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# Advancing Molecular Therapies to First Line in BRAF-Mutated mCRC: Insights From Emerging Data

**Announcer:**
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**Dr. Eng:**
This is CME on ReachMD, and I am Dr. Cathy Eng. Here with me today is my colleague, Dr. Scott Kopetz. Let's get right into it regarding first-line treatment options in BRAF-mutated tumor types for metastatic colorectal carcinoma.

Dr. Kopetz, can you please review the clinical trial data for these patients?

**Dr. Kopetz:**
Thank you, Dr. Eng. It's really an evolving area. We know that patients that have a BRAF V600E-mutated colorectal cancer have poor outcomes with standard cytotoxic chemotherapy. There's been prior work that has led to the approval of encorafenib and cetuximab in second- and third-line, and a prior first-line study, the ANCHOR study, that looked at an all-targeted therapy—encorafenib, binimetinib, cetuximab—in first line that showed certainly some activity but durability was a limitation.

And that was part of the rationale for the BREAKWATER study. This was one that was just reported out at ASCO with the PFS and OS data, and this was looking at a combination of the encorafenib–cetuximab in combination with chemotherapy, compared to a standard of care chemotherapy. And that had showed an increased response rate, which was reported out previously, and a substantial improvement in the progression-free survival, going from 7.1 months on the standard of care to 12.8 months with the combination of EC and FOLFOX, and a doubling of median overall survival—15.1 months to 30.3 months. So really encouraging data suggesting that early administration of encorafenib–cetuximab in this setting provides meaningful benefit, even though in the control arm, many of the patients had access to the encorafenib–cetuximab in later lines. So I think it is encouraging for our patients.

**Dr. Eng:**
Do you want to mention briefly about that third arm that was discontinued, just so people understand regarding why the original trial design was revised appropriately?

**Dr. Kopetz:**
Yeah. It's a great point. And I think that this was a 3-arm study and had an encorafenib–cetuximab arm, and that was halted partway through enrollment on the basis of the earlier data with the ANCHOR study, with the modest PFS benefit. But indeed, when we took a look at the data, the progression-free survival for the encorafenib–cetuximab alone in first line was 6.8 months, so very similar to the

standard of care.

And intriguingly, although this was not a powered analysis, was it had a median overall survival of 19.5 months for starting with EC versus a standard of care starting with the chemotherapy alone of 15.1 months. So a suggestion that perhaps in patients that aren't candidates for cytotoxic chemotherapy, that the EC alone may be a possibility.

**Dr. Eng:**
These findings were just pivotal, Scott, as you know, and really provides a lot of hope for our BRAF V600E newly diagnosed metastatic colorectal carcinoma patients.

So I just want to make sure that we capture the key takeaways, which is basically we now know that encorafenib–cetuximab in combination with oxaliplatin-based therapy is appropriate for newly diagnosed BRAF V600E-mutant tumor types with metastatic colorectal carcinoma. And that should be considered the new standard of care moving forward, given this improvement not only in response but also PFS and overall survival.

And I think it really also changes the way we may approach clinical trial design moving forward for other trials, because some of the other trials, we're now excluding BRAF patients. And so this has really given a lot of patients a lot of hope. And I think this is extraordinarily important. And I think you might want to also mention the other cohort that we're waiting for the final data on as well, so people are aware there's a potential that's being evaluated with irinotecan.

**Dr. Kopetz:**
That's right, yeah. So we're looking forward to that latter part that will report out. This was a randomization that was separate, enrolled after the main cohorts of BREAKWATER, and that was looking at the FOLFIRI backbone. So FOLFIRI–EC versus standard of care.

**Dr. Eng:**
Well, this has been a great review of this pivotal data regarding BREAKWATER. Our time is up, and thank you so much for listening.

**Announcer:**
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