

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



Adjuvant Nivolumab vs Observation in Resected Non-Small Cell Lung Cancer: A Randomized Clinical Trial

Dr. Jamie Chaft & Dr. Isabel Preeshagul

Editor's Note: This is a transcript of a discussion on July 31, 2026. It has been edited and condensed for clarity. To obtain credit for participation [CLICK HERE](#).

Isabel Preeshagul: Welcome, everyone. I am Dr. Isabel Preeshagul from Memorial Sloan Kettering Cancer Center, and in this accredited webinar we are going to discuss this very exciting article titled "Adjuvant Nivolumab vs Observation in Resected Non-Small Cell Lung Cancer: a Randomized Clinical Trial." [The article] was published recently, June 1, 2026, in the *Journal of the American Medical Association* (JAMA). I am thrilled to be joined by Dr. Jamie Chaft, my incredible colleague from Memorial Sloan Kettering Cancer Center, who was the lead investigator and author on this trial. Welcome, Dr. Chaft. Could you please provide us an overview of why this trial was conducted?

Jamie Chaft: That is easy, and I am glad you started with the concept that this is exciting. I am not so sure everyone would agree with that, but I think it is important, if not exciting. This study of adjuvant nivolumab was created in the era when we had first seen signals of efficacy for immune checkpoint inhibitors, first in melanoma, then in the second-line treatment of metastatic non-small cell lung cancer. When this study was designed, immune checkpoint inhibitors were not even being tested in frontline lung cancer and the concept was our adjuvant therapies for completely resected non-small cell lung cancer treated with platinum-based chemotherapy, most commonly cisplatin, really were not good enough. We were curing 5% of patients, but too many patients continued to have disease relapse and death from disease. The proposal to study adjuvant nivolumab vs standard of care was intended to improve upon that, really improve the 5% to 15% improvement in survival from chemotherapy, particularly in those patients who might still have residual disease after adjuvant chemotherapy. Nivolumab was prescribed for up to a year. Initially, the study was designed with endpoints of disease-free survival (DFS) and overall survival, and later modified based on updated data.

Isabel Preeshagul: You already briefly touched on the objectives of the trial, which was overall survival if disease-free survival (DFS) benefit was obtained. Could you talk a little bit more about that?

Jamie Chaft: The primary endpoints of this study were initially disease-free survival, and if disease-free survival was positive, overall survival. As the data evolved, we saw that PD-L1 expression by immunohistochemistry was predictive of response. Actually, how the study was originally proposed, however, the biomarker was not felt to be far enough along in development. We modified the design to look at the populations of both PD-L1 all comers [patients], the intention-to-treat population, as well as a subset [PD-L1 high ($\geq 50\%$) population]. Now, that subset would only be analyzed if the intention-to-treat population was negative. Then overall survival, again, powered if DFS is positive.

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Isabel Preeshagul: That makes sense. When looking at the methods of the study, the trial included patients that had early-stage non-small cell lung cancer that was resected. Could you talk to us a little bit about some of the key inclusion criteria?

Jamie Chaff: Those are really bridged from what is called the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) study. So, the ALCHEMIST is a huge National Clinical Trial Network (NCTN), NCI-funded initiative, looking to learn more and improve upon outcomes in patients with resected non-small cell lung cancer. Now, this is specifically for patients who did not receive preoperative [treatment]. I am sure we will get to that later because it has become our standard of care, but for patients who have had upfront resection of tumors that are 4 cm or greater or lymph node positive, what is, today stages II and III largely, but at the time was stage IB, 4 cm or greater, without EGFR and ALK alterations, and that is because at the time this was designed, it was really meant to fill an unmet need in the ALCHEMIST portfolio, where patients with EGFR alterations were offered enrollment in a trial of erlotinib, ALK rearrangements were offered participation in a trial of crizotinib. Yes, those are ancient drugs and interestingly, both studies just recently resulted as well. Then anyone else, and those with squamous cell carcinoma who were not originally part of the ALCHEMIST schema, were able to enroll first through the ALCHEMIST for central PD-L1 testing and EGFR and ALK, if not purely squamous.

The other inclusion criteria and exclusion, for that matter, are largely standard. Patients did not have to receive chemotherapy, although it was recommended. This study differs from the other adjuvant checkpoint inhibitor studies, as we did allow postoperative radiotherapy, which was still standard of care when the study was designed. Then they could not have had evidence of a contraindication to immunotherapy, and a chest CT was done after chemo and/or radiation and prior to enrollment to make sure they had no evidence of disease. Other than that, a pretty typical adjuvant study.

Isabel Preeshagul: Thank you for that. Also, thank you for highlighting what is unique about this study and the unique inclusion criteria. We know that this was a large phase 3 study, multicenter, open label, randomized across 378 sites in the US. Could you describe a little bit about the treatment arms and what that looked like?

Jamie Chaff: Pretty simple. This is a very pragmatic study. Patients were randomized to nivolumab for up to 1 year vs standard of care observation. Standard postoperative imaging was prescribed. The initial nivolumab dosing was what we had at the time, 240 mg intravenously every 2 weeks, but when the larger 4-weekly dose of 480 mg was demonstrated to be safe, with similar pharmacokinetics and pharmacodynamics; the study was modified for ease of burden on the patient.

Isabel Preeshagul: I was very happy to hear that, and I think now, with immunotherapy being offered at different intervals, it was nice to see that that adjustment was made. Now that we are talking about what the arms were [of the study], could you talk to us about the patients that were enrolled in either of those arms and some of their characteristics?

Jamie Chaff: This study was a US-based study, so the majority of our patients were Caucasian. The arms were balanced. We aimed to enroll 903 patients, and when we set a “you cannot enroll past this date,” there was a huge push and [we] wound up enrolling well over that at 935 patients. They [patients] were randomized, only 466 to nivolumab, 469 to observation or standard of care. The majority of

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patients were former smokers and most received stage-based appropriate adjuvant chemotherapy (88%). The PD-L1 breakdown was also quite standard with about a third of patients having PD-L1 high disease [$\geq 50\%$]. Now I mentioned that the stratification was PD-L1 positive vs negative based on the initial design, and with the amendment there was a risk for imbalance. However, the patients in the PD-L1 high arm were well balanced.

Isabel Preeshagul: Thank you for that. It was nice to see that you had such a robust accrual here. Now, let us dive into what the actual results showed, and if you could talk to us about the results in regard to the overall population, and then also with the PD-L1 cohorts.

Jamie Chaff: I think the longer a study takes to read out, and this was a very long study, the less dramatic the difference is going to be. Unfortunately, this was a negative study. In the intention-to-treat population, the disease-free survival in the nivolumab arm was 71 months vs 69 months in the observation arm. In the PD-L1 high population, the disease-free survival in the nivolumab arm was 90 months compared to 78 in observation. Now that is numerically better, but, with the third of the population included here, not a statistically significant result. What we did learn here, and as we have seen from all of the other checkpoint inhibitor studies, is that PD-L1 expression is not only predictive for benefit to immune checkpoint inhibitors, but it is actually prognostic in the adjuvant setting. Even without therapy, or in the placebo arm of all of the studies, we have seen read out, patients with PD-L1 high tumors have a lower chance of disease recurrence.

Isabel Preeshagul: I think in the setting—and we are going to get to it a little bit later—but in the setting of multiple different adjuvant options, after patients undergo resection, and then they undergo standard [treatment], 4 cycles of adjuvant chemotherapy, with all of these different options out there, I think it is helpful to understand what is an appropriate biomarker. How do we determine who needs more? And I feel like it is still unclear. Do you feel like that as well?

Jamie Chaff: It is, and to that point, you have to think about the risk, the safety. In this study, a quarter of patients in the nivolumab arm had a grade 3 event. Many of those [adverse events] might be lab-based and not clinically significant, but many of those are significant and there were treatment-related deaths. It is important to think about risk-benefit in this setting, and we can conclude that this is a negative study but talk about it a little in the context of the evolving landscapes. There are 4 adjuvant studies of checkpoint inhibitors. This was the first that activated, and the first that completed accrual, and the last to read out. In the time that this study matured, we saw a positive study of adjuvant atezolizumab, but that is only positive in PD-L1 positive tumors and only in bigger tumors. We saw a positive study of adjuvant pembrolizumab. However, that study was positive in the intention-to-treat population, but not in the PD-L1 high group, probably based on what I mentioned with the prognostic significance of PD-L1 expression. Then we have the Canadian Cooperative Group study of adjuvant durvalumab, which, like this one, was negative, no benefit. That group has done a subset analysis by circulating tumor DNA (ctDNA), which is intriguing for a future direction, but certainly not ready for prime time. The data here is really confusing, but it is different than what we do every day in the clinic now with preoperative therapy.

Isabel Preeshagul: If this data did anything, my hope is that it would shine a light in the neoadjuvant setting or the perioperative setting to say, “Well, maybe if there is not a signal at the tail end of a patient’s treatment journey, perhaps we need to jump ahead and catch things before patients go to the

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operating room (OR).” To your colleagues, what conclusions do you feel are appropriate to ascertain from this negative study, and how does it shine a light in the neoadjuvant and perioperative space?

Jamie Chaff: I think this stark contrast with the dirty, for lack of a better word, confusing adjuvant data is the overwhelming consistency of the neoadjuvant data, where all of us, and I will call it neoadjuvant because in all of the perioperative setting, the postoperative component has never been formally assessed.

Isabel Preeshagul: Right.

Jamie Chaff: All of the preoperative studies, with one exception, which we have not seen the data from, have been universally positive with the addition of immunotherapy to chemotherapy, increasing pathologic response rates, increasing resection rates, and increasing event-free survival. Now, whether or not that adjuvant phase adds anything, we do not have prospective data. In the clinic, that is exactly where I find this adjuvant data relevant. We should really, as you just mentioned, be finding patients who are appropriate for systemic therapy, and if they should be receiving immunotherapy, meaning they do not have an activating oncogene driver mutation or a contraindication to immunotherapy, then we should be trying to treat them preoperatively with that tumor and the draining lymph nodes inside too as the data is consistently positive for benefit. Now, whether those same patients who receive preoperative chemoimmunotherapy should receive adjuvant immunotherapy is much more of a question mark. I think we all do it with limited enthusiasm.

For the patient who has had upfront resection and adjuvant chemotherapy, I think my bar to recommend adjuvant immunotherapy, irrespective of what drug we are talking about, has been raised based on the negative durvalumab data, the negative nivolumab data, and the largely negative atezolizumab data. It is a small subset of those patients who truly benefit. It is only the highest risk tumors in a patient who you otherwise, in metastatic disease, would be offering immunotherapy, where I think we have confidence to use it in a postoperative setting, with associated risks.

Isabel Preeshagul: You completely answered my question. I was going to say if you have a clinician in the community coming to you that is saying, “Well, I know we have 2 negative studies here, but we also have IMpower010, we have the PEARLS [KEYNOTE-091] data that was positive regardless of PD-L1 expression,” even though maybe there was a signal, as you had said, “Why would I not give my patient with high PD-L1 expression, a year of atezolizumab?” You hit the nail on the head, and you answered that very clearly, and I thank you for that, and I hope that the last couple of sentences that you said ring true to someone, and someone is able to utilize those words in clinic, forthcoming. Some of my remaining questions to you are, do you feel like there are any unanswered questions from this adjuvant nivolumab data? Is there something that you feel is important about the article that we did not talk about today?

Jamie Chaff: I think that these drugs really work, and that they should work in the adjuvant setting. One of the questions that comes up is, are we just immunosuppressing our patients with chemotherapy prior to the immunotherapy and making them a setup for immune failure? There are 2 ongoing studies that are asking the question of concurrent adjuvant chemotherapy and immunotherapy. One we have seen preliminary data from [is] the NADIM adjuvant trial out of Spain, and the preliminary data looks really good, that adjuvant carboplatin, paclitaxel, plus nivolumab, will

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improve outcomes compared to adjuvant carboplatin and paclitaxel. In America, our patients are a little resistant to receive that [chemotherapy]. The study, again, through the ALCHEMIST umbrella, is studying histology-based chemotherapy with pembrolizumab concurrently vs sequentially. That will be a really interesting study to answer the question. It is concurrent vs just chemotherapy, or concurrent chemoimmunotherapy vs sequential chemoimmunotherapy, and if that makes a big difference. We may be singing a different tune in a couple of years.

Isabel Preeshagul: That might then make us question, well, who do we give adjuvant concurrent chemoimmunotherapy to vs who do we give neoadjuvant or perioperative concurrent chemoimmunotherapy [to] followed by immunotherapy? I am wondering how we would determine that and I am wondering if ctDNA would help us determine that in some way.

Jamie Chافت: I would argue if the studies are positive—it, again, is only 2 studies compared to 5 or 6 consistently positive neoadjuvant studies—and still push for preoperative therapy when it is safe and reasonable. We will always have those patients upstaged at the time of surgery who need purely adjuvant therapy, so it remains a clinically relevant question, irrespective. I would rather not. I hope we never have to have the pre- vs post-operative debate again.

Isabel Preeshagul: I agree. Unfortunately, there still are patients that come to us, as you had said, that maybe could have benefited from neoadjuvant therapy, but do not. Just a sort of selfish question for me, if you are seeing somebody in the clinic that is already slotted to go to the OR, but you think induction therapy would be appropriate, who are the people [for whom] you typically pump the brakes and say, “No, we should go with a neoadjuvant approach?”

Jamie Chافت: Certainly anyone who has lymph node-positive disease, I think, merits induction therapy. They are too often upstaged at the time of surgery. Large tumors, or tumors that are pushing a pneumonectomy or a bilobectomy, tumors where you are worried the surgeon is not going to be able to easily get it [the tumor] out. As long as they are PD-L1 positive and otherwise appropriate for immunotherapy, I would push to get preoperative therapy. I think it is always worth a phone call with the surgeon, to discuss.

Isabel Preeshagul: Thank you. You have taught me so much just chatting with you about this and allowing me to also ask some more selfish questions just to glean a little insight for my clinics going forward. I thank you for your insight and for sharing this trial on a more personal level. It was incredible. Thank you.

Jamie Chافت: Thanks for having me.