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Viewpoint on CANDOR: A Unique Combination for Patients With Multiple Myeloma at First Relapse

Announcer:
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This medical industry feature, titled "Viewpoint on CANDOR: A Unique Combination for Patients with Multiple Myeloma at First Relapse" is sponsored by Amgen. This program is intended for US physicians.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
The CANDOR study investigated the efficacy and safety of combining three powerful agents, Kyprolis® (carfilzomib), plus Darzalex (daratumumab), and dexamethasone or DKd. The benefits seen in the CANDOR study led to the approval of this combination, giving physicians a regimen with a second-generation proteasome inhibitor that looks beyond immunomodulatory agents for the treatment of patients with relapsed or refractory multiple myeloma.[1]

As the majority of patients with multiple myeloma receive an immunomodulatory agent, or IMiD, as part of their initial treatment, there's been growing interest in what their next treatment should be if they don't respond or become refractory to IMiDs. But with the approval of a regimen based on the CANDOR study results, these patients now have an IMiD-free option. What that regimen is, and the key findings that came out of the CANDOR study are what we'll be focusing on today.[1]

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to discuss the CANDOR study combining Kyprolis with Darzalex and dexamethasone is Dr. Joseph Mikhael.

Dr. Mikhael. Thanks so much for being here today.

Dr. Mikhael:
Thanks so much for having me, Dr. Caudle. It's a pleasure.

Dr. Caudle:
Well, we're excited that you're here. So to begin with, Dr. Mikhael, can you please tell us why the investigators look to combine Kyprolis, carfilzomib, with Darzalex, daratumumab, and dexamethasone? You know, what was the rationale?

Dr. Mikhael:
Absolutely, I'm happy to do so. You know, the rationale was both clinical and biological. So from a clinical perspective it was an important feature to have a unique combination of a second-generation proteasome inhibitor, as well as an anti-CD38 monoclonal antibody. This combination offers a different non-IMiD, or immunomodulatory drug-containing regimen as a triplet combination for patients with relapsed multiple myeloma. So from a clinical perspective, this was particularly important, but also from a biological perspective, because it allows us to target the myeloma cell in two separate ways together internally and externally. Internally, by carfilzomib as a proteasome inhibitor that inhibits the intracellular proteasomal activity and prevents cells from recycling excess

proteins,[2] but also from the daratumumab as an external force as this is a monoclonal antibody that adheres to the surface of the myeloma cell on the CD38 antigen triggering an immune response.[3] So this combined approach was the biological rationale to have this kind of study.

Dr. Caudle:
Thank you, Dr. Mikhael. And now can you ground us in the trial itself with an overview of how the CANDOR study was designed?

Dr. Mikhael:
Yes, of course. This was a phase three randomized open-label multicenter study, that compared the triplet combination of carfilzomib, plus daratumumab, and dexamethasone to carfilzomib and dexamethasone. Patients were randomized in a two-to-one fashion to the triplet versus the doublet combination. This was given in 466 patients with relapsed or refractory multiple myeloma. Patients were eligible if they had had one to three prior lines of therapy. Their prior therapies included bortezomib in 90%, lenalidomide in 42%, and indeed 33% of them were refractory to lenalidomide.[4]

The primary endpoint was median progression-free survival, but select secondary endpoints include overall response rate, complete response, minimal residual disease, or MRD-negative complete response at 12 months, overall survival, and safety.[4,5]

Dr. Caudle:
For those of you who are just tuning in, this is ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Joseph Mikhael about the CANDOR study and its implications on the treatment of relapsed or refractory multiple myeloma.

Now, Dr. Mikhael, we spoke a bit earlier about the rationale behind the CANDOR study, but now let's shift over to the study results. What were the key efficacy outcomes seen when carfilzomib was combined with daratumumab and dexamethasone?

Dr. Mikhael:
Well, you may remember that the primary endpoint here was median progression-free survival. So let's start with that. With a median follow-up of nearly 28 months, DKd, or the triplet combination of daratumumab, carfilzomib, and dexamethasone, improved the median progression-free survival by 13.4 months versus carfilzomib and dexamethasone. In absolute terms, this is 28.6 months versus 15.2 months, respectively, with a hazard ratio of 0.59, which means that there was a 41% reduction in the risk of disease progression or death. The 95% confidence interval was 0.45 to 0.78.[6]

The original primary analysis that had a median follow-up of nearly 17 months the primary endpoint of improved median progression-free survival had been met.[6] At that point, the median PFS was not reached for DKd, versus 15.8 months for Kd with a hazard ratio of 0.63, of which the 95% confidence interval was 0.46 to 0.85 with a one-sided P value of 0.0014.[1]

Now, when we look at the depth of response with a median follow-up of nearly 17 months,[6] we see that DKd more than doubled the chance of achieving a complete response versus Kd. So more specifically, if we look at patients in the DKd arm, they achieved an overall response rate of 84% versus 75% in the Kd arm with a P value of 0.004 that is one sided.[1]

Furthermore, the complete response rate was 2.7 times with DKd versus Kd at 28% versus 10%, respectively. Approximately 4 out of 10 patients with a complete response achieved an even deeper response of minimal residual disease negativity. Twelve percent of patients achieved MRD-negative complete response at 12 months with DKd, versus 1.3% with Kd with a P value of less than .0001 and that is one-sided.[1]

I should note that MRD-negative complete response was at the 10 to the minus 5 level defined as achievement of complete response, per the International Myeloma Working Group Uniform Response Criteria. An MRD-negative status was assessed by next generation sequencing the clonoSEQ assay at the 12-month landmark with a range of 8 to 13 months.[1]

Dr. Caudle:
And during the study, how did patients generally tolerate DKd? Were any unexpected safety outcomes seen with this combination?

Dr. Mikhael:
Adverse reactions were consistent with the known safety profile of each medication used here.[4]

Dr. Caudle:
Thanks so much for walking us through the CANDOR study, Dr. Mikhael. And before we wrap up, are there any other important insights or final thoughts you'd like to share?

Dr. Mikhael:
CANDOR supports the use of a lenalidomide-free triplet regimen that we know is effective in patients who were exposed to or refractory to lenalidomide previously.[4] And to me, this is an important concept because of the use of lenalidomide particular in maintenance therapy, and so many of our patients are in this category.

Furthermore, in the exploratory analysis, median PFS was consistent across clinically important subgroups. Some of those predefined subgroups included lenalidomide exposed, lenalidomide refractory and PI exposed patients.[4]

Dr. Caudle:
Well, that's a great way to sum up everything that we've learned today. And I'd like to thank my guest, Dr. Joseph Mikhael, for helping us better understand the impact of the CANDOR study and the clinical benefits of carfilzomib with daratumumb and dexamethasone. Dr. Mikhael, it was great speaking with you.

Dr. Mikhael:
Oh, it was a pleasure to join you today, Dr. Caudle. Thank you so much.

Dr. Caudle:
Thank you. I'm Dr. Jennifer Caudle, please stay tuned for some important safety information.

Announcer:
INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities

- New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of administration.
- Monitor patients for signs or symptoms of cardiac failure or ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse reactions until recovery, and consider whether to restart at 1 dose level reduction based on a benefit/risk assessment.
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate.
- For patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Acute Renal Failure

- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency (including renal failure) have occurred. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

- Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred. Patients with a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, and withhold until resolved.

Pulmonary Toxicity

- Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart based on a benefit/risk assessment.

Dyspnea

- Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart based on a benefit/risk assessment.

Hypertension

- Hypertension, including hypertensive crisis and hypertensive emergency, has been observed, some fatal. Control hypertension prior to starting KYPROLIS. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart based on a benefit/risk assessment.

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed. Provide thromboprophylaxis for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.
- For patients using hormonal contraception associated with a risk of thrombosis, consider an alternative method of effective contraception during treatment.

Infusion-Related Reactions

- Infusion-related reactions, including life-threatening reactions, have occurred. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration. Premedicate with dexamethasone to reduce the incidence and severity of infusion-related reactions.

Hemorrhage

- Fatal or serious cases of hemorrhage have been reported. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia

- KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Monitor platelet counts frequently during treatment. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have occurred. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

- Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred. Monitor for signs and symptoms of TTP/HUS. Discontinue if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. If PRES is suspected, discontinue and evaluate with appropriate imaging. The safety of reinitiating KYPROLIS is not known.

Progressive Multifocal Leukoencephalopathy (PML)

- Cases of PML, including fatal cases, have occurred. In addition to KYPROLIS, other contributary factors may include prior or concurrent use of immunosuppressive therapy. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue and initiate evaluation for PML including neurology consultation.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients

- In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse reactions was observed in patients in the KMP arm. KMP is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Embryo-fetal Toxicity

- KYPROLIS can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women of the potential risk to a fetus. Females of reproductive potential should use effective contraception during treatment with KYPROLIS and for 6 months following the final dose. Males of reproductive potential should use effective contraception during treatment with KYPROLIS and for 3 months following the final dose.

Adverse Reactions

- The most common adverse reactions in the combination therapy trials: anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, cough, dyspnea, and insomnia.

Please see full Prescribing Information.

Announcer:

For more information on KYPROLIS®(carfilzomib), the DKd combination, and the CANDOR study, please visit KYPROLIS-HCP.com or contact your local Amgen representative.

This program was brought to you by Amgen. If you missed any part of this discussion, please visit ReachMD.com/industry-feature. This is ReachMD. Be Part of the Knowledge.

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