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Released: 09/28/2020
Valid until: 09/28/2021
Time needed to complete: 15 minutes

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Optimizing Treatment Selection in *BRAF* V600E-Mutated Metastatic Colorectal Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “The Changing Landscape of BRAF V600E-Mutated Metastatic Colorectal Cancer Treatment” is provided by AGILE and is supported by an independent educational grant from Merck KGaA, Darmstadt, Germany.

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Dr. Kopetz:
The BRAF V600E mutation occurs in approximately 10% of patients with metastatic colorectal cancer and identifies a subtype of colorectal cancer with a poor prognosis. First-line chemotherapy invariably fails and results in a median survival of four to six months after first-line therapy. Beneficial second-line therapies have remained an unmet need for far too long. However, recent results from the BEACON clinical trial have begun to change the landscape for patients with BRAF V600E-mutated colorectal cancer.

This is CME on ReachMD. I’m Dr. Scott Kopetz, and I’m joined on today’s panel discussion by Drs. Eric Van Cutsem and Josep Tabernero. Together, we’ll evaluate the initial and subsequently updated mature findings of the BEACON trial and discuss how those findings may benefit patients with BRAF V600E-mutated metastatic colorectal cancer who have failed first-line therapy. Dr. Van Cutsem, Dr. Tabernero, welcome to the program.

Dr. Van Cutsem:
Thank you very much, Scott. I’m Eric Van Cutsem. I’m Professor in GI Oncology at the University of Leuven, Belgium, and I am happy to join this panel and to join all of you for this lively discussion.

Dr. Tabernero:
Thank you, Scott. Thank you, Eric. My name is Joe Tabernero. I’m a Professor of Medicine, Medical Oncologies, the Director of the Vall d’Hebron Institute of Oncology in Barcelona, Spain. I’m very happy also to join this conversation.

Dr. Kopetz:
Great. Thank you both. So let’s get started. Dr. Van Cutsem, first question to you. It’s no secret that first- and second-line therapies for patients with BRAF V600E-mutated metastatic colorectal cancer have, in the past, offered a very poor prognosis for the patients. Can you provide a picture of what these patients can face in terms of the prognosis, the burden of disease, and the quality of life on therapy?

Dr. Van Cutsem:
Yeah, it’s indeed a difficult subgroup of patients with metastatic colorectal cancers to treat. They often have a very aggressive disease, often extensive metastasis and often a rapid tumor progression. And therefore, we’ve been looking in different studies, not specific studies for BRAF V600E mutant patients, but general studies which included some patients with BRAF V600E mutation at the best strategy. And looking at subgroup analysis from the different studies in metastatic colorectal cancer, we came up with some recommendations that made it up to the ESMO guidelines, to the NCCN guidelines, often being set for fit patients in first-line treatment of metastatic disease for this subgroup of V600E mutant patients, with a triplet: FOLFOXIRI plus bevacizumab. In less fit patients, we

may go for a doublet of FOLFOX plus bevacizumab. And indeed, in the TRIBE-2 study, it was not clear whether triplets are really needed for these patients compared to doublets. They may go and be treated in second-line with FOLFIRI plus an angiogenesis inhibitor. EGFR antibodies added to a cytotoxic doublet, onto a cytotoxic triplet, do not seem to add a lot of activity in patients with the BRAF V600E mutation in this setting.

Dr. Kopetz:
Thank you, Eric, well described. And it's certainly a challenge to make sure that we can identify progression early in these patients, and change therapies to try to stay ahead of the disease.

With that as background, Dr. Tabernero, can you describe the therapeutic rationale supporting the use of targeted therapy for patients who have failed first or subsequent lines of therapy for BRAF V600E mutated metastatic colorectal cancer?

Dr. Tabernero:
Thank you, Scott. First of all, this is really a poor-prognosis population. And we are very excited about the data that we have from BRAF V600E inhibitors in the field of melanoma. For that particular reason, this is why we started treating in clinical trials patients with metastatic colorectal cancer that – be it the BRAF V600E mutation – with BRAF inhibitors, selective BRAF inhibitors as single agent. Unfortunately, we found that these single agents were ineffective in the metastatic colorectal population, basically due to the feedback activation of several tyrosine kinase receptors; but specifically, or more especially, the epidermal growth factor receptor would actually lead to a continued cell proliferation. We also knew from – initially from preclinical data that this EGFR activation feedback could be overcome by targeting multiple pathway nodes. And specifically, this investigator showed that the combination of BRAF inhibitor plus an EGFR inhibitor, like cetuximab, could overcome this feedback. And more importantly, also they showed that the addition of a MEK inhibitor could eventually improve the outcome at the preclinical setting. And with all this background, actually several phase 1b studies were launched combining different EGFR inhibitors, mainly cetuximab or panitumumab, with different BRAF inhibitors and eventually MEK inhibitors. And for the basis of this discussion actually, the clinical trial that at the end was the BEACON colorectal cancer study. And initially, we treat patients in a safety-led part with a type of regimen combining the BRAF inhibitor encorafenib, plus the MEK inhibitor binimetinib, plus cetuximab. And we found in this safety-led study that both the triple combination, as I mentioned, but also the double combination of encorafenib and cetuximab had a very manageable safety profile.

Dr. Kopetz:
So with that background, Eric, let's shift gears and maybe focus now on the data that emerged from the BEACON clinical trial. So we'll maybe start and have you describe some of that background.

Dr. Van Cutsem:
Yes, thank you, Scott. Indeed the BEACON study was an open label, phase 3 trial in which we randomized 665 patients between the control arm, which was defined as FOLFIRI or irinotecan in combination with cetuximab versus a doublet – encorafenib and cetuximab – versus a triplet – encorafenib, binimetinib, and cetuximab. And patients were pretreated with one or two lines of chemotherapy. We defined as primary endpoint, survival, and initially based on the biology, we defined, looking at the triplet – encorafenib, binimetinib plus cetuximab – versus control, as primary endpoint, looking at survival, and then also looking at overall response rate, according to a blind and central review, in the first 331 patients. And then also we wanted to look at, in the further analysis of the trial as secondary endpoints, at the benefit, at the activity of the doublet – encorafenib and cetuximab – versus control, and also look at the activity of the triplet – encorafenib, binimetinib and cetuximab – versus the doublet – encorafenib and cetuximab – for the different efficacy endpoints and the different safety endpoints in this study.

Dr. Kopetz:
Dr. Tabernero, can you share what the findings of this study and the initial efficacy readout were?

Dr. Tabernero:
Absolutely, so the initial readout actually shows that the two experimental arms achieved the primary objective of the study, so an improvement in overall survival compared to the control arm. If we focus on the triplet regimen – the combination of encorafenib, binimetinib, and cetuximab – there was an improvement in the median overall survival from 5.4 months in the control arm to 9.0 months in the triplet regimen, with a hazard ratio for survival of 0.52. And also, we look as a primary objective at the objective response rate by a blinded central review, and the response rate in the patients seated in the doublet regimen was 26%, compared to 2% in those patients seated in the control arm. Now, looking at the data in the doublet regimen, the combination of encorafenib and cetuximab, the median overall survival increased from 5.4 months in the control arm to 8.4 months in the doublet regimen arm, with a hazard ratio for survival of 0.60. And also, the confirmed response rate was 20% in this doublet regimen arm compared to the control arm with 2%. We also learned from the initial data that the adverse events of grade 3 or higher occur in 58% of the patients treated with a triplet regimen, in 50% in those treated in the doublet regimen, and in 61% in the control arm group.

Dr Kopetz:
For those of you just joining us, this is CME on ReachMD. I am Dr. Scott Kopetz, and here today with Dr. Eric Van Cutsem and Dr. Josep Tabernero. Together we're discussing the changing landscape of treatment of BRAF V600E mutant metastatic colorectal cancer.

So, Dr. Tabernero, the prespecified analysis from BEACON, as you mentioned, demonstrated an apparent superior outcome for the triplet compared to the doublet, but this data faded a bit on the more mature data analysis. So would you take us through the relevant findings from the updated analysis? And we can then address how these findings may impact decision-making.

Dr. Tabernero:
This shows actually how important it is to have a long follow-up in the studies, in particular the phase 3 studies, but in all kinds of studies. So what we learned from the extended follow-up is that the survival of patients treated with the experimental arms with this more prolonged follow-up actually became very similar. So, the updated analyses show that the median overall survival for the doublet combination actually was 9.3 months compared to the 5.9 months in the control arm. And with this extended follow-up, the hazard ratio for survival was 0.61. And actually, you may have picked up that the median overall survival seemed to increase from the primary analysis that we mentioned was 8.4 months to this more mature median survival of 9.3 months. Now, if we look at the data also on the triplet regimen, the median overall survival was also at 9.3 months, compared again to the 5.9 months in the control arm, with a hazard ratio for survival of 0.60. And this also has to be put in perspective because in the initial primary analysis, the median survival for the triplet regimen was 9.0 months. So, the conclusion that we could say here, right now, is that we have numerically identical median overall survival, even almost identical hazard ratio for survival, with the two experimental arms across all the different subgroups.

Dr. Kopetz:
Thank you, and it's certainly encouraging to see that median overall survival increase in the doublet arm for our patients.

Dr. Van Cutsem, there were indications of survival benefit in the triplet for subsets of patients. I wonder if you could comment on this and kind of put this in perspective, in addition, with the updated data on response rate?

Dr. Van Cutsem:
Yeah, indeed, it's important to understand for the future whether the best treatment for all patients is just a doublet or whether there are some patients were it to be a triplet, the triplet encorafenib, binimetinib, cetuximab. And now after the BEACON, with the updated survival analysis, as was just mentioned by Josep, the doublet becomes standard treatment, and that's what is approved by FDA and EMA. But in the future, we will have to learn a little bit more about subgroups. And indeed, in the BEACON study, we have seen that patients with a PS=1, patients with more than three organs involved with metastasis, and patients with more inflammation, in other words, with a high CRP – that there was a trend for a bigger benefit for the triplet versus the doublet.

Dr. Kopetz:
Thanks. So how do these updated data affect the decision-making for the BRAF V600E-mutated colorectal cancer?

Dr. Van Cutsem:
Well, in Europe, we will follow the label, which is the doublet, encorafenib plus cetuximab, and that's – at the moment, that's probably going to be the standard option for these patients in second- and third-line.

Dr. Kopetz:
Yeah, and that would be the same for my practice as well, really, utilizing the doublet. As we come to the close of our discussion today, what are the key take-home messages that you want to make sure to relay to the audience from today's discussion? Dr. Tabernero, why don't you go first?

Dr. Tabernero:
Yes, thank you. So, we can conclude that the BEACON colorectal cancer study showed that the combination of encorafenib plus cetuximab, with or without binimetinib, significantly improved overall survival and also the independently related response rate, and this compared to the standard of care in this population of patients with BRAF V600E mutation metastatic colorectal cancer. And based on all these data, and especially in the extended follow-up of survival, in most of the countries, the medical authorities are just attempting or prompting the combination of encorafenib plus cetuximab in these patients in the second-line setting or beyond with BRAF V600E mutant metastatic colorectal cancer.

Important to mention also, that there are other ongoing studies, like, for example, the first-line setting ANCHOR trial that the initial data was recently presented in the same population. Also there is discussion on another important study – a planned study at this time, and this may be a phase 3 study of encorafenib plus cetuximab plus standard-of-care chemotherapy in the first-line setting. And, obviously, the follow-up of the BEACON study plus the additional data that will be coming will also provide us information on how we should treat patients with BRAF V600E metastatic colorectal cancer.

Dr. Van Cutsem:
I don't have much to add to what Josep said; he said it very well. But, indeed, this BEACON study is a pivotal study. It's a practice-changing study. That's why first results were published in *The New England Journal of Medicine*. However, there is much to learn. I mentioned and I repeat the translation research, but especially also that other strategy first-line treatment options should be combined also for these patients because they sometimes have an aggressive behavior, chemo plus encorafenib and cetuximab.

Dr. Kopetz:
Thank you. And I think as we turn our attention towards moving the therapy in earlier-line treatments, it also brings up the questions in the future of really trying to understand more about the mechanisms of resistance and opportunities to intervene after progression on the encorafenib and cetuximab. And I think the exciting thing in my mind is not only having a great therapeutic option now for our patients, but also really kick-starting a much broader drug development effort in the space of BRAF V600E.

Well, this brings us to the end of our discussion, and I really want to thank my guests, Dr. Eric Van Cutsem and Dr. Josep Tabernero, for joining me today for the panel discussion and for sharing their insights into the changing landscape of treatment for the BRAF V600E-mutated metastatic colorectal cancer. Dr. Van Cutsem, Dr. Tabernero, it was great speaking with you today.

Dr. Van Cutsem:
Thank you very much, Scott and Josep.

Dr. Tabernero:
Thank you very much, Dr. Kopetz. Thank you.

Announcer:
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