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Case 5: Is There a Role for IO-Based Therapy in KRAS-Mutated NSCLC? What About Patients With Co-mutations in STK11, KEAP1, or TP53

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Dr. Reuss:
Hello, my name is Joshua Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at Georgetown Lombardi Cancer Center at Georgetown University School of Medicine. And in this session, we're going to discuss is there a role for immunotherapy-based treatment in KRAS mutated non-small cell lung cancer? And what about those with co-mutations in STK11 or KEAP1?

So first, for the case example, this is a 60-year-old gentleman with a history of BPH and prior tobacco use who presents to your clinic. He was originally diagnosed with stage IIB poorly differentiated non-small cell lung cancer and underwent a right lower lobe lobectomy, followed by adjuvant cisplatin and pemetrexed chemotherapy in July of 2021. Fast forward to February of 2022, where imaging shows recurrent in large mediastinal lymph nodes and several enlarged liver lesions. Liver biopsy confirms metastatic poorly differentiated non-small cell lung cancer and MRI brain is negative for intracranial disease. And NGS reveals mutations in KRAS, KEAP1, and TP53. PDL-1 is negative, and tumor mutational burden is 7 mut/Mb. This patient is completely asymptomatic and continues to actively work. What is your recommended approach?

So first, to touch base on KRAS-mutated non-small cell lung cancer, and it's an important point. KRAS mutations are the most frequently encountered mutations in non-small cell lung, cancer probably seen on the order of 30-35% of our patients. And up until recently, this was not a druggable mutation. Recently, though, we're fortunate that for the sub-mutation class of KRAS G12C, both sotorasib and adagrasib are approved in the subsequent line. But that's the key point. They're approved in the subsequent line.

For frontline treatment strategies for KRAS-mutated non-small cell lung cancer, the treatment approach should really mirror those without driver mutations looking at immunotherapy, chemoimmunotherapy, dual immunotherapy, and then dual IO plus chemotherapy strategies.

There was actually a very elegant meta-analysis presented by the FDA at ASCO in 2022 that showed that those with KRAS mutations do appear to perform equally as well as KRAS wild-type when looking across the board at IO plus chemo, IO alone, or chemotherapy-alone strategies, which is quite reassuring.

The question though, is do additional mutations impact the benefit of immunotherapy in driver mutation-negative non-small cell lung cancer, and in particular, alterations in STK11 and KEAP1? This is work that was largely driven by Nando Skoulidis out of MD Anderson, who showed that these particular alterations do appear to impact immunotherapy efficacy and may drive an immuno-resistant, immunologically cold tumor type.

So what do we see clinically? Well, here is data from both the POSEIDON trial and the CheckMate 9LA study, which looked at the incorporation of CTLA4-containing quadruplet regimens for advanced non-small cell lung cancer in the frontline setting. And while these are small numbers, you could see that in POSEIDON, the addition of CTLA4 inhibitor did appear to have a trend toward enhanced benefit over the PD-1 plus chemotherapy alone. And you could see, this was also mirrored in CheckMate 9LA, again, small numbers, but the addition of CTLA4 did appear to have a trend toward benefit in the STK mutant population.

KEAP1, similar story again, very small numbers here. We could see the addition of CTLA4 inhibitor appeared to have a trend toward numeric clinical benefits, though again, small numbers. And on the whole, you could see that really the control arm in this population did not do well, suggesting that this mutation may also really just indicate a highly-aggressive poor prognostic tumor type.

This is more data on frontline nivolumab plus ipilimumab in advanced non-small cell lung cancer when looking at KRAS, STK11, and KEAP1 mutation status. And importantly, when looking at the subgroups, the combination of nivolumab with ipilimumab did appear to elicit benefit irrespective of KRAS, STK11, or KEAP1 mutation subtype.

Additional questions though, does the presence of a KRAS mutation matter? This is work done by The Dana Farber group, which looked at the presence or absence of KRAS mutation in driving clinical benefit in STK11 and KEAP1 mutational status. And what was interesting, is when looking at an immunotherapy approach, it appeared that the presence of a KRAS mutation really seemed to drive the poor benefit of an IO-based approach with the STK11 and KEAP1 mutations compared to KRAS wild-type.

But also there's the question of, do these mutations even matter whatsoever? This is subgroup data from the KEYNOTE-042 study, so pembrolizumab monotherapy, which didn't - which showed a benefit of pembrolizumab monotherapy in patients with both STK11 and KEAP1 mutations. So again, very small subgroup data. I really caution against any widespread conclusions based off of this data. But I think the important points here are that these mutations could have implications for our treatment decision strategies for our patients.

So in summary, patients with non-small cell lung cancer who have mutations in KRAS and no other known drivers should be treated with a frontline therapy strategy that incorporates immunotherapy with or without chemotherapy. There is emerging evidence to suggest that certain molecular alterations such as STK11 and KEAP1 may impact the efficacy of an anti-PD-1/PD-L1-based treatment strategy and advanced non-small cell lung cancer. However, importantly, prospective randomized data are needed to determine the best treatment strategy for those who harbor a mutation in STK11 or KEAP1, and these trials are under development.

So with that, I want to revisit our case of a 60-year-old gentleman with a poorly differentiated non-small cell lung cancer who unfortunately had recurrence within 7 months following resection and adjuvant chemotherapy, with an NGS profile of concurrent alterations in KRAS, KEAP1, and TP53, PDL-1 negative, with a tumor mutational burden of 7 mut/Mb. And what is our recommended treatment approach here?

So for this patient, I did start this gentleman on the CheckMate 9LA regimen of nivolumab with ipilimumab, and I added in the 2 cycles of carboplatin with Paclitaxel, given the patient had already seen a pemetrexed-based regimen and he had poorly differentiated histology. However, the patient did experience progression after 4 months on therapy and has since received investigational treatment in clinical trials.

So with that, I'd like to transition to our peer discussion and introduce my colleague and friend, Dr. Charu Aggarwal.

Dr. Aggarwal:
Thank you so much, Dr. Reuss. I'm Charu Agarwal. I'm the Leslye Heisler Associate Professor for Lung Cancer Excellence at the University of Pennsylvania's Abramson Cancer Center. Thrilled to be joining Josh today to discuss these issues and management of patients with lung cancer.

Dr. Reuss:
Thank you, Dr. Aggarwal. Now, obviously, this is a really, I think, hot topic in the field of non-small cell lung cancer. Now, KRAS mutations, and particularly co-mutations in STK11 and KEAP1. And I'm going to start with the former. How do you let KRAS mutations guide your treatment practice, if at all, for our patients with advanced non-small cell lung cancer?

Dr. Aggarwal:
I think it's a very important point to just educate as well as reiterate here that KRAS mutations, especially G12C, are actionable, but they're not immediately actionable; they're actionable currently in the second-line setting and we should remember that, that there is no body of literature supporting first-line use in patients with a KRAS G12C mutation. However, it's important for us to get the molecular sequencing so that we can recognize these as well as plan for therapy.

In my practice, if a patient has a KRAS G12C mutation, I next look at PD-L1 expression. I do tend to use or favor immunotherapy alone for my high PD-L1 expressors. There is some retrospective data demonstrating that ICI alone for these patients with high PD-L1 and

KRAS-mutant lung cancers may actually do quite well. However, the absence of PD-L1 high expression, I will sort of use chemoimmunotherapy.

However, I think, Josh, you're getting to this, how do we decide for those patients that may have co-mutations with KRAS? And I think that's where it becomes a little bit more challenging because all we have so far are subset analyses of large trials.

Dr. Reuss:
Yes. That's an incredible point, Dr. Aggarwal. I couldn't agree more. I would say that with the KRAS mutation alone, I don't really let that affect my decision-making practice for advanced non-small cell lung cancer in terms of my initial treatment approach. But to your point, these co-mutations, KEAP1 and STK11, in particular, where we say biologically it really looks like these alterations may impact immunotherapy efficacy and drive an immunotherapy - I would say, drive an immunologically cold tumor. So with that in mind, if you see a patient that has a KEAP1 or STK11 mutation, what sorts of things are you thinking about? How are you letting that guide your treatment decision-making?

Dr. Aggarwal:
Absolutely. So as you very well pointed out earlier, you know, in the presence of these KEAP1 or STK11 mutations, we know that there is inherent immunotherapy resistance. We potentially should think about really amping up our strategy, combining immunotherapy combination regimens. Coming in with a quadruplet would be appropriate. You know, we do now have subgroup analysis from POSEIDON that helped us understand that but potentially these patients will do better. We have some subgroup analyses from CheckMate 9LA, and then we have some very small numbers with immunotherapy alone. And I don't think we should probably look at immunotherapy alone because we're really thinking about really gearing up our immunotherapy strategy here.

There is a prospective trial that is going to evaluate the role of quadruplet immunotherapy - chemoimmunotherapy in patients, especially with STK11 and KEAP1, and I think that will be so instrumental in our understanding and management of our patients.

Dr. Reuss:
Could not agree more. And lastly, Charu, I know that you had actually a poster presentation on this topic at ASCO this year. And first of all, congratulations on your excellent research. Could you walk us through a couple of the salient points from that research that was presented just earlier this month?

Dr. Aggarwal:
Absolutely. So we conducted a real-world data analysis using the Tempus database, using Tempus next generation sequencing and evaluating paired outcomes amongst patients with metastatic non-small cell lung cancer, who harbored a KRAS G12C mutation. And we wanted to specifically look at the PD-L1 low population, TPS less than 50%. We found that those patients had the shortest survival when treated with combination chemo and immunotherapy compared with the overall population. We also found that KRAS and other co-mutations such as STK11 and KEAP1 have a profound impact on outcomes of patients treated with chemoimmunotherapy and immunotherapy, very much in line with what we've been seeing with other subset as well as retrospective analyses. So our abstract really was adding to the body of literature that we should be thinking about these patients differently. These patients are different when it comes to PD-L1, less than 1, less than 50% is not the same as greater than 50%. And I think we are just at the precipice of individualizing treatment in the absence of a driver mutation, but in the presence of mutations such as STK11, KEAP1, and KRAS, and I think the future will hold many, many, many practical guides for us.

Dr. Reuss:
Excellent. Thanks so much, Dr. Aggarwal. So definitely stay tuned, right, as we get more data and more prospective evaluation for the ideal treatment strategy for these patients.

So just to wrap up, I think in summary, KRAS-mutated non-small cell lung cancer KRAS is definitely a known driver mutation. However, only a subset is clinically actionable, in those with KRAS G12C mutations, though it is important to point out that the current approvals are for use of these targeted agents, sotorasib and adagrasib in the subsequent-line setting and in the frontline treatment strategy and IO-based approach is absolutely appropriate and should be pursued in these patients. The presence of KEAP1 and STK11 alterations and their impact on treatment decision-making, I think there is a large body of heterogeneous data. And we definitely need more prospective data on how this will guide a treatment decision-making to bring the best treatments to our patients.

So with that, I want to thank you for your attention. And thank you, Dr. Charu Aggarwal, for this very insightful and important discussion.

Dr. Aggarwal:
Thank you so much, Josh. This was great.

Announcer:

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