

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



Editor's Note: This is a transcript of a discussion on March 25, 2026. It has been edited and condensed for clarity. To obtain credit for participation [CLICK HERE](#).

Jamie Chافت, MD: Welcome! I am Dr. Jamie Chافت, MD, from Memorial Sloan Kettering Cancer Center. In this accredited webinar, we are going to discuss the ORCHARD trial. Specifically, the arm focusing on osimertinib plus Datopotamab deruxtecan (Dato-DXd) in patients with epidermal growth factor receptor (EGFR) mutant lung cancer who have had progression on frontline osimertinib. This article was published on March 2, 2026, in the *Annals of Oncology*.

I'm joined by Dr. Jonathan Riess, MD, MS, from the University of California Davis Comprehensive Cancer Center, who is the lead author of this article. Doctor Riess, welcome, and thank you for joining us. Would you mind giving our listeners an overview of why this trial was conducted?

Jonathan Riess, MD, MS: Thanks so much, and great to be here. This trial was conducted because we still have significant gaps in the care for our patients with advanced EGFR mutated non-small cell lung cancer, particularly following disease progression on frontline EGFR therapies such as osimertinib, and now frontline options have really expanded for patients with EGFR-mutated non-small cell lung cancer. In addition to single agent osimertinib, there is the FLAURA-2 regimen with carboplatin, pemetrexed, and osimertinib, there is also the MARIPOSA regimen with amivantamab plus lazertinib.

There is no free lunch, and whenever you add treatment, an increase in toxicity and treatment burden on patients, weighing that vs the survival benefits observed in FLAURA-2 and MARIPOSA, vs single agent osimertinib. And so, with patients who do get osimertinib-containing therapy, there is good rationale for continuing osimertinib following progression because you continuously suppress the EGFR mutations and there is also that potential benefit of the CNS activity of osimertinib. There was the COMPEL study where continuing osimertinib and then layering on platinum pemetrexed after progression on initial first-line osimertinib resulted in improved clinical outcomes compared to just the second-line chemotherapy alone. This is taking a similar approach here, but with Dato-DXd, a TROP2 antibody drug conjugate (ADC). In addition, there is only modest benefit from current second-line treatment options, whether it be platinum plus pemetrexed after progression on first-line osimertinib, for example, or platinum plus pemetrexed with the addition of amivantamab, and now with the approval of Dato-DXd as a single agent, we've moved the bar, but there's still room for improvement.

Jamie Chافت, MD: Right, and we now know that Dato-DXd is approved for this population after both osimertinib and chemotherapy, so I was super excited to see this publication to learn more about the combination. So I will start by asking you, on this specific arm, what were the objectives of the trial?

Jonathan Riess, MD, MS: The primary endpoint of the ORCHARD trial was to assess the confirmed objective response rate. There were also some key secondary endpoints that

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included progression-free survival (PFS), overall survival (OS), duration of response (DoR), safety, and adverse events, and a lot of interesting exploratory endpoints characterizing the mechanisms of resistance prior to initiation of Dato-DXd with osimertinib. That was after first-line osimertinib.

Jamie Chافت, MD: So, for this trial in patients specifically with advanced metastatic non-small cell lung cancer, what were the key inclusion criteria?

Jonathan Riess, MD, MS: The key inclusion criteria were patients had to be adults 18 years age or older, 20 years of age in Japan, patients had to have locally advanced or metastatic non-small cell lung cancer harboring an EGFR sensitizing activating mutation. Patients with exon 20 insertions, for example, were excluded. Patients had to have good performance status. They had to progress on first-line of osimertinib without intervening therapy. They had to have stable asymptomatic central nervous system (CNS) metastases. Patients with CNS metastases were allowed, so that was an advantage. So, if you did not have CNS metastases they were included in the study, or patients that did have CNS metastases were allowed if they were stable and asymptomatic, and patients overall had to have adequate organ function in terms of laboratory data, kidney function, liver function, hematologic function and so forth.

Jamie Chافت, MD: Right, and if I remember correctly, they had to tolerate 80 mg of osimertinib to enroll in this study.

Jonathan Riess, MD, MS: Correct. Yes, they had to be on 80 mg of osimertinib, the FDA approved dose, to be eligible for the study.

Jamie Chافت, MD: So, what were the other key exclusion criteria? Who was not included?

Jonathan Riess, MD, MS: If you had other treatment besides osimertinib, you were excluded. If you progressed quickly, so primary osimertinib resistance, progression within 3 months on first-line osimertinib, if there was histologic transformation to small cell lung cancer or squamous cell. You were excluded if you were off osimertinib for more than 60 days prior to first dose of treatment on the study, and if you had any substantial toxicity to osimertinib. Again, patients had to be on the 80 mg dose of osimertinib and be able to tolerate that dose in the first-line setting.

Jamie Chافت, MD: So, this was only one arm of a very big study, open label phase 2, conducted at 33 different sites, 8 countries. Can you tell us about the specific interventions published in your paper?

Jonathan Riess, MD, MS: Yes, so patients that progressed on the first-line of osimertinib, they again continued the osimertinib 80 mg once daily, and then the study examined 2 dose levels of

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Dato-DXd, the 4 mg/kg dose and the 6 mg/kg dose, IV once every 3 weeks. There were premedications, with standard therapy required prior to each dose of Dato-DXd.

Jamie Chافت, MD: Right. Who enrolled in your trial? Who were the patients?

Jonathan Riess, MD, MS: The trial enrolled 69 patients. There were 35 patients in the Dato-DXd 4 mg/kg cohort, and 34 in the 6 mg/kg cohort. Median age was 62 years in the 4 mg/kg, and 63.5 years in the 6 mg/kg, respectively. The majority of patients were women, 69% and 65% in the 2 cohorts, respectively, and 6 patients in the 4 mg/kg cohort and 10 patients in the 6 mg/kg cohort discontinued treatment due to an adverse event.

Thirty-one patients in the 4 mg/kg cohort and 21 patients in the 6 mg/kg cohort had a progression-free survival event and there were 2 patient deaths in the 4 mg/kg cohort, and 1 patient died in the 6 mg/kg cohort, but those patient deaths were considered unrelated to treatment.

Jamie Chافت, MD: So, it seemed small numbers, of course, but the PFS seemed to be a little higher in the higher dose of Dato-DXd, however, there were more discontinuations, right? So, would you describe these data to us?

Jonathan Riess, MD, MS: In terms of the efficacy endpoints, looking at the 4 mg/kg and the 6 mg/kg dose levels, the response rates were comparable at 43% in 4 mg/kg cohort and 36% in the 6 mg/kg cohort. Time to response, though, was shorter in the 6 mg/kg cohort at 1.4 months vs 2.7 months in the 4 mg/kg cohort. Again, this was not intended to be a randomized study to look at this.

In terms of what was interesting were some of the key secondary endpoints. The median PFS was 11.7 months in the 6 mg/kg cohort and 9.5 months in the 4 mg/kg cohort. Median OS was 26.2 months in the 6 mg/kg cohort and 19.8 months in the 4 mg/kg cohort. The other thing that was interesting was the median duration of response. The median duration of response in the 6 mg/kg cohort was 20.5 months and then in the 4 mg/kg cohort the duration of response was 6.3 months. And then the duration of response lasting longer than 1 year was 50% in the 6 mg/kg cohort and only 20% in the 4 mg/kg cohort. This was really intriguing and suggested that the dose intensity, particularly at the beginning of treatment with the 6mg/kg cohort, could have had an impact.

Jamie Chافت, MD: It is interesting, and with the minority responding, you have to wonder, is there a biomarker hidden there somewhere? Now, to talk a little bit about safety. You already touched upon the relatively high discontinuation rate, but it seemed that the profile was consistent with what we know of both drugs individually with nothing really amplified in combination, but what did you see in your 2 cohorts?

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Jonathan Riess, MD, MS: Looking from a safety perspective, grade 3 or higher adverse events (AEs) occurred at 49% in the 4 mg/kg cohort and at 76% in the 6 mg/kg cohort. The most common adverse events are what we know about Dato-DXd and included stomatitis, nausea, and alopecia. The key AEs that were more common in the 6 mg/kg cohort were stomatitis (76% vs 66%) and nausea (74 vs 57%), the higher percentage being the 6 mg/kg cohort for all.

One thing we are all concerned about with these ADCs, and the interaction with osimertinib, is rates of interstitial lung disease (ILD) and pneumonitis, and so at the 6 mg/kg cohort it was 15%, and it was 3% at the 4 mg/kg cohort. Dose reductions occurred at a higher rate as well, 59% in the 6 mg/kg cohort vs 23% in the 4 mg/kg cohort. Now, the safety data overall was consistent with what we know about the monotherapies, so no new safety signals were identified.

Jamie Chافت, MD: It is one of these really interesting things that we thoracic oncologists have to learn is that this is different than immunotherapy-induced pneumonitis, where there is actually a dose relationship, and patients can be dose-reduced after recovery, which is a bit foreign to us from our familiarity with immunotherapy.

Jamie Chافت, MD: Right, so really great data because we have this Dato-DXd monotherapy option currently FDA-approved in later lines for EGFR-positive non-small cell lung cancer, and we are a little anxious to stop the osimertinib. It is great to see what the safety profile truly is from this small patient population.

What are your conclusions? What did you and your colleagues think of this data specifically from the Dato-DXd arms?

Jonathan Riess, MD, MS: Overall, what we concluded was that osimertinib in combination with Dato-DXd, especially the 6 mg/kg dose, did look like it provided clinical benefit to patients with EGFR-mutated advanced metastatic non-small cell lung cancer who progressed on osimertinib therapy. Again, we saw comparable response rates between the 4 mg/kg cohort and the 6 mg/kg cohort, but that intriguing 20.5-month duration of response in the 6 mg/kg cohort compared to 6.3 months with the 4 mg/kg cohort. That added efficacy was at the expense of some higher rates of known toxicity of both drugs, at the 6 mg/kg dose Dato-DXd, which is the FDA-approved monotherapy dose and the dose moving forward in future studies with the combination based on this study.

Jamie Chافت, MD: We think of second-line chemotherapy in this patient population having a response rate around 30% to 35%. Did your Dato-DXd arms meet the preplanned bar for being intriguing?

Jonathan Riess, MD, MS: It did meet it in terms of showing the response rate and durable responses with the combination. It is interesting, you have the potential for enhanced CNS

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penetration, you have the potential of mediating resistance in terms of EGFR-tyrosine kinase inhibitor (TKI) resistance mechanisms and ADC-type resistance mechanisms. There is the potential of nonoverlapping mechanisms of action, continuing the osimertinib, and getting more durable benefit. Again, we will have to see what the future studies hold.

Jamie Chافت, MD: This was a broad study, multiple arms, but not randomized, really. How do these results translate into practice today? What are we looking at in the future?

Jonathan Riess, MD, MS: I think the results highlight the potential benefit of this combination of osimertinib and Dato-DXd, so it is a new combination option where we found the dose that, weighing the risks and the benefits, appears to be effective and has a manageable toxicity profile. The 6 mg/kg dose did have more side effects. These results from the ORCHARD study are promising and suggest clinical benefit of the combination of osimertinib and Dato-DXd following progression on osimertinib.

Jamie Chافت, MD: What do clinicians have to think about to make these treatment decisions?

Jonathan Riess, MD, MS: Well, you really need to weigh the individual patient characteristics when considering treatment selection. In both the first- and second-line settings, there are multiple treatment options now and combination strategies, so we really have to involve the patient in shared decision-making. Dato-DXd is approved already as monotherapy after platinum-based chemotherapy. We wait to see the results of Dato-DXd vs platinum-based chemotherapy after osimertinib, which is a separate study. This really holds promise, analogous to the COMPEL study of continuing with osimertinib with platinum plus pemetrexed and seeing what mileage can you get by potential enhanced CNS penetration, nonoverlapping mechanisms of action, nonoverlapping acquired resistance mechanisms, and how this may impact efficacy in terms of using this combination for future studies in the first-line and the second-line settings.

Jamie Chافت, MD: Right, what are those studies? These were 2 single arms. We see small numbers, intriguing PFS, but what are we looking at moving forward in terms of Dato-DXd and EGFR mutant lung cancer, as well as the combination?

Jonathan Riess, MD, MS: We looked at the 4 mg/kg and 6 mg/kg doses of Dato-DXd with osimertinib, but there was no comparison arm, and so we really need to do randomized studies. And so there are 2 randomized phase 3 studies that are building on these results. There are TROPION-LUNG 14 and TROPION-LUNG 15 studies that are in the first- and second-line settings in advanced EGFR mutant non-small cell lung cancer. And these studies will be using the 6 mg/kg dose of Dato-DXd with osimertinib, moving forward, based on the results of this study. Another thing we need to probe further is how the combination impacts CNS activity. CNS evaluation in terms of imaging and so forth, in ORCHARD, was only required for all patients

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at baseline, and so these randomized studies are looking at more detailed CNS endpoints, which will also help examine this further.

Jamie Chaff, MD: That is great. Well, thank you, Dr. Riess, for joining me, discussing this important trial, and we certainly look forward to the randomized data in the upcoming years.

Jonathan Riess, MD, MS: Thanks so much, great to be here and chat with you.