Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/exploring-evidence-based-treatment-pathway-chemorefractory-wild-type-ras-metastatic-colorectal-cance/11873/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring an Evidence-Based Treatment Pathway for Chemorefractory Wild-Type RAS Metastatic Colorectal Cancer

Announcer: Welcome to ReachMD. This medical industry feature, titled “Exploring an Evidence-Based Treatment Pathway for Chemorefractory Wild-Type *RAS* Metastatic Colorectal Cancer,” is sponsored by Amgen. This program is intended for physicians. Here’s your host, Dr. John Russell.

Dr. Russell: This is ReachMD, and I'm Dr. John Russell. Joining me to share insights on treatment for chemorefractory patients with wild-type *RAS* metastatic colorectal rectal cancer and the findings of two clinical trials are Dr. Fernando de Zarraga and Dr. Raed Al-Rajabi. Dr. de Zarraga is a medical oncologist and hematologist with the Miami Cancer Institute, who's been practicing medicine for 16 years. Dr. de Zarraga, welcome to the program.

Dr. de Zarraga: Thank you very much for having me. I’m looking forward to participating.

Dr. Russell: And Dr. Al-Rajabi is a medical oncologist with the University of Kansas Medical Center, who's been in medical practice for over 20 years. Dr. Al-Rajabi, thanks for being here.

Dr. Al-Rajabi: Thank you for having me. It's my pleasure to be here.

Dr. Russell: Starting with you, Dr. de Zarraga, what can you share with us about the importance of precision medicine in treatment decisions for chemorefractory patients?

Dr. de Zarraga: So precision medicine is very important and has continued to evolve rapidly in the oncology space in general, and colorectal cancer is no exception. In the colorectal cancer space, it’s important not only for first-line therapy but also beyond it. Biomarker testing helps guide the development of appropriate treatment plans that may help to benefit patients. It also improves my ability to achieve those goals because it allows me to customize treatment according to specific biomarkers in each patient's genetic profile.[1,2] As patients move on to later lines of therapy, I also refer to biomarker test results that are likely to be available from testing done previously, and those results help guide my choice of therapy in the event of disease progression.

Dr. Russell: Dr. Al-Rajabi, what treatment options do you consider for your chemorefractory patients?

Dr. Al-Rajabi: When a patient is chemorefractory, I often use a targeted agent. If biomarker status indicates that the patient has wild-type *RAS** metastatic colorectal cancer, I choose an anti-EGFR therapy, usually panitumumab, also known as Vectibix®.[2] I value a product that has a long history, and I know that Vectibix® has been prescribed for over 14 years.[3] Additionally, I have found that Vectibix® is still the only fully human anti-EGFR monoclonal antibody.[3] Of course, any correlation of the fully human attribute with efficacy or safety is unknown.

Dr. Russell: Dr. de Zarraga, what is your therapy of choice for chemorefractory patients with wild-type *RAS* metastatic colorectal cancer?

Dr. de Zarraga: So I prescribe Vectibix® as well.

Vectibix® is indicated for the treatment of patients with wild-type *RAS*, defined as wild-type in both the *KRAS* and the *NRAS* genes, as determined by an FDA-approved test in metastatic colorectal cancer.[3] So it has two spaces specifically where it’s indicated. The first is as front-line therapy in combination with FOLFOX, and the second one is as monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy.[3] It's also important to note that it is not indicated for

the treatment of patients with *RAS*-mutant metastatic colorectal cancer or for those patients in whom the *RAS* mutation status is unknown.[3]

Additionally, it's important to note that Vectibix® does have a boxed warning for dermatologic toxicities, which were reported in 90 percent of patients and were severe, defined as NCI-CTC grade 3 or higher, in 15 percent of patients receiving Vectibix® monotherapy.[3]

Dr. Russell: And if we look at the clinical trials of Vectibix® in later-line treatment, Dr. Al-Rajabi, what trials do you consider when evolving a treatment plan for a patient?

Dr. Al-Rajabi: There are two trials I find most compelling regarding therapy choice for patients with chemorefractory wild-type *RAS* metastatic colorectal cancer. The first study is the 20100007 study, which is a phase 3 study from 2016, and the second is a 2014 phase 3 trial called the ASPECCT trial.[4,5] The 20100007 study analyzed Vectibix® plus best supportive care† versus best supportive care alone.[3] The ASPECCT trial was a non-inferiority study of Vectibix® versus cetuximab.[3]

Dr. Russell: And just as a quick follow-up to that, Dr. Al-Rajabi, could you tell us more about the 20100007 study?

Dr. Al-Rajabi: The 20100007 study was a phase 3, open label, multicentered randomized one-to-one study of about 377 patients with chemorefractory wild-type *KRAS*‡ metastatic colorectal cancer. They were treated with Vectibix® every two weeks, plus best supportive care, and they were compared to a group that received best supportive care alone.[3,4]

The primary endpoint was overall survival in patients with wild-type *KRAS* exon 2 in codons 12 and 13 metastatic colorectal cancer.[4] Prespecified key secondary endpoints were overall survival, progression-free survival, and objective response rate in patients with wild-type *RAS* metastatic colorectal cancer.[4] *RAS* tumor mutation status was available for 86 percent of the patients, and was determined in 324 patients using Sanger bidirectional sequencing; 270 patients, or 72 percent, had wild-type *RAS* tumors; 142 of those patients were treated with Vectibix® plus best supportive care, and 128 received best supportive care alone.[3,4] Fifty-four, or 14 percent, had mutant *RAS* tumors, and 54, or 14 percent, had unknown *RAS* tumor status.[3]

Dr. Russell: So, Dr. de Zarraga, what were some of the efficacy outcomes of the study?

Dr. de Zarraga: Well, so, the primary endpoint was met.[3] In the *RAS* subgroup, median overall survival was 10 months for Vectibix® plus best supportive care versus 6.9 months with best supportive care alone. That's a 3.1-month increase in survival and a 44.9 percent improvement over best supportive care alone.[3] The hazard ratio was 0.70, with a 95 percent confidence interval of 0.53 to 0.93 and a *P* value of 0.0135. In other words, in the *RAS* subgroup, Vectibix® plus best supportive care provided a 30 percent reduction in the risk of death.[3]

In terms of meeting progression-free survival in the *RAS* subgroup, for those patients taking Vectibix® plus best supportive care versus best supportive care alone, the outcomes were 5.2 versus 1.7 months.[3]

The hazard ratio here was 0.46, with a 95 percent confidence interval of 0.35 to 0.59, and a *P* value of less than 0.0001.[3] That's a median 3.5-month delay in disease progression.[3] Other secondary endpoints, objective response rates were evaluated by investigators per Response Evaluation Criteria in Solid Tumors version 1.1.[4] And in the *RAS* wild-type subgroup of patients taking Vectibix® plus best supportive care, the objective response rates were 31 percent versus 2.3 percent in those patients receiving best supportive care alone.[3]

It's also important to note that, per the Vectibix® Prescribing Information, there was no overall survival or progression-free survival benefit in patients treated with Vectibix® who had *RAS* mutant metastatic colorectal cancer.[3]

Dr. Russell: So now that we better understand the efficacy, Dr. Al-Rajabi, what were some of the safety outcomes of the study?

Dr. Al-Rajabi: In the *KRAS* population, 97 percent of patients taking Vectibix® plus best supportive care experienced an adverse event of any grade, including rash (39 percent versus 1 percent), dermatitis acneiform (29 percent versus 0 percent), and hypomagnesemia (28 percent versus 1 percent).[4]

Grade 3 adverse events occurred in 37 percent of patients taking Vectibix® plus best supportive care versus 15 percent of patients on best supportive care alone. Grade 4 adverse events occurred in 9 percent and 3 percent of the patients in the respective treatment arms.[4]

The incidence of infusion reactions was 1 percent in the Vectibix® plus best supportive care treatment arm.[4] Similar incidences were observed in the *RAS* subgroup.[4] Some of the adverse events seen in the study may have an occurrence rate different from those in the United States Prescribing Information. For full information, please refer to the USPI.

Dr. Russell: So, Dr. de Zarraga, based on this evidence, how has the 20100007 study impacted your treatment choices?

Dr. de Zarraga: So it has impacted my treatment choices. The efficacy and safety results in this trial are the kind of evidence we need to evolve a treatment plan for certain patients.

When I choose a treatment for my patients with chemorefractory wild-type *RAS* metastatic colorectal cancer, I take note of the fact that the primary endpoint was reached in the 20100007 study.[3] I also note the 44.9 percent increase in median overall survival and the median 3.5-month delay in disease progression for the Vectibix® plus best supportive care treatment arm versus best supportive care alone in the secondary endpoint analysis.[3]

Dr. Russell: For those just joining us, this is ReachMD. I'm your host, Dr. John Russell. And today I'm speaking with Dr. Fernando de Zarraga and Dr. Raed Al-Rajabi about two clinical trials focusing on Vectibix®, a treatment option for chemorefractory patients with wild-type *RAS* metastatic colorectal cancer.

So, Dr. Al-Rajabi, earlier you spoke about another clinical trial called ASPECCT, which I understand was a phase 3 non-inferiority study of Vectibix® versus cetuximab. Can you tell us more about the study?

Dr. Al-Rajabi: ASPECCT was a randomized, one-to-one, open-label, non-inferiority study of 1,010 patients with chemorefractory wild-type *KRAS* metastatic colorectal cancer. They were treated with Vectibix® or cetuximab. Vectibix® was administered to 499 patients§ at a dose of 6 milligrams per kilogram once every two weeks for 60 minutes. For doses above 1,000 milligrams, they were administered over 90 minutes. If the first infusion was tolerated, the subsequent infusions were administered over 30 to 60 minutes. No loading dose was required with Vectibix®. Cetuximab was initiated in 500 patients§ with a loading dose of 400 milligrams per meter square over 120 minutes and was subsequently taken once a week for 60 minutes at a dose of 250 milligrams per meter square.[3]

Premedication with an H1 antagonist was required before infusion with cetuximab. No standard premedication was required in clinical trials of Vectibix®.[5] It should be noted that the utility of premedication in preventing infusional toxicity is unknown.[3] Dose modification for dermatological toxicity and infusion reactions were required for both products.[3,5]

The primary endpoint was overall survival in the chemorefractory patients with wild-type *KRAS* metastatic colorectal cancer. The data was assessed for non-inferiority in the modified intent-to-treat population, which included all patients who received at least one dose of therapy.[3,5] The key secondary endpoints include progression-free survival, objective response rate,** and safety.[5]

Dr. Russell: And, Dr. Al-Rajabi, what were the outcomes in ASPECCT?

Dr. Al-Rajabi: Vectibix® demonstrated a statistically significant non-inferiority†† of overall survival to cetuximab.[3] The median overall survival with Vectibix® was 10.4 months versus 10 months in the cetuximab group.[3] The hazard ratio was 0.97, with a 95 percent confidence interval of 0.84 to 1.11.[3]

Median progression-free survival was 4.1 months with Vectibix® versus 4.4 months with cetuximab.[3] The hazard ratio was 1.0, with a 95 percent confidence interval of 0.88 to 1.14.[3]

The objective response rate was 22 percent with Vectibix® versus 19 percent with cetuximab.[3]

It is important to note that retrospective subset analysis across several other randomized clinical trials reported that patients with *RAS* mutated metastatic colorectal cancer, who are treated with Vectibix®, experienced increased tumor progression, increased mortality, and lack of benefit.[3]

Dr. Russell: Staying with you for another moment, Dr. Al-Rajabi, would you mind reviewing safety data from ASPECCT so we can understand the safety profile on patients with wild-type *KRAS* metastatic colorectal cancer?

Dr. Al-Rajabi: Ninety-eight percent of patients taking Vectibix® or cetuximab experienced adverse reactions across all grades.[5] The incidence of infusion reactions in patients who took Vectibix® was 3 percent, and was 14 percent with cetuximab.[5] Looking broadly at other adverse reactions, 87 percent of patients experienced skin and subcutaneous tissue toxicity while taking Vectibix® or cetuximab, and incidents of hypomagnesemia in patients taking Vectibix® or cetuximab was 27 percent and 18 percent, respectively.[5]

Dr. Russell: Now, Dr. de Zarraga; earlier, you had mentioned incidents of skin and subcutaneous toxicities. How might you approach these types of toxicities with your patients taking Vectibix®?

Dr. de Zarraga: So it's really important to take an integrated approach when we manage the disease with treatment, to also consider all of the adverse reactions that can happen as a result of the treatment. In the case of Vectibix®, prophylactic treatment has been shown to reduce the incidence of associated dermatologic toxicities.[6]

Examples of prophylactic skin treatments include topical steroids such as hydrocortisone cream, tetracycline antibiotics, skin moisturizer, and sunscreen.[6] It's also important to note that exposure to sunlight can exacerbate dermatologic toxicity. So, patient education is very important. And we tell our patients to wear sunscreen, hats, and to limit sun exposure while they are taking Vectibix®.[3]

Dr. Russell: Thank you, Dr. de Zarraga. Are there any other thoughts or takeaways you might want to share regarding these two studies?

Dr. de Zarraga: Well, Vectibix® has been around for over 14 years.[3] And clearly, the primary endpoint results in both studies reached statistical significance.[3] So that gives me confidence when I treat my patients. In other words, I look at the efficacy outcomes of the two studies. I know that with prophylaxis and other treatments for possible adverse events, I may be able to reduce the incidence of toxicities and, therefore, I can establish a routine for my patients with Vectibix®.[3]

Dr. Russell: And how about you, Dr. Al-Rajabi?

Dr. Al-Rajabi: I was very interested to see that Vectibix® was proven non-inferior to cetuximab in median overall survival.[3]

Dr. Russell: So I'd like to thank you both for providing these insights on the 20100007 and ASPECCT trial data. Before we go, Dr. de Zarraga, can you walk us through the safety profile for Vectibix®?

Dr. de Zarraga: Sure. Here's some of the Important Safety Information for Vectibix®: There's a BOXED WARNING for dermatologic toxicity. Dermatologic toxicities occurred in 90% of patients and were severe defined by (NCI-CTC grade 3 and higher) in 15% of patients receiving Vectibix® monotherapy. In Study 20020408, dermatologic toxicities occurred in 90% of patients and were severe, again defined by NCI-CTC grade 3 and higher, in 15% of patients with mCRC receiving Vectibix®. 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.

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®. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune- related effects (eg, Stevens Johnson syndrome or toxic epidermal necrolysis).

Withhold or discontinue Vectibix® for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications. Dose modifications for Vectibix® concerning dermatologic toxicity are provided in the product labeling.

Vectibix® is not indicated for the treatment of patients with colorectal cancer who harbor somatic *RAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS* and hereafter is referred to as "*RAS.*"

Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). 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 Study 20050203, 272 patients with *RAS*-mutant mCRC tumors received Vectibix® in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (the hazard ratio was 1.21, with a 95% confidence interval of 1.01 to 1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone.

Progressively decreasing serum magnesium levels leading to severe (grade 3 to 4) hypomagnesemia occurred in up to 7% (in Study 20080763) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix® treatment, periodically during treatment, and for up to 8 weeks after completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

In Study 20020408, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions, that is (NCI-CTC grade 3 to 4). Infusion reactions, manifesting as fevers, 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 with Vectibix® in combination with chemotherapy.

Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients with Vectibix®. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix®. In the event of acute onset or worsening of pulmonary symptoms interrupt Vectibix® therapy. Discontinue therapy if ILD is confirmed.

In patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix® versus the risk of pulmonary complications must be carefully considered.

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.

In an interim analysis of an open-label, multicenter, randomized clinical trial in the first- line setting in patients with mCRC, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased OS and increased incidence of NCI-CTC grade 3-5 (87% vs 72%) adverse reactions. NCI-CTC grade 3-4 adverse reactions occurring at a higher rate in Vectibix®-treated patients included rash/acneiform dermatitis (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%), primarily occurring in patients with diarrhea, hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs < 1%), and hypomagnesemia (4% vs 0).

NCI-CTC grade 3-5 pulmonary embolism occurred at a higher rate in Vectibix®-treated patients (7% vs 3%) and included fatal events in three (< 1%) 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 (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study compared with those randomized to bevacizumab and chemotherapy.

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 a 2% difference between treatment arms) were diarrhea and dehydration.

Please see the Vectibix® package insert on the home page for full Prescribing Information, including BOXED WARNING.

Dr. Russell: Well, with that information in mind, I want to thank Dr. Fernando de Zarraga and Dr. Raed Al-Rajabi for joining me to share their thoughts on Vectibix® clinical trial data in patients with chemorefractory wild-type *RAS* metastatic colorectal cancer. Dr. de Zarraga, Dr. Al- Rajabi, it was great having you both on the program today.

Dr. de Zarraga: Thank you for having me. It was great to participate.

Dr. Al-Rajabi: Thank you for having me. It was my pleasure to participate.

Announcer: The preceding program was brought to you by Amgen. This is ReachMD. Be Part of the Knowledge.

*Defined as wild type in both *KRAS* and *NRAS*.1
†BSC was defined as the best palliative care available, as judged appropriate by the investigator and according to institutional guidelines. BSC could have included antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other clinically indicated symptomatic therapy.4
‡Exon 2 in codons 12 and 13.3

§Modified intent-to-treat population that included all patients who received at least one dose of therapy.3
**Objective tumor response was evaluated by the investigator at each site using RECIST v1.1 criteria.5
††The criterion for non-inferiority was for Vectibix® to retain at least 50% of the OS benefit of cetuximab based on an OS hazard ratio of 0.55 from the NCIC-CTG CO.17 study relative to BSC.3
ASPECCT = A Study of Panitumumab Efficacy and Safety Compared to Cetuximab; mCRC = metastatic colorectal cancer; OS = overall survival.

References: 1. Diamandis M, White NMA, Yousef GM. Personalized medicine: marking a new epoch in cancer patient management. *Mol Cancer Res*. 2010;8(9):1175-1187. **2.** 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. **3.** Vectibix® (panitumumab) prescribing information, Amgen. **4.** Kim TW, Elme A, Kusic Z, et al. A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type *KRAS* or *RAS* metastatic colorectal cancer. *Br J Cancer*. 2016;115(10):1206-1214. **5.** Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type *KRAS* exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15(6):569-579. **6.** Kobayashi Y, Komatsu Y, Yuki S, et al. Randomized controlled trial on the skin toxicity of panitumumab in Japanese patients with metastatic colorectal cancer: HGCSG1001study; J-STEPP. *Future Oncol*. 2015;11(4):617- 627.