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The Evolution of Biomarker-Based Treatment in Metastatic Colorectal Cancer

ANNOUNCER: This is ReachMD. Welcome to this medical industry feature titled “The Evolution of Biomarker-Based Treatment in Metastatic Colorectal Cancer,” sponsored by Amgen.

This program is intended for physicians.

DR. JOHN RUSSELL: I’m your host, Dr. John Russell. Joining me today are Dr. Philip Philip and Dr. Kurt Tauer. Dr. Philip is a medical oncologist and a professor of oncology and pharmacology at the Karmanos Cancer Institute. Dr. Tauer is a medical oncologist at the West Cancer Center and an associate professor in the Department of Hematology/Oncology, the University of Tennessee Health Science Center.

Today, we will be talking about biomarker-driven treatment approaches to metastatic colorectal cancer.

So, Dr. Philip, Dr. Tauer, welcome to the program.

DR. KURT TAUER: Thank you.

DR. PHILIP PHILIP: Thank you.

DR. JOHN RUSSELL: So, starting with you, Dr. Tauer, why is a personalized targeted therapy so important for the first-line treatment of metastatic colorectal cancer?

DR. KURT TAUER: For the majority of patients with metastatic colorectal cancer, there are two types of treatment options. There is the personalized therapy, such as anti-EGFR for molecularly selected population, and there are therapies that are not personalized, such as the anti-VEGF treatments for an unselected population.[1-4] Personalized therapy gives us the opportunity to tailor treatments to a specific patient’s genetic profile.[4,5]

DR. JOHN RUSSELL: So, Dr. Philip, what are your thoughts on personalized targeted therapy?

DR. PHILIP PHILIP: Sure. There is no doubt that appropriately selecting therapy for patients can give them a better chance of responding to their treatment and can minimize unnecessary side effects.[4-6] That’s the reason why, nowadays, personalized medicine has become such an important thing in oncology. In metastatic colorectal cancer, the *RAS* gene is a well-known predictive biomarker for treatment outcome.[4]

DR. JOHN RUSSELL: Now what exactly is *RAS*, and what is its role in metastatic colorectal cancer? Dr. Tauer, can you give us an overview?

DR. KURT TAUER: RAS is a protein that’s part of the MAP kinase pathway that becomes activated when EGFR is engaged by ligand. Wild-type *RAS* activation by EGFR results in cell growth, survival, motility, and proliferation.[1,4,7] If *RAS* is mutated, it’s continuously active and not regulated by EGFR.[1] There are different *RAS* oncogenes, such as *KRAS* and *NRAS*, and approximately half of all patients with metastatic colorectal cancer have wild-type *RAS* disease.[1,6] So, if a tumor is free from mutations in exon 2, 3, and 4 of both *KRAS* and *NRAS*, it’s considered *RAS* wild type, and that’s a key selection criterion for treatment with anti-EGFR—panitumumab, Vectibix®.[1]

Vectibix® is indicated for the treatment of patients with wild-type *RAS* metastatic colorectal cancer, meaning those patients whose

tumors are wild-type in both *KRAS* and *NRAS* genes, as determined by an FDA-approved test. In first-line, Vectibix® is approved in combination with FOLFOX. It's also approved as monotherapy for disease that has progressed on treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Importantly, Vectibix® is not indicated in patients with mutated *RAS* or unknown *RAS* status.[1]

Note that Vectibix® has a Boxed WARNING for dermatologic toxicities, which were reported in 90% of patients and were severe in 15% of those patients receiving Vectibix monotherapy.[1]

DR. JOHN RUSSELL: So, Dr. Philip, could you tell us how the evolution of our understanding and appreciation of *RAS* testing has impacted your treatment decisions?

DR. PHILIP PHILIP: Sure. Well, it took us some time and research to get there, but the first randomized, controlled, phase 3 trial that demonstrated the relationship between the *KRAS* mutation status and the response to anti-EGFR therapy, in this case Vectibix®, was, uh, reported back in 2008. This evaluation taught us that *KRAS* status could be a predictive biomarker in treating patients with, uh, metastatic colorectal cancer.[8] And then there were additional studies with Vectibix® that added to our knowledge. A retrospective biomarker analysis from a phase 3 study of Vectibix® monotherapy was the first to use, in fact, next-generation sequencing to look beyond the *KRAS* for potentially other predictive biomarkers. It led to the understanding that additional regions in the *KRAS* gene, as well as the *NRAS* gene, were predictive of response to anti-EGFR treatment with Vectibix®.[9] So, lastly, the phase 3 PRIME trial of Vectibix® with FOLFOX reported a post-hoc analysis in 2013 that showed us not only did having wild-type *KRAS* and *NRAS* genes increase the chance of response to anti-EGFR therapy, but also that treatment was detrimental to those patients who had mutated *RAS*, whether it was *KRAS* or *NRAS*.[1,6] In terms of efficacy, the PRIME trial showed us that patients with wild-type *RAS* who were treated with first-line Vectibix® with FOLFOX had improved overall response rate, they had delay in disease progression, and a 5.6-month improvement in median overall survival compared to the control arm, which was FOLFOX alone.[1] Vectibix® has a Boxed WARNING for dermatologic toxicity. The most commonly reported adverse reactions, greater than or equal to 20% with Vectibix® plus FOLFOX were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. The most common serious adverse reactions, greater than or equal to 2% difference between treatment arms, were diarrhea and dehydration.[1]

With these trials of Vectibix®, Amgen helped innovate personalized treatment in metastatic colorectal cancer, so we now have a better way of identifying and selecting appropriate treatments for patients.[6,8,9]

DR. JOHN RUSSELL: For those who are just joining us, this is ReachMD. I'm your host, Dr. John Russell, and I have the pleasure of speaking with our guests, Dr. Philip Philip and Dr. Kurt Tauer, on the topic of biomarker-driven treatment of patients with metastatic colorectal cancer.

So, Dr. Philip, earlier you spoke about how the understanding and appreciation of *RAS* testing came to be. Now can you tell me how you're applying this to the patients that you're seeing in your office every day, and the treatment decisions you make for your patients with colorectal cancer?

DR. PHILIP PHILIP: Sure. These trials with Vectibix® established the importance of upfront testing—in this case, genomic testing. In fact, if you look at the (NCCN Clinical Practice Guidelines in Oncology for Colon Cancer) NCCN Guidelines®, they recommend that all patients with metastatic colorectal cancer should have their tumors tested for the *KRAS* and *NRAS* mutations, and that any patients with mutations of these genes should not be treated with anti-EGFR therapy.[10,11] At my own institution, the pathology lab will routinely perform extended *RAS* testing on samples from metastatic colorectal cancer, and if for some reason the oncologist doesn't check the box on the request form, the pathologist will call to double-check and see why it wasn't checked.

DR. JOHN RUSSELL: So, Dr. Tauer—so *RAS* biomarker testing, how has that impacted your practice and your treatment decisions?

DR. KURT TAUER: Well, I always test my patients for *RAS* status when they come to me. It's one of the first things that we do. We want to make sure the lab has the extended panel test that looks not just for *KRAS* exon 2, but rather to all the relevant exons in *KRAS* and *NRAS*, those being exons 2, 3, and 4, that we previously mentioned.[1] It's important to get that information before starting my patients on treatment because I want to be able to give them the treatment that's best for their type of cancer. Sometimes that means waiting for the test results, which can be hard on the patient, but if I have a patient who is getting anxious to start treatment, I can explain to them the reason I'm waiting—that their *RAS* status impacts my ability to give them the therapy that I think is best for them, and I use the data from the PRIME trial as a way to help them understand why I'm not starting their therapy right away.[6]

DR. JOHN RUSSELL: So, doctors, before we wrap up, could you both give us a fuller description of the safety profile for Vectibix®?

DR. KURT TAUER: Be glad to. Here's some of the important safety information of Vectibix®.

There's a Boxed WARNING for dermatologic toxicity. Dermatologic toxicities occurred in 90% of patients and were severe, NCI-CTC grade 3 and higher, in 15% of patients receiving Vectibix® monotherapy. The clinical manifestations of dermatologic toxicity included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.

DR. PHILIP PHILIP: Monitor patients who develop dermatologic or soft tissue toxicities while receiving Vectibix® for inflammatory and infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with Vectibix®.

Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Vectibix®.

Withhold or discontinue Vectibix® for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications.

DR. KURT TAUER: Vectibix® is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2, exon 3, and exon 4 of either *KRAS* or *NRAS*. Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents.

Additionally, in an exploratory subgroup analysis, overall survival was shorter in patients with *RAS*-mutant metastatic colorectal cancer who received Vectibix® and FOLFOX versus FOLFOX alone.

DR. PHILIP PHILIP: Progressively decreasing serum magnesium levels leading to severe (grade 3 to 4) hypomagnesemia occurred in up to 7% of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix® treatment, periodically during treatment, and up to 8 weeks after completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

DR. KURT TAUER: Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix® administration. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions.

Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix® in combination with chemotherapy.

DR. PHILIP PHILIP: Fatal and nonfatal cases of interstitial lung disease and pulmonary fibrosis have been observed in patients with Vectibix®.

In the event of acute onset or worsening of pulmonary symptoms, interrupt Vectibix® therapy. Discontinue therapy if interstitial lung disease is confirmed. In patients with a history or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix® versus the risk of pulmonary complications must be carefully considered.

DR. KURT TAUER: Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats, and limit sun exposure while receiving Vectibix®. Keratitis and ulcerative keratitis, known risk factors for corneal perforation, have been reported with Vectibix® use. Monitor for evidence of keratitis or ulcerative keratitis. Interrupt or discontinue Vectibix® for acute or worsening keratitis.

DR. PHILIP PHILIP: In the first-line setting in patients with metastatic colorectal cancer, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased overall survival and increased incidence of NCI-CTC grade 3 to 5 adverse reactions. NCI-CTC grade 3 to 4 adverse reactions occurring at a higher rate in Vectibix®-treated patients included rash and acneiform dermatitis, diarrhea, dehydration primarily occurring in patients with diarrhea, hypokalemia, stomatitis and mucositis, and hypomagnesemia.

NCI-CTC grade 3 to 5 pulmonary embolism occurred at a higher rate in Vectibix®-treated patients and included fatal events in three Vectibix®-treated patients. As a result of the toxicities experienced, patients randomized to Vectibix®, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent over the first 24 weeks on study compared to those

randomized to bevacizumab and chemotherapy.

DR. KURT TAUER: Vectibix® can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use contraception during treatment and for at least 2 months after the last dose of Vectibix®.

In monotherapy, the most commonly reported adverse reactions, greater than or equal to 20%, in patients with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.

The most commonly reported adverse reactions, greater than or equal to 20%, with Vectibix® + FOLFOX were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. The most common serious adverse reactions, greater than or equal to 2% difference between treatment arms, were diarrhea and dehydration.

Please see the Vectibix® package insert for full Prescribing Information, including **Boxed WARNING**.

DR. JOHN RUSSELL: Well, with that description of the Vectibix® safety profile, I'd like to thank Dr. Philip and Dr. Tauer for joining me today to discuss the biomarker-driven treatment of patients with metastatic colorectal cancer for our ReachMD audience.

DR. KURT TAUER: Thank you, and thanks for giving us the opportunity.

DR. PHILIP PHILIP: And thank you very much for having us.

ANNOUNCER: The preceding program was brought to you by Amgen.

This was ReachMD. Be part of the knowledge.

References: **1.** Vectibix® (panitumumab) prescribing information, Amgen. **2.** Avastin® (bevacizumab) prescribing information, Genentech. **3.** Mahipal A, Grothey A. Role of biologics in first-line treatment of colorectal cancer. *J Oncol Pract*. 2016;12(12):1219-1229. **4.** King GT, Lieu CH, Messersmith WA. Frontline strategies for metastatic colorectal cancer: new sides to the story. *Am J Hematol Oncol*. 2016;12(10):4-11. **5.** Diamandis M, White NMA, Yousef GM. Personalized medicine: marking a new epoch in cancer patient management. *Mol Cancer Res*. 2010;8(9):1175-1187. **6.** Douillard J-Y, Oliner KS, Siena S, et al. Panitumumab—FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med*. 2013;369(11):1023-1034. **7.** Gong J, Cho M, Fakih M. RAS and BRAF in metastatic colorectal cancer management. *J Gastrointest Oncol*. 2016;7(5):687-704. **8.** Amado RG, Wolf M, Peeters M, et al. Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26(10):1626-1634. **9.** Peeters M, Oliner KS, Parker A, et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. *Clin Cancer Res*. 2013;19(7):1902-1912. **10.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed August 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **11**. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed August 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.

NCCN = National Comprehensive Cancer Network.