

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



Editor's Note: This is a transcript of a discussion on April 22, 2026. It has been edited and condensed for clarity. To obtain credit for participation [CLICK HERE](#).

Isabel Preeshagul: Hi everybody, welcome. My name is Dr. Isabel Preeshagal, and I am a thoracic medical oncologist from Memorial Sloan Kettering Cancer Center. In this accredited webinar, we are going to discuss the clinical trial titled “Setidegrasib in Advanced Non-Small Cell Lung Cancer (NSCLC) and Pancreatic Cancer.” This was published in the March 25, 2026, issue of the *New England Journal of Medicine*. I am thrilled to be joined by Dr. Jonathan Goldman from UCLA, who was the senior author on this article. Dr. Goldman, welcome. Thank you so much for joining us. Could you please provide an overview about why this trial was conducted in the first place?

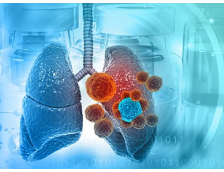
Jonathan Goldman: Absolutely. Thank you, Isabel. It is a pleasure to speak with you about this. It's an exciting time for KRAS-targeted therapies, and I am thrilled to be able to talk to you about this part of it. This is a phase 1 trial that was begun a few years ago as part of several efforts to find new ways to treat this fairly common, but previously untreatable subtype of lung cancer. We also find, in some ways, similar molecular tumors in the pancreas and in colon cancer. Up until recently, we have had no ability to specifically treat KRAS mutations. KRAS G12C mutations have been targetable by 2 oral drugs approved a couple years ago, but there is still a lot of room for improvement, particularly in our ability to treat other KRAS mutations. KRAS G12D is another subtype of KRAS mutation. It is approximately 5% of non-small cell lung cancer, not quite as common as KRAS G12C, but also a meaningful subgroup of patients. In pancreatic cancer, it is about 40%, and it is also a meaningful percentage of colon cancer. A lot of patients out there that up until now have not had a targeted therapy. We have used mostly chemotherapy and immune therapy, and they still have their role, but being able to bring in a new type of treatment was an exciting possibility that we wanted to investigate.

Isabel Preeshagul: Could you talk to us a little bit about some of the inclusion criteria for this study?

Jonathan Goldman: Absolutely. The trial did have several different phases. Early on, a relatively common phase 1 cohort of patients with KRAS G12D mutations. They needed to have a prior therapy and have progressed. But otherwise, it was a fairly open trial.

Isabel Preeshagul: Who were the people that were not allowed on this trial? What were some of the exclusion criteria?

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



Jonathan Goldman: Some of the most important exclusions were patients that we consider their performance status was not adequate for a trial. We also required that any brain metastases be under control with prior radiotherapy or surgery and not be active. There are a variety of other requirements, including kidney function, liver function, and cell counts, as we often see in our trials.

Isabel Preeshagul: Definitely, and thank you for that. Taking more of a bird's eye view, looking at this study, what were some of the specific objectives of your trial?

Jonathan Goldman: Like many phase 1 trials, the initial objectives are somewhat modest. It is to try to understand the pharmacokinetics when we infuse the drug. How long does it stay in the system? Whether there is a dose response or dose pharmacokinetic response at a linear association and to optimize some of those dosing questions. And importantly, to understand the tolerability. If I may jump to one of the main issues here is that it is a once-a-week infusion and that carries some challenges for patients. This was what was predicted to be likely the required frequency of infusion. There was a thought, could this be extended to 2 weeks? But the performance of the drug did not suggest that that was going to be a successful approach. We kept it at once-a-week infusions. We also wanted to identify the tolerability, and there are some toxicities, primarily with the early infusion. There were usually quite mild infusion-related reactions, some itching, some nausea. In fact, very few higher-grade infusion-related reactions, and those tended not to be problematic for later infusions. In my own experience, they were very well managed with slowing down the infusion rate.

Isabel Preeshagul: And these infusion reactions typically only happen in the chair. It is not an aftermath effect that happens when patients go home. It is similar to cytokine release syndrome, or something along those lines, or like the amivantamab infusion reaction.

Jonathan Goldman: Actually, I think the timing of the amivantamab reactions is a good comparator that it is often the early infusions and sometimes early in the infusion, never after the patient left the infusion center. But I would also say in severity, less significant than amivantamab.

Isabel Preeshagul: Well, I am happy to hear that, and I think it is really important, as you had mentioned, prepping the patient and making sure that they are aware of what to expect, and also prepping your staff, so that they know that this is likely to happen the first time, and we are primed, and we know how to mitigate this. When talking about the key secondary endpoints of your study, could you talk to us a little bit about what those were and what your findings were?

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



Jonathan Goldman: We also wanted to look for anticancer activity and the response rate was the major secondary endpoint. Just over 200 patients were treated in total. About 76 were treated at the recommended phase 2 dose of 600 milligrams. I think it was 44 or 45 lung cancer patients who were treated. The response rate of 36% was what was seen. We also saw progression-free survival (PFS) and duration of response that was meaningful at 8.3 months and that was gratifying.

Isabel Preeshagul: I definitely think that even with your estimated 12-month overall survival of close to 60% in patients with lung cancer, I think that's pretty good. We are thinking about this in a second-line setting and beyond. I think that is pretty promising to me and just to kind of get an overall gist of what you felt about this study and what you think next steps are, what conclusions did you and your colleagues draw based on these results?

Jonathan Goldman: The first is that this is very worthy of further study. This is a single-arm phase 1 study, so, at this point, difficult to say exactly where it would fit in among our other therapies. But comparing it to other standard of care agents in the pretreated population makes clear sense against a second-line chemotherapy. I think our expectation is that the response rate and duration of response, as well as quality of life and general tolerability will be very promising for setidegrasib. I also think that the good tolerability and the expected good ability to combine it with other standard of care agents is really promising.

Isabel Preeshagul: And I am trying to figure out how would a physician in clinic know what clinical trial to put their patient on? How do you know not to lean towards zoldonrasib? How do we know that we want to go towards this degrader option? Is there something about the patient characteristic that would help somebody choose that?

Jonathan Goldman: I think there is the common preference that many patients might have to taking a pill compared to a weekly IV infusion and I also think that the oral agents are very exciting. But the other side of the coin is that the oral agents do tend to have more side effects. I personally see more gastrointestinal (GI) side effects. Perhaps rash, but it is mostly the nausea and occasionally diarrhea that I think can be an issue, particularly with some of the Pan-RAS drugs. The other side of this opportunity is this IV drug that does have some time toxicity. Time coming into the office, and if they have to travel to get to the office, which I would never ignore. But on the positive side, those other days, I think they feel quite well, actually. Those are the ways that we are thinking about it. It would be great to get to a more scientific understanding of these differences and perhaps predictors of which patients might do particularly well on zoldonrasib for a long time, and which patients may do better with setidegrasib. But I do not think we know that yet.

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



Isabel Preeshagul: I think that is very helpful, even enough for us to be able to have a discussion like that with our patients in clinic to help them choose and kind of understand the differences here, so I appreciate that. In our final moments on this recording, is there anything else that you think remains unanswered, or any one last plug that you want to give for this beautiful study?

Jonathan Goldman: I think all of us are really feeling the excitement of these new KRAS drugs. It is almost like the excitement of EGFR or ALK at the beginning, where we just did not know that we were going to have this possibility. As you alluded to, a lot of them are being moved into the front line, at least from what I have heard, not a lot of combinatorial toxicity, meaning that we are not seeing a lot of significant immune therapy toxicities, for example, by adding in these KRAS-targeted drugs, and that is a real relief. A lot of KRAS patients may also do well with immune therapy, so having this ability to combine these approaches is very exciting. I think, probably as all of us, I continue to really encourage doctors and patients to do mutation testing early on, prior to treatment decisions, if possible.

Isabel Preeshagul: Well, this has been a tour de force of your work in this space, so I thank you for taking time to answer my questions and help everyone listening on this webinar to figure out how to navigate this space. You have been very insightful. Thank you.

Jonathan Goldman: Thank you, it was a real pleasure to speak with you.