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Clinical Considerations in Treatment Sequencing for mCRC

Dr. Falcone:
Welcome to the discussion on the treatment of metastatic colorectal cancer and, in particular, we will discuss today regarding the treatment of RAS wild-type patients with regard to treatment options after progression after the first-line. Professor Stintzing, Professor Liu, welcome to the program.

Dr. Liu:
Thank you

Dr. Stinzing:
Welcome, Alfredo.

Dr. Falcone:
Let's start with a situation in which a patient with metastatic colorectal cancer progresses on first-line FOLFOX plus the anti-EGFR cetuximab. What evidence is there to support the continued use of cetuximab following progression?

Dr. Liu:
Yes. This is a good question because for the continued use of cetuximab after first line progression we will consider is it possible, is it appropriate to use after continuation. So we have a study we call the CAPRI-GOIM study. So, this study was designed as an open-label, randomized, phase 2 study to evaluate the continued use of cetuximab in the second line setting for KRAS exon 2 wild-type metastatic colorectal cancer. So, in this setting, the chemotherapy regimen changed from FOLFIRI to FOLFOX and the cetuximab to be continued use. In this study, in this phase 2 study, we can see that the progression-free survival for the intention to treat population showed no significant difference in 6.4 months versus 4.5 months. So, among the 153 patients, 117 patients were tested by NGS with KRAS, NRAS, BRAF, and PIK3CA. Among them, only 56% of the patients were wild-type for all of the tested genes. So, from this, we can see that for the 66 cases of the whole wild-type genomic patients, the progression-free survival was longer and continued to assess cetuximab plus FOLFOX compared with FOLFOX alone. So, that is the progression-free survival is 6.9 months versus 5.3 months. So the hazard ratio is 0.56 and the OS showed longer in the cetuximab group. But, statistically, still no significant difference and that is because maybe the sample size is not so large. But, this phase 2 study showed the potential effectiveness of the continued use of cetuximab in the second line setting, especially for the KRAS, NRAS, BRAF and PIK3CA wild-type patients. So, I think, in this study we know it is very important to see what kind of patients we could be continued use for the cetuximab and, in this way, the testing method is very important and not only KRAS, we also should use a more sensitive way to test all RAS type and even including the RAF type.

Dr. Falcone:
And, as a follow up to that, Dr. Liu, can you explain the rationale or the rechallenge concept for no reintroduction, not beyond progression, rechallenge to a treatment to which the patient had previously progressed with a break between? And how this relates to the decision to take a break from the anti-EGFR?

Dr. Stintzing:
Well, I think we now understand that the concept that the tumor is not homogeneous anymore. So, it's a – we think that we have

heterogeneous tumors with clones or subclones of cells that may be RAS-mutant or that may have a resistance to the anti-EGFR treatment. So, in first line, when you treat those tumors, they respond very nicely because the majority of cells, or the majority of cell clones, are sensitive to anti-EGFR. At the time of progression, though, those frequencies might have changed, so the resistant tumor or the progressing tumor has a higher frequency of RAS-mutant tumors, or let's make it more general, of EGFR antibody-resistant clones. At the time of progression, you may find RAS mutations in the liquid biopsy, so you stop anti-EGFR treatment. So, what happens in second line if you're using a non-EGFR-containing regimen? Let's say FOLFOX and bevacizumab – you release the pressure on those clones, so you kind of reverse the tumor biology and, at the end, you may have a tumor that, again, has only a low-frequent, RAS-mutant or low-frequent, EGFR-resistant makeup and, therefore, you may be able to restart anti-EGFR treatment. So, this is basically the data and hypothesis that is behind, for example, the CRICKET study that has nicely shown in 28 patients that rechallenge is possible if you test them for, for example, RAS mutations prior to the reuse of anti-EGFR antibodies, for example, in third line.

Dr. Falcone:
Thank you, Professor Stintzing

And, Professor Stintzing, can you explain the thinking behind the AIO FIRE-4 study that you are conducting, you are coordinating, and how the rechallenge concept is being applied through the third-line setting.

Dr. Stintzing:
Well, first of all, FIRE-4 was started to analyze the maximum benefit we can get from anti-EGFR antibodies throughout the whole treatment time of patients with a RAS wild-type tumor. So, in first line, we have the question, is it possible to prevent anti-EGFR resistant by doing an early switch from FOLFIRI/cetuximab to bevacizumab plus 5FU prior to resistance? So, basically asking the questions, can we induce during the first four months, a very nice tumor response, and then stabilizing this without running into any EGFR-resistance in first-line by the use of anti-VEGF plus 5FU? So, this is the question in first-line. The question in third-line is that we want to test the hypothesis of rechallenge in a phase-III setting, using 230 patients. And, of course, before entering the third line, we have to exclude the BRAF and RAS mutations by the use of liquid biopsy. The whole trial, though, has a large translational program with several – with multiple liquid biopsies at several time points, such as baseline, prior to the early switch maintenance treatment, at the time of the end of treatment, and at the time of every progression. By doing this, we hope to have more data to integrate liquid biopsy in our treatment decision making from our patients. Well, we are planning to include 570 patients in first line. We have 490 patients so far with a recruitment rate of 15-20 patients a month. So, we hope to be done with first-line recruitment later this year.

Dr. Falcone:
Now, let's back up to the first-line setting once again, Dr. Liu, and consider you experience disease progression on FOLFOX or FOLFIRI plus bev. Under what circumstances would you continue with bev, so with bev beyond progression, and when you would consider instead to switch to an anti-EGFR agent?

Dr. Liu:
For the RAS mutant metastatic colorectal cancer, I think bevacizumab could be used at the first line and, if those patients progressed after first line, especially if progressed more in three months, I would still continue to use bevacizumab on the second line. But, this is not difficult. The difficulty is for the RAS wild-type. For the RAS wild-type, now we can separate them into the right side and left side. For the right side, normally we also will use the bevacizumab as the first line but, for the left side, RAS wild-type, normally we will use the cetuximab plus chemotherapy as the first line, and for the continued use of the cetuximab for the left side, I think we will still consider, especially for those patients after testing by the liquid biopsy still showed the RAS type was wild, we will continue use of cetuximab and we will change the second line of chemotherapy. But, for the right side, if the first line of the bevacizumab plus chemotherapy failed, at the second line, we will consider for those patients maybe the cetuximab plus a second line chemotherapy. But, still a special case, for the right side, and for those patients with the liver mets, we are going to do neoadjuvant or we are going to the potential resectable patients, we will use the cetuximab plus chemotherapy as a first line in the short time because we want to have a very high response rate to have the tumor to shrinkage to have the opportunity to have the resection of the liver mets. So, that is my clinical practice.

Dr. Falcone:
Professor Stintzing, before we close, is there anything you want to revisit or mention that we haven't touched upon?

Dr. Stintzing:
No, I think what is important is that we actually test as recommended by national and international guidelines; that we test prior to first line for the known resistant factors such as RAS mutations. That we do it for the bad prognostic factors such as BRAF mutation v600e, of course, and if you also test in first line for microsatellite instability, because by doing though, we are able to really adjust our treatment, our treatment sequence, and, in the end, will have better patient outcomes, so this will also inform our second line and help

us to make a better and an informed decision in second line.

Dr. Falcone:
And Dr. Liu, what about you? What takeaways would you like to leave our audience with?

Dr. Liu:
The very important thing for the cetuximab we will know the change of the genotype, especially for the RAS and the RAF status, they will continue to be the wild. If the genotype of the RAS and RAF will still continue to be the wild-type, I think the rechallenge of the cetuximab could be possible.

Dr. Falcone:
Well, I think this was a great and interesting discussion. I'd like very much to thank my guest, Professor Stintzing, Professor Yu Liu for helping us to really better understand treatment sequencing in RAS wild-type metastatic colorectal cancer patients after progression to first line. It was, for me, a great pleasure speaking with you both today. Thank you.

Dr. Stintzing:
Thank you so much