Transcript Details

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Comparing Targeted Therapies for Wild-Type *RAS* Metastatic Colorectal Cancer

Announcer Introduction:
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "Comparing Targeted Therapies for Wild-Type *RAS* Metastatic Colorectal Cancer," is sponsored by Amgen Oncology. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle and joining me is Dr. Matthew Dugan, who's a Medical Oncologist with New England Cancer Specialists in Scarborough, Maine.

Today we'll be discussing the results from the PARADIGM trial, which is the largest prospective randomized study of the treatment option Vectibix®, or panitumumab, for left-sided primary tumors in wild-type *RAS* metastatic colorectal cancer, or MCRC for short. The study was conducted in Japanese patients.

Dr. Dugan, thank you so much for being here today.

Dr. Dugan:
Thank you for having me. First, let's take a moment to review the Vectibix® indication and boxed warning.

Announcer
Vectibix® is indicated for the treatment of patients with wild-type *RAS*—defined as wild-type in both K*RAS* and N*RAS*, as determined by an FDA-approved test for this use—metastatic colorectal cancer, as first-line therapy in combination with FOLFOX; or as monotherapy following disease progression after treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Vectibix® is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

BOXED WARNING: 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.

Stay tuned to hear the Full Important Safety Information for Vectibix® later on in this program.

Dr. Caudle:
Before we dive into the PARADIGM study, Dr. Dugan, can you tell us about the earlier phase 3 trial called the PRIME study that evaluated Vectibix® in patients with MCRC?

Dr. Dugan:
Of course. So, the PRIME study was a phase 3 open label randomized multi-center study of the addition of Vectibix® to FOLFOX4 chemotherapy versus FOLFOX4 alone in 1,183 patients with previously untreated MCRC regardless of their *RAS* status.

A post-hoc analysis was then conducted among patients with wild-type *RAS*. This analysis evaluated progression-free survival, or PFS for short, and overall survival, also called OS. Among the 512 wild-type *RAS* patients in this analysis 259 received Vectibix® with FOLFOX4 and 253 received only FOLFOX4.

And the results showed that the Vectibix® plus chemotherapy subgroup of patients with wild-type *RAS* had significantly improved PFS

with a median of 10.1 months compared to 7.9 months in the chemotherapy-alone subgroup.

OS was also significantly improved in the Vectibix® plus chemotherapy wild-type *RAS* patients with a median OS of 25.8 months in the Vectibix®-treated subgroup versus 20.2 months in the FOLFOX4-only subgroup; a 23% reduction in the risk of death.

Dr. Caudle:
Thanks for that overview of the PRIME study, Dr. Dugan. So, with these results in mind, what clinical question did the PARADIGM trial seek to answer?

Dr. Dugan:
So, targeted therapies against EGFR, which is short for epithelial growth factor receptor, and those against VEGF, short for vascular endothelial growth factor, in combination with a standard chemotherapy regimen have both been shown to improve overall survival in wild-type *RAS* MCRC patients in recent clinical trials, although, results from trials that compare these therapies have been inconclusive. In retrospective analyses determined that the location of the primary tumor made a difference as anti-EGFR treatment increased survival in patients with left-sided tumors.

And that's why the PARADIGM trial sought to verify a survival benefit of anti-EGFR plus chemotherapy compared to anti-VEGF plus chemotherapy for left-sided wild-type *RAS* MCRC using a prospective analysis. This study was conducted in Japanese patients.

Dr. Caudle:
So, now that we understand the clinical rationale, let's zero in on the PARADIGM trial. What can you tell us about its design and endpoints?

Dr. Dugan:
PARADIGM is the first prospective and largest head-to-head trial of Vectibix® plus FOLFOX6 chemotherapy versus bevacizumab plus FOLFOX6 for wild-type *RAS* MCRC Japanese patients with left-sided primary tumors.

The study design was a phase 3 one-to-one randomized open-label multi-center study in Japan that enrolled 823 wild-type *RAS* MCRC patients with unresectable disease who had no prior chemotherapy. Patients had an Eastern Cooperative Oncology Group performance status score of 0 to 1, adequate kidney and liver function, and life expectancy of at least 3 months after enrollment.

The primary endpoints were OS for patients with left-sided primary tumor and, also for the overall population.

And the analysis set included 400 patients in the Vectibix® plus chemotherapy arm and 402 in the bevacizumab plus chemotherapy arm. The median follow-up time was 61 months.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD, sponsored Amgen Oncology. I'm your host Dr. Jennifer Caudle, and today I'm speaking with Dr. Matthew Dugan about the results of the PARADIGM trial for the treatment of wild-type *RAS* metastatic colorectal cancer with left-sided tumors.

So, now that we've introduced the PARADIGM trial rationale and design, Dr. Dugan, let's dive into the results. Did the trial meet its primary endpoints?

Dr. Dugan:
Yes, it did. The study demonstrated that Vectibix® added to standard first-line chemotherapy significantly improved OS compared to bevacizumab in Japanese patients with wild-type *RAS* metastatic CRC with left-sided tumors and the overall population.

For left-sided tumors, the median OS in the Vectibix® arm was 37.9 months versus 34.3 months in the bevacizumab arm, with a significant 18% reduction in the risk of death.

And in the overall population, the Vectibix®-treated group had a median OS of 36.2 months versus 31.3 months with bevacizumab, with a significant 16% reduction in the risk of death. In the separation in overall survival between treatment arms was observed in patients after 28 months.

Finally, I should note that for the secondary endpoint of PFS there was no difference between treatment groups.

Dr. Caudle:

And what were the results of safety data from the study?

Dr. Dugan:

The safety data reflected the known safety profiles of Vectibix® and bevacizumab, which are both well-studied treatments, and no new safety signals were observed. Vectibix® has a known 90% risk of dermatologic toxicity, including a 15% risk of severe grade 3 or higher dermatologic toxicity.

Focusing on adverse events in general in the PARADIGM study, grade 3 or higher adverse events were reported in 72% of patients in the Vectibix®-treated group, and 65% in the bevacizumab group.

The adverse events that were more common with Vectibix® than bevacizumab were acne-like dermatitis, paronychia, dry skin, and hypomagnesemia. Hypertension and epistaxis were more common with bevacizumab.

Dr. Caudle:
What caveats or limitations should the audience keep in mind when interpreting the results of the PARADIGM study?

Dr. Dugan:
Well, there are a number of important considerations in the PARADIGM study. Let's start with dosing. Bevacizumab was dosed at 5 mg/kg every 2 weeks. The recommended doses of bevacizumab are 5 mg/kg or 10 mg/kg every 2 weeks when used in combination with intravenous 5-FU-based chemotherapy. For additional information on the uses of bevacizumab please refer to the US prescribing information.

Next, we should keep in mind a couple of factors about the study population. PARADIGM was conducted in Japanese patients and hasn't been reviewed for the inclusion in US labeling. And in analyses of 1,200 patients across 14 clinical studies did show comparable pharmacokinetics in response to panitumumab between Japanese and non-Japanese patients.

Finally, I'd like to point out a number of issues regarding the study outcomes.

First, investigators modified the primary endpoint after the study began from overall survival in all patients to overall survival in patients with left-sided tumors. This change was based on evidence from 7 randomized clinical trials suggesting that the benefit of anti-EGFR antibodies combined with chemotherapy is enhanced in patients with left-sided tumors.

And the statistical analysis plan was also modified to require a two-sided P-value of 0.042 as the threshold for statistical significance in the left-sided population.

Regarding endpoints, panitumumab didn't differ from bevacizumab on PFS, and survival curves didn't separate before 24 months.

And looking at next lines of therapy, similar proportions of patients in each group received subsequent lines of therapy, but it should be noted that fewer panitumumab versus bevacizumab patients received subsequent anti-EGFR treatments, and 2 separate studies have shown that anti-EGFR treatments may prolong survival in later lines of therapy.

Now, although other response outcomes were directionally consistent for panitumumab, the study wasn't designed to establish statistical significance on these endpoints.

Dr. Caudle:
Thank you for that. Now, Dr. Dugan, given all of the data that we have reviewed what might we expect when it comes to changing treatment practices?

Dr. Dugan:
ASCO, short for the American Society of Clinical Oncology, has updated their guidelines in 2022 to include the PARADIGM study results to now recommend anti-EGFR therapy plus doublet chemotherapy as first-line treatment for patients with wild-type *RAS* left-sided MCRC. The strength of this recommendation category is strong.

And ESMO, the European Society for Medical Oncology, also included the PARADIGM study results in their 2022 MCRC guidelines which recommended anti-EGFR therapy plus doublet chemotherapy as the preferred first-line treatment for patients with wild-type *RAS* and wild-type BRAF left-sided MCRC.

So, to bring this all together, the PARADIGM study provides evidence that supports Vectibix® plus standard chemotherapy as first-line treatment for wild-type *RAS* MCRC Japanese patients with a left-sided primary tumor and the latest guidelines are now updated to reflect that recommendation as well.

Dr. Caudle:
I'd like to thank my guest, Dr. Matthew Dugan, for helping us better understand the data supporting Vectibix® for wild-type *RAS* left-sided metastatic colorectal cancer. Dr. Dugan, it was great speaking with you today.

Dr. Dugan:
Thank you for the opportunity.

Dr. Caudle:
I'm Dr. Jennifer Caudle and now let's review the full important safety information for Vectibix.

Announcer:

- In Study 20020408, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving Vectibix®. The clinical manifestations 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 the development of inflammatory or 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 that 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 (HR = 1.21, 95% CI: 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone.

- Progressively decreasing serum magnesium levels leading to severe (grade 3-4) 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 Vectibix® treatment, and for up to 8 weeks after the 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 (NCI-CTC grade 3-4). 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.

- Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated 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 Vectibix® 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®.

- Serious cases of keratitis, ulcerative keratitis, and corneal perforation have occurred with Vectibix® use. Monitor for evidence of keratitis, ulcerative keratitis, or corneal perforation. Interrupt or discontinue Vectibix® therapy for acute or worsening keratitis, ulcerative keratitis, or corneal perforation.

- 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 effective contraception during treatment, and for at least 2 months after the last dose of Vectibix®.

- In monotherapy, the most commonly reported adverse reactions (≥ 20%) in patients with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.

- The most commonly reported adverse reactions (≥ 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 (≥ 2% difference between treatment arms) were diarrhea and dehydration.

- Please see Vectibix® full **Prescribing Information**, including **Boxed WARNING**.

Announcer Close

This program was sponsored by Amgen Oncology. If you missed any part of this discussion, visit ReachMD.com/ProjectOncology. This is ReachMD. Be part of the knowledge.

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USA-954-80446