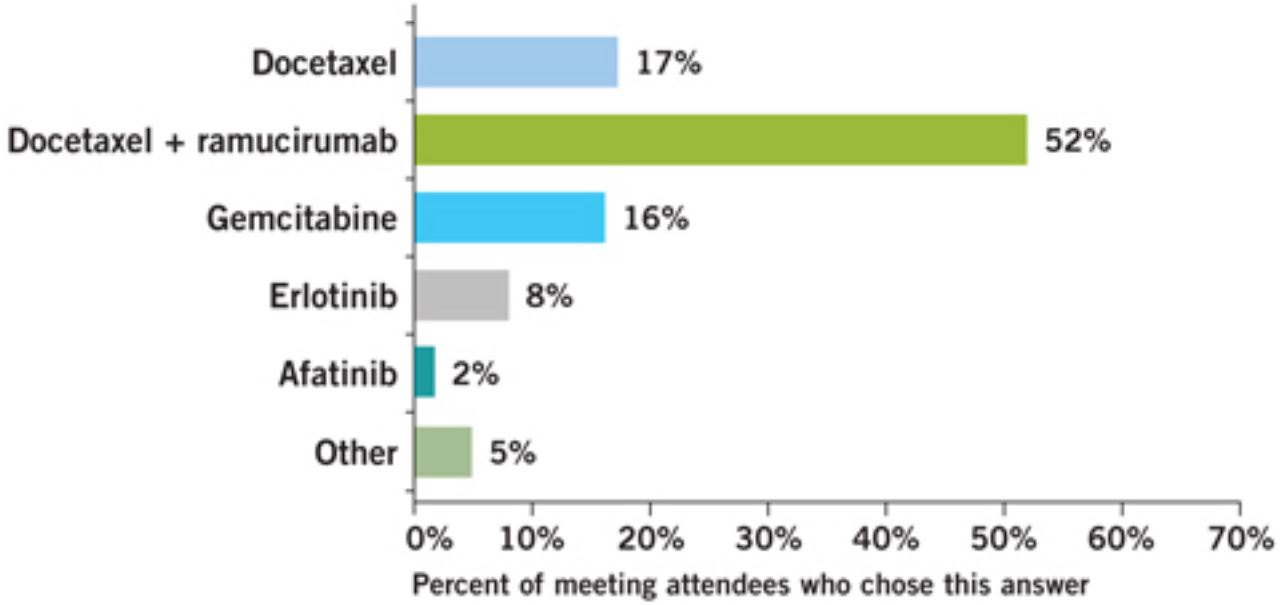
DR LANGER: The only wrong answer here is carbo/pem, pem, of course, not being approved in squamous. Any of the others are quite reasonable. I have increasingly started using *nab*/pac. In the Phase III trial, that combination with weekly *nab*/pac and q3wk carbo resulted in a significantly higher response rate compared to conventional solvent-based paclitaxel and carbo. But that's still a perfectly reasonable option. The two regimens were essentially equivalent when it came to progression-free and overall survival. You can certainly make a case for any gem combination with either carbo or cisplatin. I think all of those are reasonable.

In patients who are 70 years of age or older, we have a subanalysis, about 15% of those accrued to the Phase III trial, where the *nab*/pac/carbo combination did significantly better than conventional q3wk pac/carbo, with about a 9-month survival difference. That's being followed in subsequent randomized Phase II trials.

DR LOVE: Roy, is the amount of corticosteroids that's used typically with paclitaxel, as opposed to, of course, not using it with *nab* paclitaxel — knowing, metastatic squamous, that they're theoretically probably going to be heading toward immune therapy fairly quickly, any issue about corticosteroids and immune therapy?

DR HERBST: I think that is an advantage of a *nab* paclitaxel. As we start thinking about combinations or concurrent schedules, I think that's going to be an advantage for that regimen. That said, the weekly schedule is a bit more inconvenient. I had voted carboplatin/paclitaxel, although as we move toward the immunotherapy, I agree with you, Neil, that we need to look at *nab* paclitaxel a little bit more.

A 65-year-old patient with mSCC of the lung receives first-line therapy with carboplatin/*nab* paclitaxel and responds to 4 cycles of treatment but then experiences disease progression 3 months later. The patient is started on an anti-PD-1 antibody but experiences disease progression. What would be your most likely treatment recommendation?



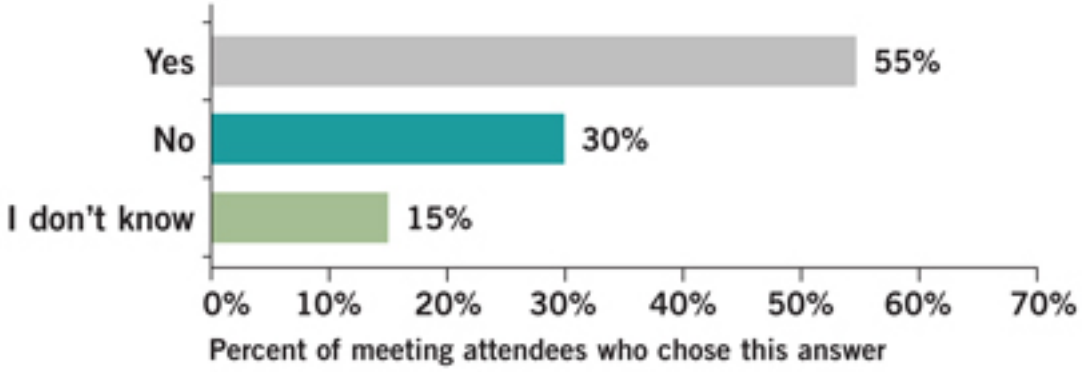
DR LOVE: Corey, we know that second-line therapy, people are thinking about anti-PD-1 nowadays in squamous cell, but we wanted to find out what people do after that because, unfortunately, with all the excitement about checkpoint inhibitors, most people are going to progress. So the question is: What's next?

We asked the audience the same kind of case, except let's assume they get carbo/*nab*, which is what was the most common answer in this audience. They respond but then have disease progression. They get an anti-PD-1, but then they have progression. What's your third-line therapy? What are your thoughts about this, Corey?

DR LANGER: I agree with the response that the majority of you chose. But, remember, this was actually a second-line study. Docetaxel plus or minus ramucirumab was done in patients who had had disease progression generally toward the late stages of prior platinum therapy. That study predated the PD-1 era. Nevertheless, this is now essentially third-line treatment but second-line cytotoxic therapy. We have Phase III data that show clear response, PFS and overall survival benefit for ramucirumab independent of histology — essentially equal results for both adeno and squamous. I would concur.

The one exception here are the really good responders, those who've gone 6 months/a year or more before progression either on the PD-1 or then off the original carbo. In those cases, in select individuals, I've actually reintroduced the platinum and partnered it with one of the drugs they hadn't gotten originally, so perhaps gem/carbo. I realize that's not even in the NCCN guidelines, but I've seen good results with that.

A patient with metastatic adenocarcinoma of the lung experiences disease progression after first-line chemotherapy followed by maintenance. Would you order an anti-PD-L1 assay on the tumor?



DR LOVE: Obviously, the FDA's now reacting to the nonsquamous world and PD-1 antibodies. Maybe, Roy, you can talk about what the current indications are in nonsquamous cancer for nivo and pembro. And this very practical question is: If you have a patient with a metastatic nonsquamous cancer, an adenocarcinoma, do you get an anti-PD-1 assay? What do you think, Roy?

DR HERBST: I would say yes. The question is: Which assay, and where do you send it? If you look at the recent approvals, nivolumab was approved without a companion diagnostic. However, there is what's called the complementary diagnostic. If you read the label and if you look at the presentations in the *New England* paper that just came out, it's quite clear that people do better if they have staining for PD-L1. So, it is, in my opinion, nice to know that, because 50% of the patients who were negative for PD-L1 had very minimal benefit in that study.

For pembrolizumab, which is also now approved, it is approved with a companion diagnostic — by the way, a different companion diagnostic — and for that the data again show that patients would do better if they're PD-L1-positive.

Bottom line: You have the ability to give an immune checkpoint inhibitor to everyone, regardless of assay. But I personally believe that if you know the biomarker and you start to understand the biomarker, it can help you to decide when and how to put these agents forward.

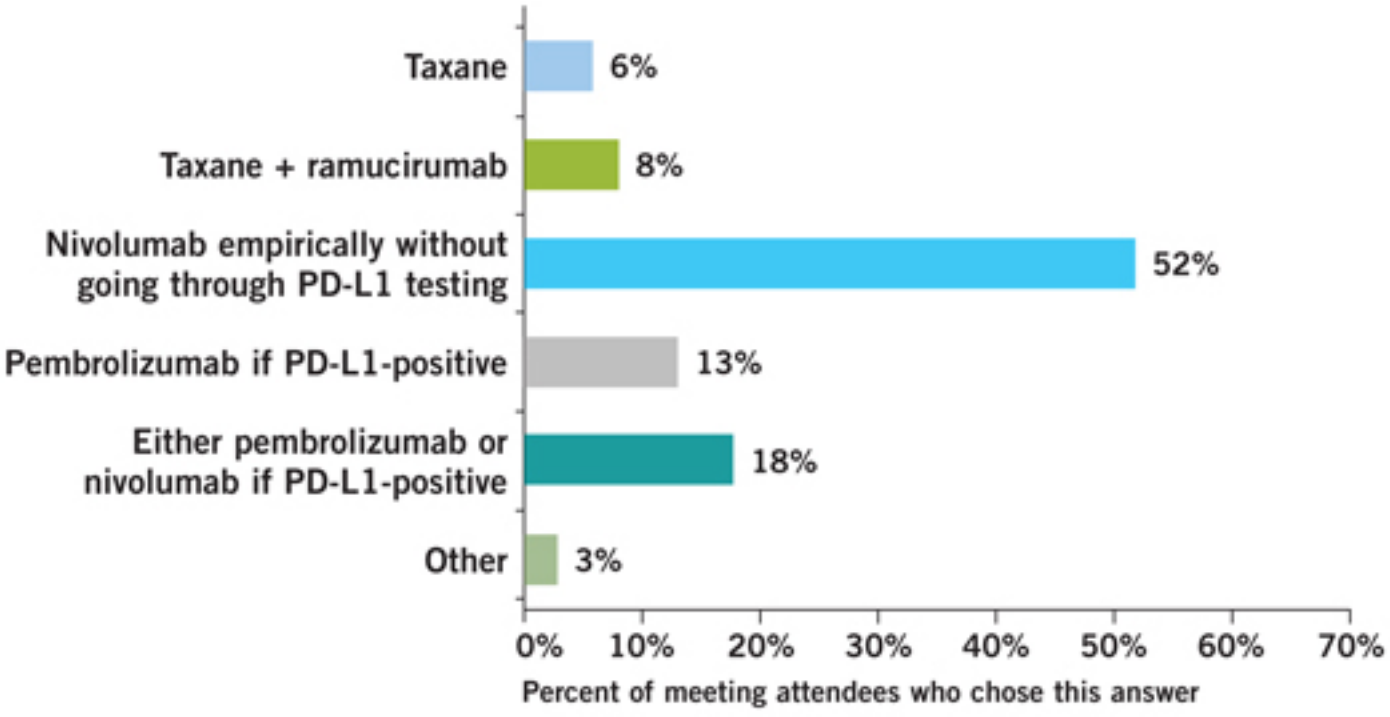
The other thing that's important is: Many of these patients will not respond. Isn't it nice to know by the biomarker early on if they are in that positive group when you're thinking, "Do they have pseudoprogression? What's going on? How long should you push things?" So I'm in favor of the assay, though I must say I'm still a bit confused myself which assay and where to send it.

DR LOVE: Maybe you can straighten us out a little bit, Corey. It seems, empirically, you have a patient with, let's say, an adenocarcinoma. They've had disease progression. You know you're looking at a horrendous prognosis in that situation. Maybe you decide, "Hey. I want to just give an anti-PD-1. I don't care what the PD-L1 assay is." It seems like you could do that with the nivo but you can't with the pembro at this moment. Is that the case?

DR LANGER: That is the case. I agree with Roy. There's tremendous confusion here. The expeditious answer is, "No." The scientific answer is, "Yes." And I don't think either one is wrong.

The pembro data, at least its approval, is paired with a companion diagnostic in the second line. I think Roy's brought up a good case. Maybe you'll stick with the drug longer if there's a question of pseudoprogression or some toxicity. Remember, though, as you'll see shortly in the Phase III trials, nivo is at least as good, if not better, than docetaxel. It's never worse. Even in the group that's PD-L1-negative by the BMS assay, survival curves overlapped and toxicity was considerably less. So you can make a case for "No" on that basis.

A 65-year-old patient with metastatic adenocarcinoma of the lung with no targetable mutations receives carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance during which disease progression occurs. What would be your most likely treatment recommendation?



DR LOVE: We presented this situation of a patient with an adenocarcinoma that gets chemo/bev then has progression. It looks like most of the audience would just go ahead with nivo. Is that what you think you would do?

DR HERBST: This is a tough question. Nivo, that you can do. You don't need a new biopsy. You don't have to figure out where to send it out. You can give the patient nivolumab. Probably about 1 in 4, maybe a little less, will benefit. But when they benefit, it's extraordinary. That's the amazing thing. So, certainly, that's the easiest thing to do. The patients are going to want that. In fact, they're coming in for that. Although I would say that, if you do the biomarker, that could help you at that point to get a sense for how likely they are to benefit. I would like to see biomarkers done, though the path of least resistance is to go with the nivolumab in this way.

DR LOVE: The next time we ask this, should I put, "Do PD-L1 assay. If positive, give pembro. If negative, give nivo," or "Give nivo either way," or what?

DR HERBST: The assays are all different. We're still actually waiting for some randomized data for the pembrolizumab using the biomarker. But if you do the biomarker and it's positive — and the more stringent biomarker is the one that came out with pembrolizumab — only 20% of the patients will have that positive biomarker. I think you've got a slam dunk. You know that the patient's going to do pretty well with pembrolizumab.

If they're negative, then you really have to think. We have to discuss with the patient. Certainly you could use nivolumab. You could think about the chemo combinations just discussed — ramucirumab, other options. I'm hoping a year from now when we sit here, we have other combinations. For those negative patients — and that's more of a research question —we need to think about: How are we then going to enhance the immune response in those patients? But right now, I think the default, Neil, is going to be to give those patients nivolumab. And I understand why.

DR LOVE: When you say "other combinations," other CTLA-4/PD-1, or other "other"?

DR HERBST: Certainly the CTLA-4/PD-1 combination, or PD-L1 combination, makes sense there. There are a host of other agents that are known to target regulatory T cells or affect enzymes and other aspects of the immune microenvironment. Those trials are ongoing.

DR LOVE: Clinical trials are ongoing?

DR HERBST: There are. There are many clinical trials. I think the amazing thing is: The clinical trials now are throughout the community. There is much availability for immune combination trials. That could be another way to do this. If you have a trial running in your practice, you could think about triaging the patient toward that.

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