

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



Editor's Note: This is a transcript of a discussion on June 12, 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 the article "Final efficacy and safety data from the phase I/II ARROW study of pralsetinib in patients with advanced *RET* fusion positive non-small cell lung cancer." It was published in the *Journal of Clinical Oncology* in March 2026, and I am honored to be joined by Dr. Justin Gainor from Harvard University and Massachusetts General Brigham Cancer Institute, who was the lead senior author on this paper. Dr. Gainor, thank you so much for joining us today. Welcome. If you could please provide a high-level overview of why this trial was conducted and why you think it is important.

Justin Gainor: Great. Thanks so much for having me. It is great to have the opportunity to discuss this trial. We know that *RET* fusions define a distinct molecular subset of non-small cell lung cancer. The ARROW study was designed back before we had good therapies for *RET* fusion-positive lung cancer. This was designed back in the day when we were exploring and really asking the question, is *RET* a bona fide driver? We were trying to use multikinase inhibitors, like cabozantinib, vandetanib, and we were not really seeing good activity with those agents. This study was conducted to evaluate pralsetinib, a selective *RET* inhibitor in patients with *RET* fusion-positive lung cancer. This particular manuscript was the final safety and efficacy analysis, and it added an additional 42 months of follow-up. It allowed us to report long-term results, as well as some of the survival data.

Isabel Preeshagul: Yes, I think it is always so nice when we have updated data and patients being on treatment longer just gives those that are about to embark upon this journey a little bit more information about how they might do and how long they can expect to be on treatment. In regard to the specific objectives of the trial, I know the primary endpoints for the ARROW study were overall response rate and safety. Could you talk to us a little bit about some of those secondary endpoints and why those were chosen?

Justin Gainor: This was a pretty straightforward design. Beyond response rate, we looked at duration of response, clinical benefit, overall survival, and progression-free survival (PFS). As we have done with other drivers, CNS activity is important for targeted therapy. We did have prespecified CNS response rate as one of our outcomes as well. Then a number of exploratory analyses looking at outcomes related to fusion partners, as well as outcomes related to geographical region of the world based on some of the data that we were seeing.

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Isabel Preeshagul: It is helpful to know, and you touched upon something that we are going to talk about later on about CNS efficacy, because we always worry about patients with driver alterations, specifically *RET* fusions and brain metastases. When looking at the methods and the key inclusion criteria, I was really happy to see that you allowed patients with CNS metastases as long as they demonstrated stability and no neurological symptoms.

Justin Gainor: One of the other aspects of the study that evolved over time is that in the initial iteration of the protocol, first-line patients were not eligible for participation in the study unless they were not candidates for platinum doublet chemotherapy. That was since modified in an amendment in 2019 to really open it up. When we look at some of the outcomes data, and we look at those who had received prior treatment vs treatment naïve, there is a difference in timelines of when those patients were recruited to the study.

Isabel Preeshagul: I am so glad that amendment was made. I accrued a couple of patients to that after the amendment, so I appreciate that. That calls into question the thought about sequencing because a lot of times if patients were started on chemotherapy, maybe the *RET* fusion was not known initially. It further emphasizes the importance of next-generation sequencing in the frontline setting, but my question is, did you include any patients that maybe had received prior *RET* fusion therapy like selpercatinib or anything along those lines?

Justin Gainor: This study was done contemporaneously with the LIBRETTO-001 study. Dose escalations had started around the same time, and so both studies had excluded patients on each treatment. As we know, now, in clinical practice, there are patients who perhaps stop one because of toxicity and move on to the other. I think these agents are a lot more similar than they are different. In my own practice, I do not move from pralsetinib to selpercatinib, and vice versa, if it is in the setting of disease progression. It is really only if we see there is a tolerability concern.

Isabel Preeshagul: If we could move on to some of the results of this study because that was really exciting. Can we talk a little bit about some of the key findings that you found in regard to survival, and a little bit about how that plays into the primary and secondary endpoints?

Justin Gainor: It is a good and important question. We have reported in the past objective response rate, and that really has not changed. We saw in the overall patient population, 70% of patients responded to pralsetinib. That really mirrors what I have seen in clinical practice. Where this manuscript extends our knowledge base is with respect to the survival data. In the overall treatment population, the overall survival was approaching 4 years, specifically, it was a median of 44.3 months. When you break this down into the treatment-naïve and previously treated patients, it is what you would expect that the median overall survival in the treatment-naïve patients was 50.1 months, and among those who had received prior platinum double chemotherapy it was 39.7 months. It is important to put that into context. You know

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acknowledging that this is a single-arm study, and there's not a comparison arm. If we look at the Global Multicenter RET (GLORY) registry that Dr. Alex Drilon and others had put together when we were using the multikinase inhibitors, the median survival in that retrospective analysis was only 6 to 7 months. This does really give us helpful information in the long-term outcomes for these patients.

Isabel Preeshagul: I agree, and anytime we see numbers up in the 3-, 4-, 5-year range, patients are not only wanting to have improved progression-free survival, but also overall survival, so those are very comforting and promising numbers. At least when this data came out, I was happy to see that with the additional 42 months of follow-up data included. I am going to ask a more challenging question that you probably get asked all the time, and that is you have a patient in your clinic with stage IV non-small cell lung cancer harboring a *RET* fusion, how do you choose between selpercatinib and pralsetinib? Can you talk a little bit about how the toxicity profiles might help you there? Overall, could you walk us through why you might choose one over the other?

Justin Gainor: It is a great question and is the most common question. We saw at ASCO we have randomized phase 3 data for both compounds. Both LIBRETTO-431 and the AcceleRET-Lung study that Dr. Sanjay Popat presented in both situations. The *RET* inhibitors resulted in significant improvements in progression-free survival compared to platinum plus pemetrexed. Acknowledging all of the dangers of cross-trial comparisons, the LIBRETTO-431 phase 3 data had a longer median PFS in both the control arm and the experimental arm. In my own practice, some of it comes down to comfort with dosing of each drug. This is a rare patient population, only 1% to 2%, and if you have familiarity with one drug you tend to gravitate towards that drug. To your point, toxicity profile is also really important, and selpercatinib and pralsetinib have distinct toxicities. Briefly, to summarize the data from the ARROW study, the most common adverse events, including grade ≥ 3 were ALT elevation, AST elevation, and cytopenias. We saw hypertension in 27% of patients, of which grade ≥ 3 was 15%. That is something where you want to be aggressive in managing the blood pressure. When you are seeing these patients in clinic, that is not a unique toxicity to pralsetinib. Both selpercatinib and pralsetinib can cause hypertension. When we break down what are the adverse events that really distinguish these drugs? For selpercatinib, the unique toxicities are dry mouth, which is mainly grade 1 and grade 2, but having dry mouth for years on therapy can be quite disruptive to patients. We have also seen a somewhat strange side effect, which is chylous effusions in about 7% of patients, something we described with your colleague, Dr. Drilon. That is really important to recognize because the time to onset is about 7 to 10 months into treatment. You are treating a patient with lung cancer, they have a new pleural effusion, your initial instincts might be that is disease progression, but it is not. It is a unique toxicity. We see chylous/pleural effusions more with

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selpercatinib than pralsetinib. In terms of unique toxicities with pralsetinib, the one thing that clinicians really have to be mindful of is infection. We saw that with the AcceleRET-Lung data, that there was a much higher rate of infection, including fatal infections in the pralsetinib arm. That was not a signal seen in the ARROW study, but it was seen in the phase 3 (AcceleRET-Lung) study. We need to understand that better.

Isabel Preeshagul: I totally agree and I am so glad that you brought up the chylous effusions because so often we see patients with progressive effusions, and if they already have a history of a malignant effusion, you immediately think that might be evidence that there is continued seeding and they are actually progressing, and some may not even tap that, but by tapping and understanding the makeup of that fluid, you really can figure out that this is more of a dose toxicity and a drug toxicity as opposed to cancer progression. That is really key. I am not sure about you, it might have just been unique to the patient population that we were seeing, but we saw a lot of QTc abnormalities, and I found myself having to get serial EKGs and really monitor that for patients, especially with some drugs that we already have them on, that prolonged QTc. Did you see that a lot?

Justin Gainor: We definitely see it with selpercatinib. That is one of the other differentiators between the 2, with more QTc abnormalities with selpercatinib and more hypersensitivity reactions after anti-PD-1/PD-L1 therapy. Granted, we should not be using anti-PD-1/PD-L1 therapy in patients with *RET* fusion positive disease. With pralsetinib, it is more cytopenias, more infection.

Isabel Preeshagul: We only have a little bit of time here, but there is something to be said and maybe some education on our end that can happen in regard to the specific *RET* fusions that are out there, and one *RET* fusion does not equal another, and there are some that may be more high risk as opposed to low risk. Do you manage these high-risk patients any differently? Are you quick to add chemotherapy to their tyrosine kinase inhibitors? What are your thoughts about the high-risk patients?

Justin Gainor: That is a really important question. We know that the most common fusion partner is *KIF5B* and then there are some less common ones, like *CCDC6*. When we were just reporting response rates, in the early days, we were saying that we could see activity regardless of the fusion partner. Now that we have longer follow-up, and we look at the durations of response, we do see that there is a difference. *KIF5B* tends to have a lower duration of response. Biologically, why might that be? It looks like *KIF5B* has a stronger promoter, and it is possible that the upstream promoter of *KIF5B* is just stronger, and so you are getting increased expression, and so you just need to hit the kinase harder. Right now, does that impact my clinical decision making? No, but I think your point is a good one, which is, are there intensification strategies we

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should be thinking about? We need to do the clinical trials to evaluate that, but in practice, I am just using upfront TKI monotherapy.

Isabel Preeshagul: Fair enough. I would love to see a study that would help us focus on escalation vs not, and what that would look like for our patients. Similar to the EGFR ctDNA-shedding study, if they are still shedding, do we need to add more or not? What would that look like? We are almost at time. Could you give us a one-line elevator pitch about the ARROW study and if there is anything burning left that we did not really cover that you might want to share with our audience today?

Justin Gainor: The quick summary is that pralsetinib is very active in patients with *RET* fusion-positive lung cancer with high response rates, durable progression-free survival, and now we are seeing overall survival approaching 4 years. The major questions moving forward: we need to understand how resistance develops and what to do at the time of resistance. These agents, pralsetinib and selpercatinib, they are still not curative. We need to think about developing new strategies at the time of resistance.

Isabel Preeshagul: I definitely agree. I do not think we know enough about resistance. Even if we search for it, we always say, ideally, if someone is progressing, you should try to obtain a biopsy of the site of progression, but in full transparency, I do not really know what to do with those results as of right now. I am hoping that those results may glean a little bit more about what to do in the future, but most of the time, if they are progressing on *RET* fusion, if there is not another *RET* fusion therapy, if there is not another trial, I am looking at standard of care chemotherapy. Are you doing something different in your practice?

Justin Gainor: The short answer is no.

Isabel Preeshagul: Food for thought for now. Well, I really thank you, Justin, for joining us today, for teaching me. I have been scribbling notes down over here to just take back to my clinic and at least have a more enlightening discussion about the ARROW data. I just thank you for your time.

Justin Gainor: Great. Thanks so much for having me.