

Dato-DXd: A Path to Potential Approval in NSCLC



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As part of a *Satellite Sessions* program, CancerNetwork hosted a panel discussion focused on advancements in non–small cell lung cancer (NSCLC) treatment and developments in both antibody-drug conjugate (ADC)–based approaches and targeted therapies. The program brought together experts from City of Hope, including the Orange County Lennar Foundation Cancer Center, Long Beach Elm, and Duarte Comprehensive Cancer Center locations, to discuss efficacy and safety results from the phase 3 TROPION-LUNG01 study (NCT04656652).¹ The trial evaluated datopotamab deruxtecan (Dato-DXd) in patients with nonsquamous NSCLC. Together, the panel discussed whether this agent warrants FDA approval and how to manage treatment-related toxicities for this patient group.

The panel was led by **Ed Kim, MD, MBA**, who is physician in chief at City of Hope Orange County Lennar Foundation Cancer Center, vice physician in chief of the City of Hope National Medical Center, professor in the Department of Medical Oncology and Therapeutics Research, and Construction Industries Alliance City of Hope Orange County Physician in Chief Chair. Panel members included **Nishan Tchekmedyian, MD**, associate clinical professor in the Department of Medical Oncology and Therapeutics Research and deputy physician in chief at the City of Hope Orange County Lennar Foundation Cancer Center; **Suchi Gunasekaran, PharmD, BCOP**, clinical pharmacy manager and PGY1 residency program coordinator at City of Hope–Chapman; **Rachel Mashburn, PharmD, MPH**, executive director of pharmacy at City of Hope Orange County; **Danny Nguyen, MD**, assistant clinical professor in the Department of Medical Oncology and Therapeutics Research at City of Hope Orange County Lennar Foundation Cancer Center; **Arya Amini, MD**, associate professor in the Department of Radiation Oncology and chief of thoracic radiotherapy

at City of Hope Comprehensive Cancer Center - Duarte; **Krushangi Patel, MD**, assistant clinical professor in the Department of Medical Oncology and Therapeutics Research at City of Hope Long Beach Elm; **Percy Lee, MD, FASTRO**, professor and vice chair of clinical research in the Department of Radiation Oncology and medical director of Orange County and Coastal Region Radiation Oncology at City of Hope Orange County; and **George Bernard Semeniuk III, MD**, clinical professor in the Department of Medical Oncology and Therapeutics Research at City of Hope Orange County Lennar Foundation Cancer Center and City of Hope Newport Beach.

Efficacy and Safety Data of TROPION-LUNG01

The TROPION-LUNG01 study randomly assigned patients 1:1 to receive either 75 mg/m² of docetaxel once every 3 weeks (n = 305) or 6 mg/kg of Dato-DXd once every 3 weeks (n = 299). Patients were stratified by histology, actionable genomic alteration, anti-PD-L1 monoclonal antibody in most recent prior therapy, and geography. The data cutoff was March 29, 2023.

The dual primary end points of the study were progression-free survival (PFS) by blinded independent central review (BICR) and overall survival (OS). Secondary end points included objective response rate (ORR) and duration of response (DOR) by BICR and safety. Efficacy analysis included patients assigned to Dato-DXd (n = 234) and docetaxel (n = 234) with nonsquamous histology.

The median interim OS was 13.4 months (95% CI, 12.1-16.4) and 11.4 months (95% CI, 10.1-13.8) in the nonsquamous population in the Dato-DXd and docetaxel arms, respectively (HR, 0.79; 95% CI, 0.60-1.02).¹ Furthermore, those with nonsquamous disease had a median PFS of 5.5 months (95% CI, 4.3-6.9) and 3.6 months (95% CI, 2.9-4.2) in each arm, respectively, with an HR of 0.63 (95% CI, 0.51-0.79).

Patients with nonsquamous disease had an ORR of 31% (95% CI, 25%-38%) and 13% (95% CI, 9%-18%) in the Dato-DXd and docetaxel arms, respectively. A complete response was observed in 2% and 0% of patients, and a partial response was observed in 30% and 13% of each arm. The median DOR was 7.7 months (95% CI, 5.6-11.1) and 5.6 months (95% CI, 5.4-6.0), respectively. Additionally, the disease control rate was 80% (95% CI, 75%-85%) and 61% (95% CI, 55%-67%) in the Dato-DXd and docetaxel arms, respectively.

Any-grade or grade 3 or higher treatment-related adverse effects (AEs) were reported in 88% and 22% of the Dato-DXd arm and 88% and 21% of the docetaxel arm. Any-grade AEs of special interest in either arm included stomatitis/oral mucositis in 57% vs 22%, ocular events in 20% vs 11%, and adjudicated treatment-related interstitial lung disease (ILD) in 8% vs 3%.

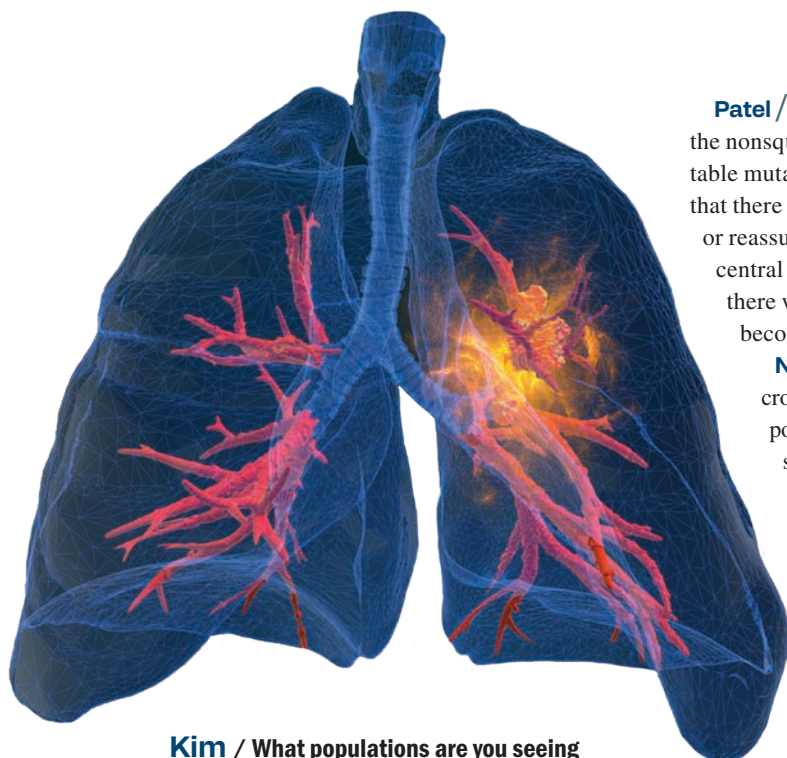
Addressing Unmet Needs for Patients Without Actionable Genomic Alterations

Kim / In your practice, what percentage of patients with NSCLC do not have actionable genomic alterations? What is the greatest unmet need in treating this patient population, and how are you approaching second-line treatment in patients with nonsquamous [disease] without actionable genomic alterations?

Nguyen / In California, we have a very large Asian population. I would say [approximately] 60% to 70% have some sort of actionable mutation that we find. The greatest unmet need for the patients who do not have actionable mutations is just trying to find some effective therapy that can also be given conveniently and with minimal toxicity. For the patients in the second line with nonsquamous [disease] without actual genomic mutations, I am sending them for clinical trial evaluations. [For the many] things that we do not perceive as actionable right now, or at least do not have approvals, we might have something in the clinical trial setting that is targeting some special mutations that they might have. I am [often] sending these patients for clinical trial evaluations [for] second opinions.

Semeniuk / I would say 50% [of patients] have actionable mutations. If you do not have an actionable mutation, we're stuck, because then we have to fall back on [docetaxel] plus or minus [ramucirumab, which] is a pretty pathetic second-line therapy for these patients. It is still in the National Comprehensive Cancer Network [NCCN] guidelines. It is still a standard of care. We try to find clinical trials if we can, but we rely on that as our fallback. I do look at the PD-L1... and...at how long patients have had an initial response. But in general, it comes down to docetaxel-[ramucirumab]. Sometimes if they have received something different than [carboplatin and pemetrexed], then I will switch to gemcitabine or another agent.

Patel / I see [approximately] 30% or so [who] do not have actionable genomic alterations, and we do see quite a bit of Asian patients. We have a lot of diversity down in the Long Beach area. The greatest unmet need is what people can tolerate, and for some of the older patients—after they have gone through months of triplet therapy—trying to offer them another chemotherapy can be challenging. But that is what we have, that standard of care. There are a couple trials we have open right now that are early phase. If patients maintain their performance status through the triplet therapy, and if we can catch their progression early and they have not declined, then that becomes a good option for them.



Kim / What populations are you seeing referred by your fellow medical oncologists?

Amini / Specifically for stage IV, we see more of the oncogenic drivers. Two-thirds have a driver or actionable mutation and one-third do not, for at least what I am seeing. The 2 populations for stage IV we see are [those with] symptomatic lesions that need radiated brain metastases, which may or may not need to be radiated.... Then the [patients with] oligometastatic [disease]... [who], before we had our clinical trials, we were [treating] off trial where they are on their first-line therapy, [which is] starting to fail them in a few sites, and we are radiating them to try to keep them on that therapy.

Kim / Percy, from an Orange County standpoint, are you seeing [many] differences to what Arya is saying?

Lee / It is very similar. Sixty percent with genetic mutations are actionable. We get a skewed population, right? There are typically more favorable oligometastatic sites that we can radiate. Then the discussion is maintaining them on the systemic therapy they are on because there are no good other options or clinical trials or radiation.

Panel Perspectives on Dato-DXd Efficacy and Safety

Kim / What are your thoughts on these efficacy and safety data? Are there any things about the trial design that make you pause regarding its relevance to nonsquamous NSCLC? If so, what additional data would you like to see?

Patel / Certainly, Dato-DXd is providing a decent option in the nonsquamous group. That is, those who do not have targetable mutations. For trying to isolate it, the concern would be that there are not good OS data yet. The reliability or reassurance is that there are good PFS data. It also has central nervous system [CNS] penetration. Certainly, if there were patients who have CNS involvement, this becomes a good option.

Nguyen / I like the PFS data. I agree that the OS [HR] crossing 1 [makes me] wish we would have a little more positive data in that respect. I do like the fact that it also seems to be well tolerated. It is a good alternative to just plain, old docetaxel. At least for the [patients with] nonsquamous [histology], it represents a good alternative option. Certainly, having more treatment options for these patients is welcome.

Tchekmedyian / One of the big unmet needs is what Dr Patel said, which is having an active agent in the CNS. We lose patients in the CNS, and we are thankful to our radiation colleagues who helped so much with advanced techniques there. We need more drugs that go there. I like the fact that [Dato-DXd] has a relatively high ORR. If I have a patient who is symptomatic or [needs a positive] response, and if there is a signal in the brain, I like that, too.

Nguyen / The data seem to be a little more positive in patients who do have actionable alterations, and it looks like it got lumped all together. Perhaps teasing out which genomic alterations had improved responses would be nice. There [are] so many that we check for now. It will help us to determine for those specific patients [whether] Dato-DXd is a good option.

Amini / [Did investigators] look at brain response rates?

Kim / We will see some of those data as they continue to mature. [Many] people are starting to report that at least there is some activity that you can see there.

Approval Debate for Dato-DXd

Kim / Should [Dato-DXd] be approved for this patient population?

Semeniuk / This [most likely] will be approved. Early studies with this drug demonstrated that there is similar efficacy despite different dose levels of 2, 4, 6, and 8 mg/kg. The big problem with this drug is the stomatitis. I would have no hesitation if it were approved to use it in a lower dose or dose reduce early if patients did run into toxicity.

The intention-to-treat analysis did come back positive for the PFS, which, if you do the math, was not very much—[approximately] 7 weeks. I get a little queasy when I start looking at studies that have multiple primary end points because, statistically, I know there are issues about how you are going to run the study [and] how you are going to do your analysis.

There are different ways to do it, and the FDA is giving guidance on it. What we do know is that the efficacy is much better if you have an actionable mutation. We will see that in the phase 2 TROPION-Lung05 study [NCT04484142].² I would shy away from this for [patients with squamous disease], based on the histology. The other issue is the ILD. This drug does cause ILD, and there were [several] grade 5 ILDs, which you have to discuss with patients. [Docetaxel also] had ILD, but the difference was 8% vs 4%. That underscores that we have to be careful about not only the efficacy but [also] balancing the risk-benefit analysis and the toxicity, which is what the FDA will do. I do not know [whether] it will be approved specifically for histology, but we will have to see.

Nguyen / I would like to see this drug on the market for patients with nonsquamous [disease] without actual mutations. If you have actual mutations in the second line, this could be an option, but you are probably looking at other clinical trials testing newer things that are targeting those mutations.

Patel / It certainly seems like there is enough benefit in the PFS area and in a specific group of patients...with the nonsquamous [disease]. I would not give it to somebody who has squamous cell carcinoma and I, in practice, would not give it to somebody who has another targetable treatment. I would consider it in somebody [with] CNS disease, and I would consider it in patients who do not have other therapy or who cannot tolerate docetaxel.

Tchekmedyan / There is room for the drug. We always take patients in specific situations into account. If there is a patient who is at a very high risk for neutropenia and fever that we think has a high mortality, we would shy away from the drug that causes more of that. If we think there is a patient who has a very high risk for pneumonitis who maybe got radiation in the lungs instead of the pelvis or [elsewhere], then we might go [forward with] the drug that favors that. Those are the types of [scenarios] that would go through my mind.

Lee / This is not specific to this, but they are looking at the patient profile. There are very few African American patients, which is typical for these studies. You wonder [whether] it works for everybody. I mean, as it may be, I am not a medical oncologist, but looking at the PFS curve, they all cross at 16 months. That is much better than the standard of care. The question is: If it does not translate over survival as sequencing, which one do you get first?

Semeniuk / With regard to squamous, it looks like the HR is [more than] 1. It was detrimental to give this drug to a [patient with] squamous [disease]. I do not know what the FDA is going to do about that.

Kim / It has to be a nonsquamous indication because there was harm, as you say, George. I am going to ask our pharmacist now. You get to put your FDA hat on. What do you think, Suchi?

Gunasekaran / I would agree with our oncologists, but we disagree with them often in a very healthy way. I would love to see this come to market. We have a lot of [patients in] clinical trials who have seen benefit from this drug, and the opportunity for it to be there, especially with the CNS data, is compelling. I agree, it is well tolerated. I would love to see this on the market.

Mashburn / I would agree. I would just add, given the [AE] profile of the stomatitis, to make sure the patient's given a steroid mouthwash early on and start it prophylactically. [Having a] pharmacist available to provide that education would be key.

Kim / Am I going to be the only contrarian in the room? I think it is going to be a tough sell. It [may be for] a subset [of patients]. From a patient aspect, do I want the drug approved? Absolutely. We always like to have options for the patients, but just as all of you alluded to, this is tight.

Semeniuk / I could see the FDA not approving this too.

Kim / What if you were the FDA?

Nguyen / I would invite this group to the Oncologic Drugs Advisory Committee.

Managing Toxicities in Dato-DXd Treatment

Kim / Are there some good techniques for stomatitis, mucositis, and ocular toxicities that would help any of our medical colleagues here?

Mashburn / [For managing] stomatitis, we do. On the ocular side...maybe we would consider partnering with ophthalmologists early on and having a patient seen before each treatment. We do not have a lot of options there. We have a steroid eye drop, but I do not know that we are as comfortable with it. We would want to involve other professionals.

Gunasekaran / With the ocular toxicities, some more

experience with real-world patients is needed. Making sure they are seen by an ophthalmologist and have an eye exam before every dose seems very cumbersome, but that is what we are doing today. We are comfortable. We do not know how we can dose reduce, [whether] we would, or [whether] that would help any of the [AE] management.

Patients with stomatitis underreport, quite honestly, and it often gets to a point where it is more difficult to manage. Even though you are giving them prophylaxis, they might not be as [adherent]. Having that pharmacist or someone in the care team available for them to reach out to [and to] enforce the importance of it early on, but sometimes it gets to that point where it is very difficult to reverse.

Tchekmedyan / The first thing that helps is having the patient take off their mask and looking in their mouth. Making sure there is some education for physicians, advanced practice providers, and nurses to look inside the mouth and examine the gums, the buccal mucosa, the tongue, and underneath the tongue to see whether there are aphthous ulcerations is important. No. 2, if it is a patient who might have herpes-associated lesions, think about that and occasionally you can find one; you can even swab it and identify it. Those patients may benefit from acyclovir. No. 3 [includes] the magic mouthwash types of things. No. 4 is... dexamethasone swish and spit rinses. Sometimes we forget that, and they have to be compounded. You have to know the places in your community that do this and can get it to the patient quickly. For most, it works better when you get it before they start the drug. I always talk about a care pack for that, and I know putting that in the label makes everything so complex, but from an education standpoint, getting the patient a [care pack] they can use is very helpful. That is how you keep people out of the hospital.

Semeniuk / The dexamethasone is a great pearl. Same with ocular toxicity; you start eye drops early and up front. With the ILD from these drugs, it is different from the pneumonitis we see from the immune therapies and checkpoint inhibitors. The guidelines are very different. The breast colleagues check CT scans every 9 weeks. You are going to have to adopt that because once the patient has a mild cough, they are done. You want to catch grade 1 pneumonitis up front. This is very different from if you have lung toxicity from a checkpoint inhibitor; you can let them go to grade 2. Even in the NCCN [guidelines], they are saying that, in certain circumstances, you can go to grade 3, and if they rapidly resolve, you can challenge them where you cannot with these ADCs.

Kim / That is an important point. We lull ourselves into [saying] we are used to ILD now because of different drugs that are on the market, but there are differences for sure. We are at least more accustomed to having a multidisciplinary team help us out and raising the flag of awareness earlier than later.

Semeniuk / That is a great point. On the immunotherapies, it is hard to find a hepatologist or a gastroenterologist. It is [also] hard to find dermatologists but not pulmonologists. Pulmonologists are around, and getting them involved up front and following up with you does help. ■

REFERENCES

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