Transcript Details

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Released: 11/27/2024
Valid until: 11/27/2025
Time needed to complete: 1h 03m

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Incorporation of guidelines-concordant care for advanced NSCLC with second-line targeted therapies

Announcer:
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Dr. Yu:
This is CME on ReachMD, and I'm Dr. Helena Yu.

Dr. Gubens:
And I'm Dr. Matt Gubens.

Dr. Yu:
So, Matt, let's start our discussion with a case. So I have a 67-year-old former smoker who initially presented with stage IV disease with a large 8 cm right upper lobe primary and metastatic disease to lymph node and bone. His initial molecular testing identified a KRAS G12C mutation, along with a concurrent KEAP1 mutation. PD-L1 expression was 40% in the tumor.

And so with that sort of initial presentation, what do you discuss with your patient regarding systemic treatments, both now and in the second-line setting where we have that KRAS mutation?

Dr. Gubens:
Of course, always exciting to find a targetable mutation, but there's some discussion with the patient to say, even though we have a drug for this, it really is a second-line drug, so we do have to start with our standard systemic therapy.

I do talk about the standard options of immunotherapy and chemoimmunotherapy, doublet immunotherapy. And essentially, your patient had a co-mutation, which I think that there's some really interesting data, but maybe not completely definitive in terms of whether we choose immunotherapy alone versus chemoimmunotherapy. I would at least do chemotherapy. I would consider nivolumab/ipilimumab as well for your patient, and then, again, hold a KRAS inhibitor for the second-line.

How did you approach the patient?

Dr. Yu:
Yeah, exactly. So the emerging data about STK11 and KEAP1 is intriguing and you're absolutely right. That might be a patient where I think about 9LA or the POSEIDON regimen. But for now, or at least for this patient, we did have a discussion about sort of the different options. And I think he was a little scared off by the dual checkpoint, the IO/IO combinations, and so we did start on carboplatin, pemetrexed, and pembrolizumab a la KEYNOTE-189, and he actually had great clinical benefit with shrinkage of his primary mass and lymph nodes and had some sclerosis of his bone lesions.

He did well for about 10 months, but then did develop worsening shortness of breath, had a new right-sided effusion. Thoracentesis was

performed, confirmed that the new effusion was malignant. And then we discussed starting one of those KRAS inhibitors. And so we have both adagrasib and sotorasib as potential options.

Do you have one that you prefer, or is there equipoise for you between the 2?

Dr. Gubens:
There's no head-to-head data. Don't expect that anytime soon. I have generally been reaching for adagrasib lately. I think the data are a little more robust in terms of benefit. As you know, the sotorasib didn't quite clear that hurdle of compellingly beating docetaxel in the second line, which was disappointing. But I think either is appropriate. I happen to choose adagrasib as my second line. Though I have to warn patients and kind of proactively educate them on hepatotoxicity that we have to follow and kind of other side effects like edema, GI toxicity, CPK elevations, creatinine elevations. Really, these are not as simple as some of the other oral therapies that we use in a targeted setting.

What about you?

Dr. Yu:
Absolutely. I think the challenge is not as straightforward. And although there is some efficacy, obviously not as much as we see with some of the other targeted therapies directed against EGFR and ALK. I also sort of have a slight preference towards adagrasib. I also was compelled by some of the CNS data that they presented. Of course, this patient didn't have preexisting CNS metastases, but that generally has been what I have had reached to. But again, I think no head-to-head data in there is equipoise.

So I started him on adagrasib 600 BID. He did have a pretty quick response to adagrasib as well. We had to put a pigtail PleurX catheter in, but actually his effusion coming 1 to 2 months on therapy did abate and some of his lung lesions also decreased. And so a good partial response.

Exactly like what you said in terms of side effects. He did have some elevation in his liver function tests, and we ended up dose-reducing because of that, as well as some GI toxicity. But again, I think a lot of these toxicities we're well versed to manage do respond to dose reductions. And he actually still is on adagrasib therapy.

I think we have this first generation of KRAS inhibitors, but I think you and I, and probably many others, are looking forward to the next generation. What excites you in the KRAS space in terms of kind of novel therapies? And if a patient asks, “What do you have next for me, Doc?” how do you answer that?

Dr. Gubens:
Right there on the front page of the NCCN Guidelines is saying that clinical trials are a key component to our care of these patients. And I really tell patients we have a lot of things.

We also have this mutation that’s been so hard to target over the years. We're really kind of figuring it out, and I think aside from these exciting G12C inhibitors, now there's pan-KRAS inhibitors that I think will be very encouraging for the rest of the KRAS slice of the pie. So, really, stay tuned. Granted, still for second line and beyond, but we're going to see some combinatorial approaches in the first line with chemo/chemoimmunotherapy and, again, some novel drugs pan-KRAS.

Dr. Yu:
Yeah, a very exciting space, and I think more to come. With that, our time is up. We hope you found this quick case review helpful, and thanks so much for listening.

Announcer:
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