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Navigating the Evidence: Emerging Frontline Combination Strategies in KRAS G12C NSCLC

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Dr. Burns:
Welcome. This is CE with GLC, and I'm Dr. Timothy F. Burns, a professor of medicine at The Ohio State University Comprehensive Cancer Center. And today, I'd like to talk to you about the emerging data on combining KRAS G12C inhibitors in combination with standard of care therapies in the frontline setting.

So for a number of years, we've had the KRAS G12C inhibitors in the second-line setting as single agent. They have not moved to the first-line setting because their response rates and progression-free survival are not better than what we see with chemoimmunotherapy at this point, or immunotherapy in some cases for the high population. However, we know that these patients did just not do as well. So there have been a number of efforts to see if we combine KRAS G12C inhibitors with immunotherapy based on data that we found preclinically. And although the first attempt of this failed with a drug called sotorasib due to high liver toxicity, I will say there have been a number of attempts since, and these have, for the most part, been successful.

The first study I'll briefly talk about is a study called KRYSTAL-7, which is adagrasib, a first-generation KRAS inhibitor, with pembrolizumab. And what you can see from your slide is that there was a response rate in the 60% range, and in the PD-L1–positive population there was a progression-free survival benefit of 27.7 months. To put this in perspective, if we look at KEYNOTE-024, you'd expect a response rate of 46% and progression-free survival 7.7. So, very promising, and there are 2 trials ongoing, both with pembro alone and chemo with pembro.

The next drug I'd like to talk about is a next-generation KRAS G12C inhibitor called olomorasib, which has increased potency and tolerability, and that's also been combined with pembrolizumab. And what we'll notice from this study, which is quite remarkable, is if we look at patients with all PD-L1, including negative and positive, the response rate is about 70% and the PD-L1 greater than 50 about 78%, and these appear to be durable. We now have additional follow-up on this population. And I think what's most remarkable is that even in the PD-L1–negative populations, we're seeing response rates close to 60%; in the less than 50, again, in the 60s; and in the 1 to 49 in the 60s as well. And again, these responses appear to be quite durable.

There are also other inhibitors out there as well. One called calderasib with pembrolizumab, very early days, as you can see on your slide today. However, responses are seen quite remarkably, 60% in the 1 to 49, and actually 88% in the greater than 50. Again, small numbers, but again showing that this combination can be effective.

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And then finally we have the Krascendo 170 study. This is divarasib. This is again a next-generation KRAS G12C inhibitor with a longer half-life, combined with pembrolizumab, and there's a press release saying that divarasib may be better than our standard agents, a single agent. So it's also been combined with immunotherapy. And again, early days. We have the PD-L1–positive cohort with promising response rates in the 60s, as well as in the PD-L1–negative, similarly. Now, we don't have really a breakdown of how many of these patients are high versus low, but again, a potentially promising PFS of 19.3 months.

Well, what about chemoimmunotherapy? So many times in the frontline setting, we'll use chemoimmunotherapy. And interestingly, there's 2 studies to date that have really tried to address this. One is with olomorasib; the other was calderasib. And what you can see is the response rates are in the 60s or in some cases in the 50s, which actually isn't much better than we might expect with chemo/IO alone. And this really raises the question: Is adding chemo better than KRAS G12C with pembrolizumab? And that's a question I think that's an active area of research.

And so on that note, I'd like to encourage everybody, and as you can see from this last slide looking at the current ongoing phase 3 studies, there are multiple studies out there for patients, regardless of their PD-L1 status, whether they need chemotherapy or don't need chemotherapy. The olomorasib in one trial actually has all 3 cohorts covered. Also, we have a divarasib and calderasib and adagrasib. So I would again encourage you to enroll your patients in one of these first-line trials.

Well, with that, our time is up. I hope that you will find these perspectives useful for your practice, and I want to thank you again for listening.

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