CASE BASED PANEL DISCUSSIONS: LUNG CANCER

Stage IIIA Node-Positive Lung Adenocarcinoma with ALK Rearrangement

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TRANSCRIPT

Dr. Justin Gainor: Moving onto our next case, we have a never-smoking 57-year-old gentleman with Stage IIIA, that is N2 node-positive lung adenocarcinoma with a single, non-bulky mediastinal lymph node that was positive, who's felt to be a good candidate for surgery. His molecular marker testing shows an ALK rearrangement. What do you favor as an initial treatment strategy? So, I'll start with Ana, your thoughts here.

Dr. Ana Velazquez Manana: I think that this case is one, again, that we would discuss our tumor board and discuss with the patient what would they prefer. Going straight up for surgery, in which many of our patients, I would say, have strong feelings towards; getting tumor removed completely versus trying to provide here is there a role for neoadjuvant chemotherapy. Given the fact that this patient has ALK rearrangement, I would not use regimens that we discussed on the prior case of chemotherapy combined with immunotherapy to avoid toxicity, and plus those patients who were excluded from all of the trials. So, here, if it is a very good surgical candidate and the surgeons would offer surgery, I would go for surgery and offer chemotherapy in the adjuvant setting alone without immunotherapy. The other question comes if you have a clinical trial like ALCHEMIST open at your particular institution, then this should be discussed and offered to the patient. But that will be my initial thoughts.

Dr. Justin Gainor: So, if you've put the outbreak arrangement aside in your institution for N2-positive patients, what percentage go to upfront surgery versus induction therapy followed by surgery?

Dr. Ana Velazquez Manana: It will really depend on the size of the tumor. And if a lobectomy is achievable, to be very honest, I would say most patients are going straight for surgery. But we've been doing induction neoadjuvant chemo for a couple of cycles. We've been doing it regularly, to be honest, on patients who do have larger, bulkier tumors without clear N2 disease, though, I would say. So, taking both things into account, this patient, we would take to surgery if the surgeons felt they were a very good surgical candidate.

Dr. Justin Gainor: Steven, I'm hearing bulk plays a role in decision making. The first question is, putting the ALK rearrangement aside for Stage III N2-positive patients, at your institution, role of upfront surgery versus induction therapy. And then we can talk about the ALK rearrangement.

Dr. Stephen Liu: The ALK makes it really interesting. I will say if it's documented N2, biopsy-proven, we do neoadjuvant for all of our patients first. So, we don't take anyone right to surgery with N2. If it's bulky N2, we're probably going to go a chemoradiation route and really not favor surgery at all, at least upfront. If it's single-station bulky, then we can talk about neoadjuvant therapy and consider it. But generally, if it's bulky nodal involvement, we're going down maybe a chemoradiation direction. We try to make our decisions about resectability and the appropriateness of surgery upfront, and that's based on the initial response to therapy. So, if it's single-station, non-bulky, mediastinal involvement that's documented, again, not just on PET but biopsy-proven, we would do neoadjuvant chemotherapy four cycles upfront.

Dr. Justin Gainor: I would say that that mirrors our practice as well. I would say that bulky disease, especially in light of the PACIFIC data, I feel perfectly comfortable with definitive chemoradiation followed by PD-1. But non-bulky, especially one or two nodal stations, usually, we're doing induction therapy followed by surgery. How does the ALK rearrangement change your decision-making here?

Dr. Stephen Liu: That's a great question. And it really is tempting to just give an ALK inhibitor; they're so well-tolerated; they're so effective; you can almost guarantee some reduction. Question is what does it mean? Because we often don't consider TKI therapy to be curative. And would it influence the surgery in any way? I think most of our surgeons would probably say, “No, it wouldn't.” Even though we would get an initial response. I think that I agree exactly with what Ana said that if we have a trial, that's definitely the route we want to go, but it's sort of an easy way out. So, without a trial, in this setting, I could say that we would probably do neoadjuvant chemotherapy because I think that contributes to the rate of cure surgery. We would not do radiation too based on the LungART study. And off study, despite the lack of data, I probably would offer adjuvant ALK TKI therapy.

Dr. Justin Gainor: I think it begs the question, which is that we now have nine targets in the metastatic setting with FDA-approved therapies. And it's going to be impossible to do randomized Phase III studies for all of them in the neoadjuvant consolidation period, just given the rarity of some of these alterations. So, how much data do we need to start extrapolating? Is EGFR enough?

Dr. Justin Gainor: Stephen, like you, I would be tempted to give adjuvant ALK inhibitor here, acknowledging the complete lack of data, except I would draw the parallel with EGFR and say, “In this case, I'm going to extrapolate there.” Again, acknowledging complete lack of data.

Dr. Ana Velazquez Manana: Would you make the same decision if the patient was not a surgical candidate **[06:55 inaudible]** route?

Dr. Stephen Liu: I would, yes. And I think of ALK as a little different because, generally, in EGFR, the response rate – and this is mostly based on work that you lead, Justin – the response rate is very low in EGFR, but it's non-zero. But for ALK, it’s pretty close to zero. We generally don't see responses, I think, of ALK and ROS1 is pretty immune, non-responsive tumors. So, I really don't see much benefit with durvalumab in that setting. So, after chemoradiation, again, despite no EGFR data even until LAURA reads out, but I just don't think durvalumab makes sense, I think the rate of relapse is so high. And again, maybe even more so because ALK is so CNS-tropic that the risk of **[07:51 inaudible]** is so high that I would favor TKI in that setting. And this is heart-to-heart with the patient saying that we don't have evidence for it, that there are side effects, that I don't know if this is something that they need or will derive benefit from. But I still think that there's some value in it.

Dr. Justin Gainor: I agree with you. I also think that for ALK, in particular, it has such a metastatic phenotype that for someone presenting with Stage III disease, unfortunately, the risk of recurrence is going to be so exceedingly high that adding the ALK inhibitor post definitive therapy may make sense.

Dr. Stephen Liu: I sort of acknowledged also from a public health standpoint, these are very expensive medicines, for years, we don't have duration of therapy. I would not consider that standard. And I'd say the standard option would not be to use TKIs in that setting. And ideally, what would work is some sort of biomarker, some sort of marker of residual disease to tell us that this person is in fact not cured and that we'll need more therapy. In the absence of that, we have to make decisions in the individual setting. And for a Stage IIIA ALK-positive, I agree my concern for relapse is so high. I think the therapeutic window is so high ‘cause I think the ALK inhibitors are just so well-tolerated. When you look at drugs like alectinib and brigatinib, I think the tox is so low. If you look at some of the other agents, where maybe the toxicities are a little more notable, especially chronically, maybe that therapeutic window is a little smaller, and I think their decision gets a lot tougher – like for MET, for BRAF. I don't know if I make the same recommendations there. But for ALK, the risk of metastasis is so high and the tolerability is so good that I think I would recommend it, at least discuss it with the patient. I don't know if you have a different line of thinking, Ana.

Dr. Ana Velazquez Manana: No, I agree, I would. And the other question I was going to pose which is not really this case, but where we're going into the unresectable space on a patient who you would treat with definitive chemo RT; do we really believe that putting the patient through all that toxicity of chemo plus radiation versus bringing on unresectable disease earlier and ALK/TKI, where do we draw the line of risk and benefit and toxicity in this space, too? And I don't know that we have tons of.

Dr. Justin Gainor: It's a good question. I think, in my view, whenever there's a potentially curative therapy, I think we have to prioritize that. So, I wouldn't not use definitive chemoradiation in some of the Stage III who has an ALK rearrangement, I still think we have to do that. But it's how can we expand treatment? And to your point about toxicity, the biggest fear I have in mind in that situation is really a pneumonitis risk, that where I worry the most.

Dr. Ana Velazquez Manana: Definitely. I agree. My practice is to give the chemoradiation as, I think, everybody would agree. But I think as I am doing it similarly and taking into account when you have an elderly patient who are **[11:39 inaudible]** maybe semi-borderline, we're putting them through daily radiation. You may not be able to get all of the chemotherapy in because of counts and other limiting factors with toxicity, the percentages of cure also in the data is not the greatest. And adding that data we're having for TKIs extrapolating from the EGFR space really is on DFS and not particularly for overall survival makes me wonder and question. And I think all of these things are things we have to talk through and wonder what are the best steps moving forward.

Dr. Stephen Liu: I think you have to ask the question. I think it's a great question. You have to challenge the paradigms and dogma. Is there more value in starting with TKI and then using radiation or surgery or some sort of consolidation? I think those are the types of questions that we'll be faced with.

Dr. Justin Gainor: Well, great case and great discussion. So, I think we're going to hand things over for the discussion of the next case.