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### Metastatic Colorectal Cancer: A First-Line Treatment Approach to Wild-Type RAS Patients

ANNOUNCER: This is ReachMD. Welcome to this medical industry feature titled “Metastatic Colorectal Cancer: A First-Line Treatment Approach to Wild-Type *RAS* Patients,” 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 Associate Professor in the Department of Hematology/Oncology at the University of Tennessee Health Science Center.

Today, we will be talking about their approaches to the first-line treatment of patients with wild-type *RAS* metastatic colorectal cancer.

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

DR. PHILIP PHILIP: Thank you for having me.

DR. KURT TAUER: Thank you.

DR. JOHN RUSSELL: So, Dr. Philip, to get us started, we've heard that colorectal cancer is the third most common type of cancer here in the United States,<sup>1</sup> but what specifically is a wild-type *RAS* metastatic colorectal cancer?

DR. PHILIP PHILIP: In wild-type *RAS* metastatic colorectal cancer, tumors do not have mutations in either the *KRAS* or the *NRAS* genes and they represent approximately half of metastatic colorectal cancers.<sup>2,3</sup> In other words, half of them are wild-type *RAS*.

DR. JOHN RUSSELL: And I know you individualize care for your patients, so what are the treatment goals for these particular patients?

DR. PHILIP PHILIP: Well, certainly we look into extending survival as the primary goal, especially in first-line treatment, but we also take into account potential side effects

DR. JOHN RUSSELL: Great. So, Dr. Tauer, for the same patient population, what are your treatment goals?

DR. KURT TAUER: Sure. Giving patients a treatment, I believe is right for their particular disease. Which means, in part, looking at the patient's *RAS* status before starting them on first-line treatment. Understanding the importance of the *RAS* status in first-line treatment comes from the PRIME study of Vectibix®.<sup>3,4</sup>

DR. JOHN RUSSELL: So, speaking of Vectibix®, Dr. Philip, in what population do you prescribe Vectibix®?

DR. PHILIP PHILIP: So, 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 is also approved as monotherapy for disease that has progressed on treatment with fluoropyrimidine-, oxaliplatin-, irinotecan-containing chemotherapy regimens. Importantly, Vectibix® is not indicated in patients with mutated *RAS* or unknown *RAS* status.<sup>2</sup>

Please also note that Vectibix® has a Boxed WARNING for dermatological toxicities, which were reported in 90% of patients and were severe in 15% of patients receiving Vectibix® monotherapy.<sup>2</sup>

DR. JOHN RUSSELL: So, Dr. Tauer, you earlier had mentioned the PRIME study. Could you talk about how it's impacted first-line

treatment of these patients with wild-type *RAS* metastatic colorectal cancer?

DR. KURT TAUER: Sure, PRIME was a phase 3, open-label, multicenter trial that randomized previously untreated patients to Vectibix® plus FOLFOX or to FOLFOX alone, which is the chemotherapy we usually use in first-line.<sup>2,5,6</sup> Originally, the primary analysis looked at patients with wild-type *KRAS*, but subsequent post-hoc analysis looked at 512 patients who did not have mutations in *KRAS* or *NRAS*.<sup>2</sup> The post-hoc analysis was driven by a greater understanding and appreciation of what wild-type *RAS* means.<sup>3</sup> Data from this population were compelling and led to an updated indication for Vectibix® and this data also led to the (NCCN Clinical Practice Guidelines in Oncology) NCCN Guidelines® for Colon Cancer and Rectal Cancer to recommend panitumumab, Vectibix®, plus FOLFOX as first-line treatment option for certain\* patients with wild-type *RAS* metastatic colorectal cancer.<sup>2,7,8</sup>

\*See the guidelines online at NCCN.org for the full recommendation.

DR. JOHN RUSSELL: So, certainly an important study. Dr. Philip, do you have anything to add on this topic?

DR. PHILIP PHILIP: So, PRIME changed how we treat metastatic colorectal cancer by giving us a compelling reason to determine *RAS* status before prescribing first-line treatment. It also showed us that we have an agent with a survival benefit which is something we are looking for all the time, and that was appropriate for a specific patient's genetic profile.<sup>2,3</sup>

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 metastatic colorectal cancer treatment.

So, Dr. Philip, earlier you spoke a bit of how *RAS* status is a key factor in your first-line treatment decision that was informed by the clinical studies of Vectibix®. Could you go into a little bit more detail regarding the data for Vectibix® in this wild-type *RAS* population, and the importance it has in your practice.

DR. PHILIP PHILIP: So, there was a 5.6 month increase in median overall survival versus FOLFOX alone, 25.8 months with Vectibix® plus FOLFOX versus 20.2 months with FOLFOX alone.<sup>2</sup> This is what we are trying to achieve with our first-line treatments—to extend survival, giving patients more time.<sup>2,4</sup> These data supported this outcome. The progression-free survival is also longer with Vectibix®—10.1 months with Vectibix® plus FOLFOX versus 7.9 months with FOLFOX alone, so this delaying in the progression-free survival may indicate that the treatment is working.<sup>2,9</sup> The overall response rate improved with Vectibix®—58% with Vectibix® plus FOLFOX versus 45% with FOLFOX alone—and this shrinking in the tumor is really an important goal for us clinically, especially in patients who have a high tumor burden, and who may benefit from a good, objective response.<sup>2,4</sup>

DR. JOHN RUSSELL: So, from that data, it certainly sounds efficacious, but that's only one part of when you're making a treatment decision. So, what about the safety profile of Vectibix®, Dr. Tauer?

DR. KURT TAUER: Of course. In the PRIME trial, the safety profile in the post-hoc analysis of patients with wild-type *RAS* was similar to that which was observed with the primary analysis of the wild-type *KRAS* patients.<sup>2</sup> 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.<sup>2</sup> The most common serious adverse reactions, greater than or equal to 2% difference between treatment arms, were diarrhea and dehydration. Vectibix® has a Boxed WARNING for dermatologic toxicity.<sup>2</sup> In our clinic, it's standard for us to use prophylactic measures for these dermatologic toxicities, such as topical steroids, tetracycline-based antibiotics, moisturizers, and sunscreen. These practices may help us reduce the likelihood of side effects related to the dermatologic toxicity.<sup>2,10</sup>

DR. JOHN RUSSELL: So, certainly we've talked about a lot of data. Dr. Philip, how would you say this data has changed your treatment approach to the patients with wild-type *RAS* metastatic colorectal cancer?

DR. PHILIP PHILIP: Sure. I always order the expanded *RAS* testing up front before even I start any treatment—so that's very important for me. I also consider the patients in front of me as individuals, so I look at what is their *RAS* status, what is their own goals in terms of therapy, and that's very important in making an overall treatment plan for the patient.

DR. JOHN RUSSELL: Great. And now I'm going to turn to you, Dr. Tauer. How has this data changed your treatment approach to these same patients?

DR. KURT TAUER: We always try to communicate with our other healthcare team members. I like to make sure that I've talked with the radiologist, the surgeon, and the pathologist so we get all the information we need in treating the patients, so that we're all on the same

page regarding our goals before moving forward with treatment.

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 post marketing 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 non-fatal 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 Vectibix®'s safety profile, I want to thank Dr. Philip and Dr. Tauer for joining me today and sharing their insights and practices for first-line metastatic colorectal cancer with our ReachMD audience.

DR. KURT TAUER: Thanks to you, Dr. Russell, as well.

DR. PHILIP PHILIP: Thank you very much, again, for this interview.

ANNOUNCER: The preceding program was brought to you by Amgen. This was ReachMD. Be part of the knowledge.

**References:** 1. American Cancer Society. *Cancer Facts & Figures 2018*. Atlanta, GA: American Cancer Society; 2018. 2. Vectibix® (panitumumab) prescribing information, Amgen. 3. 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. 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. Mahipal A, Grothey A. Role of biologics in first-line treatment of colorectal cancer. *J Oncol Pract*. 2016;12(12):1219-1229. 6. Douillard J-Y, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705. 7. 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. 8. 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. 9. Sidhu R, Rong A, Dahlberg S. Evaluation of progression-free survival as a surrogate endpoint for survival in chemotherapy and targeted agent metastatic colorectal cancer trials. *Clin Cancer Res*. 2013;19(5):969-976. 10. Kobayashi Y, Komatsu Y, Yuki S, et al. Randomized controlled trial on the skin toxicity of panitumumab in Japanese patients with metastatic colorectal cancer: HGCSG1001 study; J-STEPP. *Future Oncol*. 2015;11(4):617-627.

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NCCN = National Comprehensive Cancer Network.