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Need-to-Know Data for a Treatment Option in Advanced RCC

Announcer:

Welcome to ReachMD.

This medical industry feature, titled "Need-to-Know Data for a Treatment Option in Advanced RCC," is sponsored by Bristol-Myers Squibb. This program is intended for U.S. health care professionals only.

Here's your host, Dr. John Russell.

Dr. Russell:

It's an unfortunate reality that patients with advanced renal cell carcinoma, or RCC, often face poor outcomes, especially if they have one or more risk factors.[1] But could we be entering a new era when it comes to survival expectations for some patients with the most common type of kidney cancer?[2,3]

Coming to you from the ReachMD Studios in Fort Washington, Pennsylvania, I'm Dr. John Russell. Joining me to share her perspective on treating certain patients with advanced RCC is Dr. Jeanny Aragon-Ching, a Clinical Program Director of Genitourinary Cancers at the Inova Schar Cancer Institute in Fairfax, Virginia. Dr. Aragon-Ching is a paid consultant for Bristol-Myers Squibb.

Dr. Aragon-Ching, welcome to the program today.

Dr. Aragon-Ching:

Oh, thank you so much, Dr. Russell. It's nice to be here.

Dr. Russell:

So doctor, to get us started, can you share your perspective on the advanced RCC treatment landscape today?

Dr. Aragon-Ching:

Yes, so, as we think about RCC, it's important to note that many patients – nearly about a third – are diagnosed with advanced disease.[4,5] So the five-year survival rate for metastatic kidney and renal pelvis cancer is only about 12 percent.[6]

So another point to consider is that approximately 75 to 80 percent of patients with advanced RCC present with one or more risk factors according to the IMDC, or what we call International Metastatic RCC Database Consortium.[7] So this is dependent on the number of risk factors present, and we refer to these patients as either intermediate- or poor-risk, and their prognosis tends to be worse.[7]

So the good news is that the treatment landscape is rapidly evolving, and we now have additional treatment options available to us. Among these options are combinations using immune checkpoint inhibitors, which are really changing how we think about treating this disease.

Dr. Russell:

Dr. Aragon-Ching, now many of us are familiar with immune checkpoint inhibitors, but can you expand on their role in advanced RCC, specifically?

Dr. Aragon-Ching:

Yes, so immune checkpoint inhibitors have represented an important step in the treatment of some cases of advanced RCC. With a growing amount of data in this disease area, we've come to understand how these therapies may impact certain patients in the first-line setting.

An example of this is the combination of *Opdivo* (nivolumab) and *Yervoy* (ipilimumab).[8] *Opdivo* plus *Yervoy* was approved by the FDA in 2018 for the treatment of intermediate- or poor-risk patients with previously untreated advanced RCC, and this is based on the data from the pivotal CheckMate -214 study.[9]

But before we get into the data from this trial, I want to mention that *Opdivo* is associated with Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when *Opdivo* is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.[9] It is also important to note that *Yervoy* has a **Boxed WARNING regarding immune-mediated adverse reactions**, which will be shared shortly with additional Important Safety Information about *Opdivo* plus *Yervoy*.

Listeners can also find the full prescribing information for *Opdivo* and *Yervoy*, including **the Boxed WARNING for *Yervoy***, by visiting Opdivo-H-C-P-dot-com and navigating to the Prescribing Information, or by calling 1-855-OPDIVO-1.

Dr. Russell:

So doctor, you mentioned the CheckMate -214 study. Could you tell us about the results from that study?

Dr. Aragon-Ching:

Yes, so we now have extended data available from the CheckMate -214 clinical trial and it's a median follow-up now of 32.4 months, and we'll cover that in a few minutes, but first I really want to talk about the primary analysis. CheckMate -214 was a Phase 3, randomized, open-label study evaluating *Opdivo* plus *Yervoy* versus sunitinib in patients with previously untreated advanced RCC.[11]

So in the experimental arm, patients received *Opdivo* 3 mg/kg IV – this is the dose – plus *Yervoy* 1 mg/kg IV every three weeks for the first four doses, followed by *Opdivo* 3 mg/kg IV every two weeks. In the comparator arm, patients received sunitinib 50 mg orally once daily for four weeks, followed by two weeks off every cycle.[9] So the study had three co-primary endpoints – so that was overall survival, or OS, progression-free survival, or PFS, and overall response rates, or ORR, in the intermediate- and poor-risk patients, per IMDC criteria, and this was assessed by an independent radiographic review committee.[11] Now, the efficacy analysis included 425 patients in the combination arm and 422 patients in the sunitinib alone arm. The safety analysis also included favorable-risk patients, for a total of 1,082 patients.[9]

So, for the complete study design and recommended dosing, listeners can refer to the full prescribing information for *Opdivo* and *Yervoy*.

The results of the primary analysis, with a median follow-up time of 25.2 months, were really exciting for intermediate- and poor-risk patients.[12] The *Opdivo* plus *Yervoy* combination showed a statistically significant improvement in Overall Survival compared to sunitinib, reducing the risk of death by 37%.[9] Also, the median Overall Survival was not reached for *Opdivo* plus *Yervoy*, while it was 25.9 months for sunitinib.[9] It's also worth mentioning that the OS benefit was observed really regardless of expression level of the PD-L1 biomarker.[9]

Additionally, *Opdivo* plus *Yervoy* demonstrated statistically significant, superior results for Overall Response Rates.[9] If you look at the combination, it delivered an Overall Response Rate of approximately 42% versus 27% for sunitinib.[9] And of the patients treated with *Opdivo* plus *Yervoy*, 9% achieved a complete response compared to 1% for sunitinib and 32% of the patients treated with *Opdivo* plus *Yervoy* achieved a partial response versus 25% for sunitinib.[9] And lastly, the median PFS was 11.6 months for *Opdivo* plus *Yervoy* and 8.4 months for sunitinib. And this translated to a hazard ratio of 0.82, which did not reach statistical significance.[9]

That said, in the CheckMate -214 trial, *Opdivo* plus *Yervoy* resulted in fewer overall Grade 3 or 4 adverse reactions compared to sunitinib: so 65% with the combination versus 76% with sunitinib.[9] Serious adverse reactions were observed in 59% of patients receiving *Opdivo* plus *Yervoy* and in 43% of patients receiving sunitinib.[9,10] Now in patients receiving both *Opdivo* plus *Yervoy*, the most frequent serious adverse reactions reported in 2% or more of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency and colitis.[9] Continue listening for additional important safety information throughout this podcast.

Dr. Russell:

So doctor, can you tell us about the extended follow-up data from CheckMate -214?

Dr. Aragon-Ching:

Yes, so *Opdivo* plus *Yervoy* has been studied for a median follow-up time of 32.4 months in these patients, and what we're seeing with this extended follow-up is that the combination delivers a chance for durable responses and has continued to show improvements in overall survival compared with sunitinib.[13,14]

First, in this follow-up analysis, the median Overall Survival still had not been reached among intermediate- or poor-risk *Opdivo* plus *Yervoy* patients compared to 26.6 months for sunitinib, a reduction in the risk of death of 34%.[13,14] What's even more interesting is that responses measured by the trial investigators showed a complete response rate of 11% in patients who received *Opdivo* plus *Yervoy* versus 1% with sunitinib.[13,14] Additionally, nearly 90% of the complete responses seen with *Opdivo* plus *Yervoy* were ongoing at the time of the analysis.[13,14]

So if we look at the overall response rates, it was 42% with *Opdivo* plus *Yervoy* compared with 29% for sunitinib.[13,14] Partial responses were seen in 31% of patients treated with the combination versus 28% with sunitinib.[13,14] And, similar to what we saw with the primary analysis, the median duration of response has not been reached for intermediate- or poor-risk patients who responded to *Opdivo* plus *Yervoy*, compared with 13 months for sunitinib.[14]

Now, before we move on, I'd also like to cover the most common adverse reactions reported in 20% or more patients treated with *Opdivo* plus *Yervoy* in the CheckMate -214 study. These reactions were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, decreased appetite, dyspnea and vomiting.[9,10] So continue listening for additional important safety information throughout this podcast.

Dr. Russell:

So to bring this all together, Dr. Aragon-Ching, what are your thoughts on what we just reviewed?

Dr. Aragon-Ching:

So I think the results from the CheckMate -214 trial are really meaningful for several reasons. First, we observed a survival benefit and continue to see the potential for durable responses in intermediate- and poor-risk advanced RCC with the combination of *Opdivo* plus *Yervoy*.[13,14]

Secondly, this is the longest follow-up data we have on an immunotherapy combination in the first-line, intermediate- and poor-risk RCC setting, so it really adds to our understanding of the efficacy and safety of this treatment option.[13,14]

Lastly, after years of using targeted therapies for initial treatment of advanced RCC, we now have another standard of care in our armamentarium for patients with intermediate- or poor-risk advanced RCC.[14, 15]

Dr. Russell:

If any of our listeners out there want to learn more about *Opdivo* plus *Yervoy* in this patient population, where can they go for more information?

Dr. Aragon-Ching:

So, I would encourage other physicians to visit Opdivo-H-C-P-dot-com for more information on *Opdivo* plus *Yervoy* for certain patients with advanced RCC and full prescribing information for Opdivo and Yervoy, including the Boxed WARNING for *Yervoy* regarding immune-mediated adverse reactions.

Dr. Russell:

Thank you, Dr. Aragon-Ching. Before we go, we have a few more important details about *Opdivo* plus *Yervoy* to review.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).[9]

Opdivo (10 mg/mL) and *Yervoy* (5 mg/mL) are injections for intravenous use.[9,10]

Announcer:

Important safety information is as follows:

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests, at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients.

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) of patients.

Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients.

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (41/547) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients. Hyperthyroidism occurred in 12% (66/547) of patients receiving this dose of OPDIVO with YERVOY. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) of patients.

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients.

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16% (90/547) of patients.

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. Encephalitis occurred in one RCC patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure.

Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients.

Based on mechanism of action, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO or YERVOY and for at least 5 months after the last dose.

In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse

reactions in nursing infants from OPDIVO or YERVOY, advise women not to breastfeed during treatment and for at least five months after the last dose.

In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%).

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including **Boxed WARNING regarding immune-mediated adverse reactions for YERVOY** by visiting Opdivo-H-C-P-dot-com and navigating to the Prescribing Information or by calling 1-855-OPDIVO-1.[11]

Dr. Russell:

That's all the time we have for today, but I'd like to thank my guest, Dr. Jeanny Aragon-Ching, for helping us better understand these important findings.

Dr. Aragon-Ching, it was great speaking with you today.

Dr. Aragon-Ching

Thank you so much for having me as well.

Announcer:

This program was sponsored by Bristol-Myers Squibb. If you missed any part of this discussion, visit ReachMD.com. This is ReachMD. Be part of the knowledge.

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7356US1903274-01-01 12/19