available therapy is also considered when deciding whether an accelerated approval should be withdrawn or whether there may be an alternative path to verify clinical benefit.

While sotorasib was the first KRAS G12C inhibitor to receive FDA approval, there are numerous competitor drugs currently being developed for non-small cell lung cancer. Adagrasib is the other KRAS G12C inhibitor farthest along in drug development, and it is the only other drug in class that has FDA approval to date. Adagrasib was granted accelerated approval in December of 2022 and the confirmatory randomized trial, KRYSTAL-12, is ongoing. KRYSTAL-12 evaluates the same patient population as CodeBreaK 200, has the same docetaxel control arm, allows for crossover, and also has a PFS per BICR primary endpoint. Per clinicaltrials.gov, the estimated primary completion date of KRYSTAL-12 is in May of 2025.

We note that the applicant has a planned randomized trial in the first-line setting. CodeBreaK 202 randomizes patients with KRAS G12C

scheme -- I think it's figure 2 -- which they also showed in their analysis, is actually not quite correct. The scan data is shared with investigators, as well as the COP assessment and the BICR. The investigator was never a gatekeeper, per se, in order for the BICR to receive information. In that regard, again, they were blinded to treatment assignment at all times, and there was no communication between the investigators, the COP assessment, and any of the BICR assessments.

With regard to -- I think you had a third question. Can you repeat your third question that was in embedded in there?

DR. NIEVA: Yes. I'd like to know the nature -- we do blinded independent central review because we presume it to be more competent or informed. So the fact that the first blinded independent central review seemed to have a large number of errors is concerning. So I'd like to know if that's something that's been acknowledged by the vendor or if the vendor stands by their

initial assessments, and I'd like to know if there was a systematic nature to the types of errors that were being made.

DR. FRIBERG: So to clarify, the BICR process and the independent imaging reads were entirely independent. As I mentioned, no information was sharing. Also to put it into some context, less than 10 percent of the total reads that were performed by the BICR went through the COP process.

That being said, this aggregate data that was identified as having some discordances through the mechanisms that we described was through routine and outlined in the imaging charter communications with the imaging vendor. That led to an independent quality review at the level of the imaging vendor, and ultimately that led to them independently, without regard to saying which of the individual scans were involved; or without, again, knowledge of the treatment assignments, that led to their independent evaluation, reader retraining, and ultimately the three scans that had

their values changed.

So in that regard, the auditing that the FDA brings up would only have been possible through this communication with Amgen that, again, was without regard to treatment assignment, and the global 100 percent re-reads should have nullified that. So again, no imaging charter violation and the re-reads should have accounted for all of this.

DR. MADAN: Okay. Thanks.

DR. SINGH: Dr. Madan, may I be permitted to just respond, since it was basically said that the FDA is being inaccurate? I think that we did say within our presentation that this was a very confusing process for us to elucidate. We called it a potential violation, and we did try to gain a deeper understanding. Nevertheless, we considered this to be, in totality, just an atypical interaction, triggering a series of re-reads, which again speaks to just the global concerns regarding the fidelity of this endpoint. I'll end there.

DR. MADAN: Thank you, Dr. Singh.

Dr. Shaw, you have the next question.

DR. SHAW: Thank you very much. Pamela Shaw, Kaiser Permanente, Washington Health Research Institute. I just had a couple of quick follow-up questions regarding the BICR re-read process. I just wanted to understand, were those completely new people from that vendor or new organization that were re-reading it -- so that would be the first time they saw the scans -- or was it some of the same people reading the same scans a second time?

DR. FRIBERG: Thank you, Dr. Shaw. They were three separate new individuals, new radiologists, who were independent from anyone who had ever seen a scan on the study.

DR. SHAW: Okay. Great. Thank you. I think that completes my questions about the BICR.

Then I just had another second question, which related to understanding some of these sensitivity analyses, and we've heard the term "pessimism" being used in some of those imputations, where we think about those people that stop treatment or the early crossovers, and we

heard about this imputation process where we take the 58 percent, the top 50 percent, in terms of best progression events in the imputations.

For me, what I understood -- and maybe this is a question for Dr. Song, and you can tell me if I'm interpreting this correctly -- is that we've learned about the people, particularly, I'm going to call it the doxa [ph] arm -- I don't pronounce it very well -- that the early switchers had better survival. I think it was a 42 percent hazard ratio. And also, there was a differential better survival being censored for the standard arm.

So the idea that this 50 percent imputation is optimistic, I'm confused because the way I think about it, if I'm going to impute this progression, I want to think about people with a similar prognosis. So I'm actually wondering, rather than just taking the progression times, did you think about doing an imputation, or did anyone do an imputation, where you think about people with similar prognosis, similar survival, and then look at the progression times, the progression-free

survival times, amongst those who had, obviously, better survival that we're getting censored on one arm versus the other?

I don't know if that question made sense, because I'm not sure if an optimistic implication was done because the survival wasn't considered, and it seemed like there was a survival difference or at least some evidence of that.

DR. MADAN: Maybe I can try to distill that, and you can correct me if I'm wrong, Dr. Shaw. But you're asking, basically, with the statistical extrapolations, were they done with patients of similar characteristics so you could have a more accurate imputation?

DR. SHAW: Yes, in terms of the prognosis, because I'm concerned that this term "optimism" is giving us all comfort, and I'm not sure they were optimistic at all because they didn't consider one of the most important characteristics of the patient, which was prognosis, and somehow conditionally imputing on prognosis, based on survival times.