

# Assessing Immunotherapy Options for PD-L1 NSCLC



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**C**ancerNetwork hosted a panel discussion on non-small cell lung cancer (NSCLC) as part of a *Satellite Sessions* program focused on Winship Cancer Institute of Emory University in Atlanta, Georgia. The program assessed PD-L1 biomarker utility in treating patients with metastatic NSCLC without driver mutations. Additionally, dual immunotherapy options among this patient subgroup were discussed, along with safety profiles.

The panel was led by **Ticiana Leal, MD**, associate professor and director of the Thoracic Medical Oncology Program in the Department of Hematology and Medical Oncology at Emory University School of Medicine. Panelists included **Ioana Bonta, MD**, adjunct clinical assistant professor at Morehouse School of Medicine in Atlanta; **Venu Konala, MD**, medical oncologist at Georgia Cancer Specialists; **Irina M. Knudsen, NP**, nurse practitioner at Emory University Hospital in Atlanta; **Conor E. Steuer, MD**, associate professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine; **Carlos Franco, MD, FACP**, medical oncologist at Georgia Cancer Specialists; and **Jennifer Wilkinson Carlisle, MD**,

assistant professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

**Leal** / What is your general approach for patients with NSCLC without a driver mutation? How do you see PD-L1 as a marker, and how does that influence your decision?

**Bonta** / Does the PD-L1 marker influence your decision? Yes, maybe. If there is somebody with PD-L1 [expression of] more than 50%—I have a patient with a lower volume of disease, PD-L1 80%, 90%, 100%—I am comfortable using immunotherapy [as a] single agent. One problem I have about PD-L1 is that this does not come from the data but...from my experience. If you have a patient [who] has PD-L1 done through different institutions or...panels, there can be some discordance.

What is your preferred category of category 1 of immunotherapy-based regimens? I think of them as interchangeable. I do not think one combination, chemotherapy-immunotherapy, has any advantage over another. This is real, the power of habit. Once you get used to a combination, I tend to keep using the combination. My go-to is carboplatin-pembrolizumab [Keytruda], for instance, or chemotherapy and pembrolizumab [Table]. I can also use

**TABLE. Top Discussed NSCLC Trials<sup>1-4</sup>**

TRIAL NAME	DRUGS	TOP-LINE EFFICACY	SAFETY
<b>Phase 3 KEYNOTE-407 (NCT02775435)<sup>1</sup></b>	Pembrolizumab plus chemotherapy vs placebo plus carboplatin and paclitaxel/nab-paclitaxel	OS: (HR, 0.71; 95% CI, 0.59-0.85) PFS: (HR, 0.62; 95% CI, 0.52-0.74)	Pembrolizumab vs placebo arm, 98.6% vs 98.2% had an AE; grade 3-5 immune-mediated AEs occurred in 13.3% vs 3.2%
<b>Phase 3 KEYNOTE-189 (NCT02578680)<sup>2</sup></b>	Pembrolizumab plus chemotherapy vs pemetrexed and platinum chemotherapy	OS: (HR, 0.60; 95% CI, 0.50-0.72) PFS: (HR, 0.50; 95% CI, 0.42-0.60)	AEs occurred in 99.8% in the pembrolizumab group vs 99.0% in the placebo group; infusion reactions occurred in 27.9% vs 13.4%
<b>Phase 3 EMPOWER-Lung 3 (NCT03409614)<sup>3</sup></b>	Cemiplimab plus chemotherapy vs placebo plus chemotherapy	Median OS: 21.1 months (95% CI, 15.9-23.5) vs 12.9 months (95% CI, 10.6-15.7); (HR, 0.65; 95% CI, 0.51-0.82; <i>P</i> = .0003)	TEAEs: 96.5% any grade, 48.7% of grade 3 or higher
<b>Phase 3 IMpower150 (NCT02366143)<sup>4</sup></b>	Atezolizumab, carboplatin, and paclitaxel vs bevacizumab, carboplatin, and paclitaxel	Median OS: 19.0 months vs 15.0 months (HR, 0.86; 95% CI, 0.73-1.01; <i>P</i> = .07)	TRAEs 94.3% vs 95.9% of any grade; grade 3/4 was 43.0% vs 59.4%
<b>Phase 3 CheckMate 227 (NCT02477826)<sup>5</sup></b>	Nivolumab plus ipilimumab vs chemotherapy	Durable OS in combination vs chemotherapy (HR, 0.77; 95% CI, 0.66-0.91)	Per protocol, patients discontinued nivolumab at 2 years of treatment; at 4-year analysis, all but 1 patient had discontinued treatment in the chemotherapy arm
<b>Phase 3 POSEIDON (NCT03164616)<sup>6</sup></b>	Durvalumab with or without tremelimumab plus chemotherapy vs chemotherapy alone	The median PFS was 5.5 months (95% CI, 4.7-6.5) in the durvalumab plus chemotherapy arm, 6.2 months (95% CI, 5.0-6.5) in durvalumab plus tremelimumab and chemotherapy vs 4.8 months (95% CI, 4.6-5.8) in the chemotherapy arm	Any-grade AEs occurred in 92.7% vs 88.6% vs 89.5% with grade 3/4 TRAEs in 44.6% vs 51.8% vs 44.4%

AEs, adverse effects; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TEAEs, treatment-emergent adverse events; TRAEs, treatment-emergent adverse effects.

atezolizumab [Tecentriq] and cemiplimab-rwlc [Libtayo]. What do you do for the PD-L1 [expression] less than 1%? This is where I am considering not using immunotherapy [as a] single agent. If I cannot do chemotherapy, I am [considering] dual immunotherapy combinations.

**Konala** / I agree with most of what Dr Bonta said. If it is adenocarcinoma, my go-to regimen would be—if the PD-L1 [expression] is less than 50%—using platinum-[based chemotherapy] with pemetrexed and pembrolizumab. In squamous [disease], when I look at the cross-trial comparison, I feel cemiplimab has slightly better efficacy data. I do not know whether it is in squamous compared with other histologies. I am using more cemiplimab in squamous histology. For PD-L1 [expression] less than 1%, I am going with a dual immunotherapy agent, plus or minus chemotherapy. These mutations—*STK11*, *KEAP1*, *KRAS*—all play an important role in determining the prognosis. There [are] more data with durvalumab [Imfinzi] plus tremelimumab [Imjudo], and ipilimumab

[Yervoy] plus nivolumab [Opdivo], in those situations. **Knudsen** / I share those similar trends. I like the dual immunotherapy-only combination for the small subset of patients who have refused treatment at various centers, and we figure [it out] because they do not want chemotherapy. Having a chemotherapy-free agent helps in those situations. And for the PD-L1 negatives and squamous, I do favor chemotherapy and dual immunotherapy. **Leal** / [Women] are underrepresented in the [phase 3 EMPOWER-Lung 3 (NCT03409614)] trial. Look at the numbers; they are small. Another issue with some of these trials is the lack of representation of the patients that we see in the clinic. Certainly, the number of female patients in immunotherapy trials across the board is surprisingly low. Is there a difference there? The subset is too small. Take that with a grain of salt, I would say. In terms of when you look at the data and think about your patients, if chemotherapy-immunotherapy is your preferred strategy, do you prioritize certain patient...or disease characteristics, and in what patients would you use [the regimen from] IMpower150?

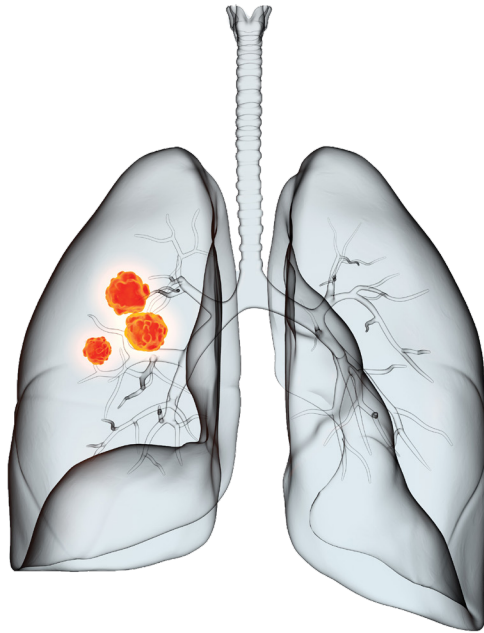
What do you think about the PD-L1 negative subsets across these trials with longer-term survival?

**Steuer** / The first step is knowing...your platinum partner agent... which would be paclitaxel for the squamous [disease] and typically pembrolizumab for adenocarcinoma. [No] PD-L1 inhibitor is better than another one. We did not talk about monotherapy. There used to be a lot more immune monotherapy, but I have moved more toward chemotherapy plus immunotherapy unless there is a low volume of disease or [a frail patient].

I have started incorporating doublet immunotherapy more for PD-L1 low-negative squamous cells. I would never consider using bevacizumab [Avastin]. If there [are] no data that [are] better, then why give someone 4 drugs if you can give them 3 drugs? It just adds toxicity. What challenges remain? Specifically, PD-L1-negative patients, but in general, it is logistics with genomic testing. Everything remains a bit of a challenge when you have to see a patient and wait to have the genomic result in PD-L1, and they have to wait on therapy.

Whether it is you and their disease status or patient [preference], you want to start therapy right away. You start chemotherapy, and then you get back the results. Logistics [are] a challenge. PD-L1-negative patients do not do as well and obviously do not respond to immunotherapy as well. We have made some strides, certainly as a population. Then, as I mentioned, high-risk mutations, *STK11*, etc, can make these patients significantly challenging to treat as effectively as we would like.

**Bonta** / Do I prioritize histology vs PD-L1? I like them both, but I need histology to be able to start treatment. There are instances where I have to start treating without the PD-L1, but I do not want to start treating without the histology. The quadruplet regimen [with atezolizumab, bevacizumab, carboplatin, and paclitaxel]—I agree, I am not using it frequently. I do not [believe] I have used it over the [past] 6, 7, 8 months. In the beginning, when the IMpower150 data came out, we had this subset analysis where patients who had the most benefit appeared...to be patients with *KRAS* mutations and liver disease. If I have somebody with a high burden of disease, a lot of tumors [tissue] in the liver, and [they happen] to [have] *KRAS* alteration, this is when I will consider bevacizumab. Added toxicities, like high blood pressure and urinalysis, but if you do not have those things, maybe some fatigue, I was lucky



[patients] were able to tolerate it fairly well.

I struggle with logistics. Do we have the PD-L1, [do we] have the genomic testing; what other logistics are there? You have to get the scans [for those patients], and they have to see the radiation therapist. In the academic setting, it may be a little easier because you have everything under 1 roof, but in the community setting, your infusion center may be in point A and the radiation oncology across the street, and then the actual office somewhere else. Those challenges remain. You have transportation, you have financial difficulties, financial barriers, and so on.

**Konala** / We need to find some... markers other than PD-L1 [and] PD-L1 [expression] less than 1% to target. We have other approaches in diseases like melanoma where you are combining nivolumab with relatlimab [Opdualag], which is a LAG-3 antibody, which is less toxic vs nivolumab-ipilimumab or dabrafenib [Tafinlar]—trametinib [Mekinist]. Trying other strategies to see if we can overcome the resistance in this population would also help, taking some leads from the other tumors.

**Franco** / What was the rationale for including PD-L1 [expression] in less than 1% of patients in the immunotherapy trials?

**Leal** / PD-L1 is not a perfect biomarker, and as we were talking about before, it is a heterogeneous biomarker. There were data from the early trials that the PD-L1-positive subgroup of patients, early on from the pembrolizumab data, you could see that there was an incremental benefit. When you look at the data, they still benefit from immunotherapy, just not as much. They are still better than chemotherapy.

**Steuer** / With all the caveats of cross-trial comparisons, [CheckMate 227 (NCT02477826) showed] very good data that nivolumab-ipilimumab, whether by itself or with chemotherapy, had for PD-L1-negative patients, and probably better than we have seen in the other studies.

**Knudsen** / The other thing, too, is the duration of response. Even with nivolumab plus ipilimumab, when you look across trials with all the caveats, the duration of response is also significant in the PD-L1-negative subgroup. It is interesting that for chemotherapy plus ipilimumab-nivolumab, the duration of response is less than the ipilimumab-nivolumab alone.

**Steuer** / [CheckMate] 227 was a complicated study, statistically designed and reamended multiple times. I get a little nervous

when we start going too deep into the subgroups there. Who remembers TMB [tumor mutational burden]? I wrote an editorial with [Suresh S. Ramalingam, MD] in the *Journal of Clinical Oncology* on the TMB portion of it when they initially published that, and then that kind of fell away.<sup>7</sup> The data [are] surprisingly good for PD-L1–negative [patients].

**Leal** / Are there certain situations where you would preferentially choose dual immunotherapy without chemotherapy?

**Bonta** / Again, I [prefer] the preferential immunotherapy or the dual immunotherapy as opposed to the combination.

**Carlisle** / I feel the same. If I feel compelled to add a CTLA-4 inhibitor, I feel like I want to keep at least 2 cycles of chemotherapy because it is not the chemotherapy that makes the regimen hard to tolerate.

**Leal** / Then you mentioned the site of metastasis, such as liver, [preferring] bevacizumab. Anybody else [have] any thoughts on the site of disease? Would that impact your treatment approach?

**Franco** / [If I saw] brain metastases, definitely. [I would give] a combination of bevacizumab and ipilimumab. There are a lot of data on melanoma as well as lung cancer.

**Steuer** / I never bought the liver data that [were] pushed hard for 1 year or 2. That is a group analysis. I cannot remember brain data from chemotherapy-immunotherapy, but it also shows a response. I do not know how they directly compare. I do not think the site or volume of the disease helps me decide my treatment approach, or if [the] liver is taken over by disease, I am [likely] not only going to give immunotherapy.

**Leal** / We talked about 2 vs 4 cycles. What about CTLA-4 duration of therapy? Do we need continued maintenance or is a short course of CTLA-4 preferred? If you are going to choose a CTLA-4 inhibitor, how do you choose and what strategy do you find is preferred in what you see in terms of the data?

**Konala** / In [the phase 3] POSEIDON [trial (NCT03164616)], we did not see much benefit in PD-L1 [expression] less than 1% with 1 priming dose. I do not know whether they need continuous CTLA-4 inhibition in the CheckMate trials because using that 1 dose in liver cancer worked in that patient population, but I did not see that in 1 [dose].

**Leal** / As we think about strategies for our patients who may have comorbidities, organ dysfunction, struggling with symptoms due to their underlying comorbidities, as well as their cancer, we now have long-term safety on a lot of these regimens, and a lot of us are comfortable in managing some of the toxicities.

In terms of the grade 3 or higher treatment adverse events [AEs], they can be quite significant. However, the rates of discontinuation certainly are lower, and we are able to manage these toxicities. Events leading to death across the trials were quite low, and perhaps as we get more experience in managing

these, hopefully, we can salvage patients before these toxicities become life-threatening. With the chemotherapy immunotherapy regimens, the main toxicities were from the chemotherapy backbone.

Myelosuppression, by far, was the most common higher-grade toxicity that we saw, but certainly, immune-mediated AEs, the majority of the time, were grade 1 and 2 in nature. We know some of these can be life-threatening and severe. This is, again, cross-trial comparison, but to give you an overall look in terms of safety and immune-related AEs, keep in mind that some of these AEs were reported a bit differently across trials. Sometimes, that is why the numbers could potentially look a bit different across trials.

Looking at the toxicity profiles of the dual-immunotherapy plus chemotherapy regimens across trials, interestingly here, when you look at the high-grade events, I was surprised when I initially saw the data because [they] did not look too [different] from what you would see for chemotherapy-immunotherapy. Certainly, there has always been a concern about immunotherapy toxicities when you add the CTLA-4 inhibitor, and the fact that these regimens used lower-dose ipilimumab in CheckMate 227 and [phase 3 CheckMate] 9LA [NCT03215706] and the POSEIDON trial limited the CTLA-4 inhibition, you are seeing sort of a tolerability of this regimen that looks pretty favorable, in my opinion.

**Carlisle** / I have seen some weird [adverse] effects with CTLA-4 inhibitors, such as high-grade fevers that require inpatient workup, and nothing comes out with each dose that eventually limits that. Or if [a couple of] patients—maybe they are just on the top of my mind because it is hard to manage an itch with no rash at all that doesn't respond to topicals or orals, that it is more bothersome toxicities that maybe are not even listed.

**Bonta** / A big one that I hear frequently is fatigue. It is quite a range from grade 1 fatigue, “I need to take a nap 20 minutes in the afternoon,” to almost a [hypothetical] type of fatigue [where] the patient may be slumped in a wheelchair, and you have to work up adrenal insufficiency.

**Leal** / Is it adrenal insufficiency, or [could it] be something else?

**Bonta** / Sometimes, but not always. I find it difficult because fatigue is such a common symptom of cancer—depression, you do not sleep well, you are tired in the morning—it is very hard to sort out. . . . I had my endocrinologist teach me what I have to order, and I looked at the cortisol level, and at least I screened for that, and that is sufficient. It is easy to fix if you find it. ■



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