

# Evaluating Immunotherapy Options Based on Mutations for NSCLC



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**A**s part of a *Satellite Sessions* program focused on Duke Cancer Center, Cancer Network hosted a panel discussion on non-small cell lung cancer (NSCLC). The program was conducted to assess the efficacy and durability of immunotherapy responses in patients with NSCLC. Immunotherapy options, particularly in combination with chemotherapy, were discussed, along with comparing dual and single-agent immunotherapy measures.

The panel was led by **Neal E. Ready, MD, PhD**, professor of medicine and member of the Duke Cancer Institute. Panelists included **Joel Rivera Concepcion, MD, JD**, assistant professor of medicine and member of the Duke Cancer Institute; **Jeffrey Melson Clarke, MD**, associate professor of medicine and member of the Duke Cancer Institute; **Laura Alder, MD**, assistant professor of medicine and member of the Duke Cancer Institute; and **Afreen Idris Shariff, MD, MBBS**, associate professor of medicine, Medicine, Endocrinology, Metabolism, and Nutrition, and member of the Duke Cancer Institute.

## Clinical Scenario Discussion of NSCLC Adenocarcinoma

**Concepcion** / This is a case I had... I initially [received] this patient and then [enrolled] them in a clinical trial. This is a 47-year-old [woman], a former smoker. Her set of symptoms [included] lower back pain. She was [experiencing] weakness in the lower extremities and loss of sensation.

She also had left arm pain. When they did the imaging, especially looking for the lower back pain, they found multiple diseases in multiple organs, specifically in the left lung mass. It was a 5-cm left lung mass, with metastasis in the bones, liver, right adrenal gland, and especially the lower back. The pain was because she had [an] L3, 4-cm lesion that was pressing on the spinal cord.

Because of the mass and symptoms, she was initially seen by neurosurgery, [which] was using decompression, and then using that tissue was where we did the pathology, which was positive for adenocarcinoma, and it was CTF1 positive. All the clinical signs and histology we discussed with pathologists just to be sure, and we all felt that it was of a lung primary. When we did the biomarker testing, we found out that it was a *KRAS* G12D, but also [that it carries] *STK11*-positive mutation, and it was PD-L1 negative.

[W]hat will be the ideal treatment? It is either chemotherapy plus pembrolizumab [Keytruda], chemotherapy plus cemiplimab-rwlc [Libtayo], ipilimumab [Yervoy] plus nivolumab [Opdivo], chemotherapy plus nivolumab and ipilimumab, or chemotherapy plus durvalumab [Imfinzi] and tremelimumab [Imjudo].

**Ready** / Based on the *KRAS* and *STK11*, what are the chances of responding to single-agent PD-L1 immune checkpoint therapy?

**Concepcion** / One of the ideas is not only the *STK11* prognosis factor but the idea that it does not respond well to immunotherapy. It also correlates with the PD-L1 negative/PD-L1 less than 1%. It

is always hard to know how much association there is, but even with the negative PD-L1 and with *STK11*, when using single-agent immunotherapy, there is no strong advice for that.

[An article] was recently published in the *Journal of Thoracic Oncology*....<sup>1</sup> They look into the *STK11* and *KEAP1* mutations in stage IV NSCLC and went through all the data, especially the phase 3 POSEIDON [NCT03164616], the phase 3 CheckMate 9LA [NCT03215706], and also the phase 3 KEYNOTE-189 [NCT02578680] [trials], which had a small group of studies.<sup>2-4</sup> It was mostly retrospective and exploratory in view—[we] looked into that and tried to assess if having *CTLA-4* would show some benefit or not. In POSEIDON, it initially did...as have some of your analyses that show a tendency for improvement. [It did] in KEYNOTE-189. There was another factor that they saw.

The whole idea is that chemoimmunotherapy should take precedence in this population. They also mentioned that in patients who are PD-L1 negative, not all *STK11* [mutations] are the same, especially when they have concurrent mutations as well. If they have a *KRAS* mutation as well as the *STK11*, or maybe a *KIP1*, or the quantum mutations with loss of heterogeneity, or truncated mutation, specific in certain actions of *STK11*, or missing mutations, and this whole idea that not all *STK11* [mutations] are the same, and maybe in those populations with negative PD-L1; maybe have a triplet that is like *STK11*, *KIP1*, *KRAS*, PD-L1 negative 1%, that could be some idea of using the *CTLA-4*. The consensus was [considering] a chemoimmunotherapy-based approach.

### Inhibitors and Mutations Drive the NSCLC Conversation

**Ready** / There [are] some data that dual immunotherapy may be better for patients with *KRAS/STK11* [mutations] because single-agent responses are very low. There [are] some exploratory data from dual immunotherapy that it may be better. This patient went on a clinical trial.

**Concepcion** / [The patient went on a phase 2a trial] with bemcentinib [NCT05469178], the AXL inhibitor; it is [done in the frontline setting].<sup>5</sup> It is chemotherapy, pembrolizumab, and then they add the AXL inhibitors.

**Ready** / There is some evidence that AXL inhibitors may overcome *STK11* mutation, loss of *LKBI*. There are some upfront clinical trials looking at immunotherapy plus the AXL inhibitor. We have a trial open.

**Clarke** / Have you ever gotten any pushback from insurance?

**Concepcion** / No, but I cannot remember a specific instance where I felt that I needed to carry on with the chemotherapy, but no, generally not.

**Clarke** / OK, the last time I did that, I had to write a letter to justify my decision.

**Alder** / I have the *STK11* alteration frontline trial; if anyone has

“The whole idea is that chemoimmunotherapy should take precedence in this population.”

— Joel Rivera Concepcion, MD, JD

any patients, send them my way. Unfortunately, [my patient] just got her first cycle of chemotherapy, and her bone disease has blown up. She got the first cycle of chemotherapy a few days ago, and now her shoulder is all eaten up with this cancer.

**Clarke** / Is it not the trial reaction?

**Shariff** / It is not the trial reaction. She is in a lot of pain, unfortunately. Hopefully, better days are ahead.

**Clarke** / Is this a study worth traveling for, given the portal option?

**Shariff** / I am glad that you brought up the concurrent *KRAS* mutations, with those being so prevalent within the NSCLC patient population. We have to reexamine other methods from them because they do not respond well to the single-agent immunotherapy, so I appreciate that. ■

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