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Safety Considerations and AE Monitoring for Trial Participation With Combination Regimens

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Dr. Burns:
Welcome. This is CE with GLC, and I'm Dr. Timothy Burns, professor of medicine at The Ohio State Comprehensive Cancer Center. And today, I'd like to talk to you about safety considerations and AE monitoring for trial participations with patients getting some of these KRAS G12C inhibitor combinations.

So these combinations seem to be quite promising, but I think it is important that we understand kind of the potential side effects of these and how we'd manage this. And so the first trial I'd like to cover, you can see in your slide, is KRYSTAL-7, which is the combination again of adagrasib and pembrolizumab. And in this trial, you do have high frequency of kind of GI side effects, nausea, diarrhea that need to be managed. There were increases in liver enzymes, and this is not just adagrasib; this has been seen with other agents. I think what's important for both adagrasib and the other agents I'll talk with is most of these are paper toxicities. The patient's not symptomatic from these. Often these will resolve with a dose hold. Rarely need steroids. And patients that have these, as shown by the graph on your slide, actually can do quite well. And so though there was a lot of early concern about this, I think liver function enzymes are something that, with just frequent monitoring, we can manage quite well.

The second drug I'd like to talk about is olomorasib and pembrolizumab. Now, olomorasib is a next-generation KRAS G12C inhibitor with improved potency and tolerability. And what you notice is that you see less frequency of GI toxicities, mostly grade 1 and grade 2 when you see them, and rarely grade 3 for diarrhea, only 7%. Again, relatively well tolerated. Again, we see these ALT and AST increases, something to keep in mind. Most patients did not need to be dose-reduced or even discontinued from these. And again, managing liver functions is really a matter of just holding the drug for a couple days and seeing if they go down. And if not or if they were quite high, considering steroids, although that was an infrequent event, and really these were asymptomatic events but need to be monitored for.

Similarly, the KANDLELIT-004 trial, calderasib with pembrolizumab, very early days, not a lot of data available. However, it does seem to have a pretty good tolerability and with low frequency of grade 3 events, at least with the pembro and calderasib with like 25% grade 3. Now, some of the toxicities, grade 1 and 2, the question is how much diarrhea are we seeing here? Just to keep in mind, a grade 2 diarrhea is 4 to 6 bowel movements, and so something as we get more data to keep an eye on. But overall, pretty well tolerated.

The last study we'll talk about is Krascendo 170, which is divarasib with pembrolizumab. Similar to adagrasib, divarasib has a long half-

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life, and with these agents that have long half-lives, we see higher rates of GI toxicity. Again, pointing out that diarrhea was in 75% of patients, and grade 3/4 was almost 18%. Also, high grades of nausea and vomiting. So when using an agent like divarasib, or potentially adagrasib, aggressive managing and prophylaxis of GI toxicity is likely necessary. Also, elevated liver function enzymes. However, most of these, in fact, all these seem to be reversible with dose holds and potentially steroids if needed. Going forward in the phase 3 trial, they are recommending aggressive prophylaxis, including dexamethasone, and we'll have to see how these side effects improve in the phase 3.

So really, some take-home notes. So there are many of these are looking promising. It is likely that we have a KRAS G12C inhibitor in combination with immunotherapy, and so really, we have to keep in mind the management of these toxicities. So depending on the agent, GI toxicities, diarrhea, nausea, and vomiting can be issues, especially with adagrasib and divarasib. So really aggressive prophylaxis with those agents may be helpful. The liver function enzymes do need to be monitored. Again, most of these are low grade. Most of these are in the 200s. They do not require steroids if they're relatively low grade. It does require a dose hold and making sure that the liver enzymes aren't getting worse. But generally, this is something that, as we've gotten more experience, seems to be quite manageable. In terms of autoimmune toxicities, we don't seem to see them more frequently than we do with pembrolizumab alone, and again, they should be treated as we do for pembrolizumab.

Which really brings me to my last point, is that when you're using immunotherapy, whether it's in combination or single agent, your toxicities, you really need to coordinate between professions and to kind of have a multidisciplinary approach involving your endocrinologist, your pulmonologist, and rheumatologist, depending on what the side effect, and this is important really for clinical trials or just in practice.

Well, I think our time is up. I hope that you'll take these perspectives back into your clinic and watch out for future trials. And thanks so much for listening.

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