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Addressing the Challenge in Rechallenge Strategies for mCRC

Announcer:
Welcome to CME on ReachMD. This activity, titled "Addressing the Challenge in Rechallenge Strategies for Metastatic Colorectal Cancer" is provided by Agile.

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Dr. Ciardiello:
My name is Professor Fortunato Ciardiello. This is a CME activity on ReachMD, and the topic of today is to illustrate to the audience the rechallenge strategies with anti-EGFR monoclonal antibodies in metastatic colorectal cancer in order to help the physicians to optimally treat the patients with refractory metastatic colorectal cancer.

The epidermal growth factor receptor is a relevant growth factor receptor for the pathogenesis of metastatic colorectal cancer. It's expressed in the majority of tumors, and anti-EGFR monoclonal antibodies as selected monoclonal target therapies is changing the treatment landscape for these patients.

Today with me will be Professor Erika Martinelli. Hi, Erika.

Dr. Martinelli:
Hi. This is Erika Martinelli. I am associate professor and medical oncologist, and I'm very happy to be here to discuss the rechallenge in metastatic colorectal cancer patients.

Dr. Ciardiello:
To start our conversation, let's talk before about the current treatment strategies for patients with metastatic colorectal cancer having a RAS wild-type disease and basically to define holding to guidelines. What are the scenarios for first-line therapy and for second-line therapy for these patients in order to understand how we can use rechallenge with anti-EGFR therapies and when to use it?

I have a question for you, Erika. Given the guidelines for the first 2 lines of treatment, in the subsequent lines of treatment, when we talk about refractory metastatic colorectal cancer patients, what is the possibility of rechallenge treatment by using anti-EGFR therapy?

Dr. Martinelli:
So first of all, we have to consider that in patient with RAS wild-type metastatic colorectal cancer, especially in left-sided metastatic colorectal cancer, it is strongly recommended, and this is also on the last version of guidelines, to use the anti-EGF receptor in combination with chemotherapy, and this is what has been present on the guidelines. The recommendation for right-sided is not so strong, so in this case we do not recommend to use anti-EGF receptor, but in left side, this is the treatment. At progression, this kind of patient received, in the vast majority of the cases, chemotherapy in combination with anti-angiogenic drug. But of course, we have to consider that after our first- and second-line failure in a patient who responded very well to anti-EGF receptor in first-line, we can consider the rechallenge.

But before entering, of course, in this conversation, we should address: What is the concept of rechallenge? If a patient responded very well in first line, and at certain time point the disease progressed, this is why there are some mutated clones that are responsible for

progression – we stop the first-line treatment, started a second-line treatment, eventually, with the anti-angiogenic drug in combination with chemo, and of course, we give to the patient an anti-EGF receptor free. We give the possibility to kill the mutated clones. The RAS wild-type clones rise again, and so the disease become again sensitive to anti-EGF receptor blockades. So in this case, we call rechallenge strategies, so it's very important to understand what we mean when we say anti-EGF receptor rechallenge in RAS wild-type metastatic colorectal cancer.

Dr. Ciardiello:
Thank you. Thank you, Erika. This is really fascinating because basically this helps us to identify those patients with the refractory metastatic colorectal cancer that most likely will benefit from rechallenge therapies with anti-EGFR drugs. What our audience can learn from this part of the presentation is that patients should be RAS wild-type metastatic colorectal cancer patients that responded very well to first-line treatment with chemotherapy plus an anti-EGFR monoclonal antibody, and then at the beginning of third-line or further line of treatment, before starting rechallenge with anti-EGFR monoclonal antibodies, were tested by liquid biopsy to evaluate the status of the disease. Only patients with liquid biopsy test at the RAS wild-type disease are suitable for anti-EGFR rechallenge and will benefit from this treatment.

Now, Erika, I have again a question for you. Can you help us to understand which are the clinical data to support what I said on EGFR rechallenge value for metastatic colorectal cancer patients?

Dr. Martinelli:
Yes, we have to say that the study for rechallenge had started long time ago. Initially, we have only retrospective trial, but I will say that we have now phase 2 trial that demonstrate the effectiveness of rechallenge. First of all, I would like to comment on the CRICKET study. This is a phase 2 trial in which patients who responded in first line to anti-EGF receptor received as a rechallenge treatment irinotecan plus cetuximab, and the primary endpoint of the trial was response rate. But if we consider the post hoc analysis made for circulating tumor DNA, we see the RAS wild-type patient and the mutated patient, the activity of cetuximab plus irinotecan treatment as a rechallenge was only found in RAS wild-type that were wild-type at the ctDNA analysis. We have a PFS [progression-free survival] median of 4 months and a median overall survival of 12.5 months. This is the first prospective trial, but we have also another trial that we have conducted here.

We used a different strategy for rechallenge, in fact, we used the combination of cetuximab with immunotherapy, an immune checkpoint avelumab. These patients in the CAVE and metastatic colorectal cancer trial were MSS [microsatellite stable]. And we have as a primary objective with median overall survival that, in our intention-to-treat population, was reached, and, in fact, we're reporting the 11.6 months. But also in this case, if we see the activity of patient that were RAS wild-type at ctDNA analysis, so we're performing the liquid biopsy just before the treatment of cetuximab and avelumab, you can clearly see that important benefit that the patient with RAS wild-type circulating DNA had. In fact, we reported in the CAVE trial a median overall survival of 17.3 months and a median progression-free survival of 4.1 months, but we have to admit that this is a very interesting data. This is a refractory population, so this is very important to get this information.

And more recently, we also conducted another phase 2 trial [VELO]. This a randomized phase 2 in which, in the same population of CAVE and the CRICKET trial, the patients were randomized to receive trifluridine/tipiracil plus panitumumab versus the standard that was trifluridine/tipiracil alone. And you can see also here from the slide that the benefit of the combination treatment that is trifluridine/tipiracil plus panitumumab was showed, especially in patients that were RAS wild-type at the ctDNA analysis. Now we have a median progression-free survival of 4.5 months versus 2.6 for the control arm with a hazard ratio 0.48. And if you consider the super selected population, so the patients who at baseline do not present any mutation in RAS genes – BRAF, EGF receptor, ERBB2 and PI3 kinase – you can see that here the benefit of the rechallenge strategy with trifluridine/tipiracil plus panitumumab is very high. We have a median progress-free survival of 6.4 months.

Dr. Ciardiello:
Erika, according to the data you have presented, the 3 trials – CRICKET, CAVE, and VELO – clearly show that in RAS wild-type patients, a liquid biopsy assessment before treatment with anti-EGFR monoclonal antibody, either cetuximab or panitumumab, in combination with the irinotecan in the CRICKET trial, with avelumab in the CAVE trial, or with panitumumab in the VELO trial, there is a significant activity and relevant clinical efficacy of these treatments for patients that were treated correctly in the rechallenge setting.

For those of you just tuning in, you are listening to a CME activity on ReachMD. I am Professor Fortunato Ciardiello, and here with me today is Professor Erika Martinelli. We are discussing a very fascinating topic for the therapy of metastatic colorectal cancer in the chemorefractory setting, the challenges and the possibility of anti-EGFR rechallenge.

Therefore, Erika, can you tell us where the field is going in terms of anti-EGFR rechallenge therapies to optimize this treatment option?

Dr. Martinelli:
So you're right. The field is evolving, and we have several ongoing trials on the rechallenge as a topic. But you can see that here from this slide in that we have the PARERE, the PULSE trial, the FIRE-4. In this trial, you can see, especially for PARERE and PULSE, the patient will be selected according to the liquid biopsy. So this is an evolution of what we have seen before, and in this case, we found that patients may be rechallenged only with panitumumab or in combination with irinotecan. But I will point your attention on these other 2 studies that are ongoing, and we are coordinating these 2 studies: the CAPRI 2 GOIM trial and the CAVE-2 GOIM trial. You can see in the first study, in the CAPRI 2 GOIM trial, that patients may receive a rechallenge with irinotecan/cetuximab if they will be RAS wild-type at liquid biopsy. And also in the CAVE-2, we have the evolution of the CAVE trial, because in CAVE trial, we used the cetuximab in combination with avelumab. Now we have, according to the results of liquid biopsy, a randomized phase 2 trial in which patients will be randomized to receive cetuximab plus avelumab or avelumab alone. In this case, we will see the contribution of immunotherapy to the combination with the cetuximab.

Dr. Ciardiello:
Thank you, Professor Martinelli. This is a very comprehensive analysis of the current ongoing trials, and the results of these studies will tell us which is the optimal strategy for using the rechallenge concept with anti-EGFR monoclonal antibodies.

Now before we wrap up, Dr. Martinelli, can you share with us at least one take-home message for our audience on anti-EGFR rechallenge therapy and the role of all anti-EGFR monoclonal antibodies, such as cetuximab?

Dr. Martinelli:
Yes. We have to consider in the continuum of care that rechallenge is an active treatment. We have showed the results, very interesting, very fascinating. We get important PFS and important overall survival. Of course, this is active, but we have to select the patient. We have to initially select the patient according to clinical criteria, so the patient who responded in first line to anti-EGF receptor treatment, to guide our decision for the rechallenge strategy. Never forget to perform the liquid biopsy because only according to results of liquid biopsy we will know that the rechallenge strategy will be effective for metastatic colorectal cancer patient.

Dr. Ciardiello:
Thank you. Thank you again, Erika. Unfortunately, that is all the time we have today, so I would like to thank our audience for having listened to us today. Thank you again, Erika, for joining me and for sharing all of your valuable insight on this topic. Was really great again to speak with you today.

Dr. Martinelli:
Thank you very much.

Announcer:
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