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/treating-relapsedrefractory-multiple-myeloma-with-a-triplet-therapy/10793/

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Treating Relapsed/Refractory Multiple Myeloma with a Triplet Therapy

RMD Announcer:

Welcome to ReachMD. This medical industry feature, titled “Treating Relapsed/Refractory Multiple Myeloma with a Triplet Therapy” is sponsored by Bristol Myers Squibb. This program is intended for US audiences only.

To view the information presented during this program, please visit ReachMD.com/Matous. That’s M A T O U S.

Here to talk about POMALYST (pomalidomide) is Dr. Jeff Matous, who was paid a fee by Celgene, a Bristol Myers Squibb company, for participating in this program. Here he is now.

My name is Dr. Jeff Matous.

I’m from the Colorado Blood Cancer Institute in Denver, and I see many patients with multiple myeloma every day. The treatment landscape for myeloma has evolved rapidly in the past few years. Because of that, it’s important for me and the medical community to stay up-to-date on currently approved therapy options that may benefit our patients.

One of those treatments I use as a foundational therapy is POMALYST, either as part of a doublet regimen in combination with dexamethasone or as a triplet regimen with dexamethasone and daratumumab for patients who have received prior lenalidomide and a proteasome inhibitor.

Before we review the efficacy and safety data for a POMALYST-based triplet regimen, let’s review some Important Safety Information for POMALYST.

POMALYST® (pomalidomide) is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

POMALYST + dexamethasone + daratumumab is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
Information about POMALYST + dexamethasone + daratumumab does not appear in the POMALYST Prescribing Information (PI).

Please see the daratumumab full PI for a complete discussion of Important Safety Information at www.darzalex.com.

Important Safety Information BOXED Warnings.

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.**
- **POMALYST is only available through a restricted distribution program called POMALYST®.**

Venous and Arterial Thromboembolism

- **Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patients underlying risk factors.**

Please listen to important safety information throughout this podcast and see the full prescribing information for Pomalyst, including Boxed WARNINGS, at www.POMALYSTHCP.com

POMALYST was studied in a Phase 3, multicenter, randomized, open-label trial of POMALYST + low-dose dexamethasone vs high-dose dexamethasone in patients with relapsed/refractory multiple myeloma who had received at least 2 prior treatment regimens, including REVLIMID and bortezomib, and demonstrated disease progression on or within 60 days from the last therapy. A total of 455 patients were enrolled in the study.

Some key exclusion criteria included serum bilirubin greater than 2.0 mg/dL, AST/ALT greater than 3.0 times the upper limit of normal, and CrCl less than 45 mL/min. The primary endpoint was progression-free survival, or PFS. A secondary endpoint was overall survival, or OS. Treatment continued until disease progression.

Patients were randomized in a 2:1 fashion, so that 302 patients received POMALYST + low-dose dexamethasone and 153 patients received high-dose dexamethasone.

Patients in the POMALYST + low-dose dexamethasone arm received 4 mg of POMALYST orally on Days 1 to 21 of 28-day cycles with 40 mg of dexamethasone once daily on Days 1, 8, 15, and 22. Patients in the high-dose dexamethasone arm received 40 mg of dexamethasone once daily on Days 1 to 4, 9 to 12, and 17 to 20 in each 28-day cycle.

Patients older than 75 years of age received 20 mg of dexamethasone, with the same respective dosing schedules.

Patients receiving POMALYST, as well as any other patient with a history of deep venous thrombosis or pulmonary embolism, were required to receive prophylaxis or antithrombotic treatment.

In the study, the majority of patients (94%) were refractory to REVLIMID (lenalidomide). Seventy-nine percent of patients were refractory to bortezomib and 74% were refractory to both REVLIMID and bortezomib.

To access the full prescribing information for REVLIMID, including boxed warnings, please visit REVLIMIDHCP.com

Study results demonstrated a 30% reduced risk of death for POMALYST + low-dose dexamethasone vs high-dose dexamethasone. The median OS for POMALYST + low-dose dexamethasone was 12.4 months with a 95% confidence interval of 10.4 and 15.3 months. For high-dose dexamethasone, the median OS was 8 months with a 95% confidence interval of 6.9 and 9 months. The hazard ratio was 0.70 with a 95% confidence interval of 0.54 and 0.92; the P value was 0.009. The OS data cutoff was March 1, 2013 and was based on the intent to treat population of 455 patients.

For the primary endpoint, POMALYST + low-dose dexamethasone doubled the median PFS of high-dose dexamethasone. The median PFS for POMALYST + low-dose dexamethasone was 3.6 months with a 95% confidence interval of 3.0 and 4.6 months versus 1.8 months for high-dose dexamethasone, which had a 95% confidence interval of 1.6 and 2.1 months.

The hazard ratio was 0.45, with a 95% confidence interval of 0.35 and 0.59. The P value was less than 0.001. The PFS data cutoff was September 7, 2012.

Both PFS and OS were based on the assessment by the Independent Review Adjudication Committee (RAC) review at the final PFS and OS analyses.

Recently there was a study proving the safety and efficacy of a POMALYST-based triplet regimen in patients with relapsed/refractory myeloma.

POMALYST plus low-dose dexamethasone was studied in combination with daratumumab in a trial of 103 patients without a comparator arm. This trial led to the FDA approval of this POMALYST-based triplet regimen.

The median patient age in the trial was 64 years, and all of the patients enrolled had previously received REVLIMID.

89% of the patients enrolled in the trial were refractory to REVLIMID, while 71% were refractory to bortezomib and 64% of patients were refractory to both REVLIMID and bortezomib.

Patients received 4 mg of POMALYST once daily for days 1-21 during a repeated 28-day cycle in combination with 40 mg of low-dose oral or intravenous dexamethasone per week.

In addition to POMALYST and low-dose dexamethasone, patients received 16 mg/kg of daratumumab as an intravenous infusion weekly for the first 8 weeks, every 2 weeks from weeks 9 to 24, and every 4 weeks from week 25 until disease progression.

On days with a daratumumab infusion, patients received 20 mg of dexamethasone as a pre-infusion medication, with the rest administered the day after the daratumumab infusion. Additional information on reduced doses of dexamethasone is shown at the bottom of the screen.

Patients who received a reduced dose of dexamethasone received the entire 20-mg dose before the daratumumab infusion. A reduced dose of dexamethasone at 20 mg a week was given to patients older than 75 or to patients with a body mass index (BMI) less than 18.5.

Patients in the trial were treated until disease progression.

Now that we've reviewed the study design and dosing information, let's dive into the efficacy results and safety profile for POMALYST + low-dose dexamethasone in combination with daratumumab.

59% of patients studied in the trial achieved a response with POMALYST + low-dose dexamethasone in combination with daratumumab, with 42% reaching a very good partial response or better.

The overall response rate was 59.2%, with a 95% confidence interval of 49.1 and 68.8. The overall response rate was comprised of a 7.8% stringent complete response, 5.8% complete response, 28.2% very good partial response, and a 17.5% partial response.

The median time to response was 1 month, while the median duration of response was 13.6 months.

The median time to respond range was from 0.9 to 2.8 months. The median duration of response range was from 0.9 plus to 14.6 plus months.

Patients in the study were treated for a median of 6 months, and 13% of these patients discontinued treatment due to adverse reactions.

The median treatment duration range was from 0.03 to 16.9 months.

The most common adverse reactions occurring in at least 50% of patients treated with POMALYST + low-dose dexamethasone in combination with daratumumab were neutropenia (95%), lymphopenia (94%), thrombocytopenia (75%), anemia (57%), infusion-related reactions (50%), fatigue (50%), and upper respiratory tract infection (50%).

Other adverse reactions included, Cough (43%), Diarrhea (38%), Constipation (33%), Dyspnea (33%), Nausea (30%), Muscle Spasms (26%), Pyrexia (25%), Back pain (25%), Insomnia (23%), Arthralgia (22%), Vomiting (21%) , Dizziness (21%), and Chills (20%).

Grade 3 or 4 hematologic adverse reactions that were greater than 20 percent included neutropenia (82%), lymphopenia (71%), anemia (30%), and thrombocytopenia (20%).

The overall incidence of adverse reactions was 49%. Serious adverse reactions reported in ≥5% of patients included pneumonia, which occurred in 7% of patients.

There are certain Warnings and Precautions to keep in mind when using daratumumab.

The first warning and precaution involves infusion reactions. Healthcare professionals should interrupt daratumumab infusion for infusion-related reactions of any severity. Permanently discontinue the infusion in case of anaphylactic reactions or life-threatening infusion reactions and institute appropriate emergency care.

The second warning and precaution is interference with cross-matching and red blood cell antibody screening.

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test), which may persist for up to 6 months after the last daratumumab infusion. Type and screen patients prior to starting treatment. Inform blood banks that a patient has received daratumumab.

The third warning and precaution is neutropenia. Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding daratumumab until recovery of neutrophils.

A fourth warning and precaution is thrombocytopenia. Monitor complete blood cell counts periodically during treatment. Consider withholding daratumumab until recovery of platelets.

A fifth warning and precaution is that Daratumumab can interfere with the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

The last warning and precaution is Embryo-Fetal Toxicity. Since it can cause fetal harm advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception.

The results of this trial show that POMALYST + low-dose dexamethasone in combination with daratumumab is a treatment option for patients who are refractory to REVLIMID and who have received a prior proteasome inhibitor.

Some patients may not be a candidate for a triplet regimen. For those who are likely to benefit from a doublet, consider using POMALYST in combination with low-dose dexamethasone, an all-oral regimen for relapsed refractory multiple myeloma.

To learn more about the overall survival and safety data from the Phase 3 trial for POMALYST + low-dose dexamethasone, please visit Pomalyst.com.

The results of both POMALYST + low-dose dexamethasone and POMALYST + dexamethasone in combination with daratumumab support the use of POMALYST as a therapy in patients with relapsed/refractory multiple myeloma who have received prior lenalidomide and a proteasome inhibitor. Now, let's review some Important Safety Information for POMALYST.

POMALYST has boxed warnings for Embryo-fetal toxicity and venous and arterial thromboembolism.

Embryo-Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.**

POMALYST is only available through a restricted distribution program called POMALYST REMS®.

Venous and Arterial Thromboembolism.

- **Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.**

CONTRAINDICATIONS FOR POMALYST

- Pregnancy: POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If POMALYST is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.
- Hypersensitivity: POMALYST is contraindicated in patients who have demonstrated sever hypersensitivity (e.g., angioedema, anaphylaxis) to pomalidomide or any of the excipients.

CONTRAINDICATIONS FOR DARATUMUMAB

- Daratumumab is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation.

WARNINGS AND PRECAUTIONS FOR POMALYST

- Embryo-Fetal Toxicity & Females of Reproductive Potential: See Boxed WARNINGS
  - Males: Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 4 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm.
  - Blood Donation:Patients must not donate blood during treatment with POMALYST and for 4 weeks following discontinuation of POMALYST therapy because the blood might be given to a pregnant female patient whose fetus must not be exposed to

POMALYST.

- POMALYST REMS® Program: See Boxed WARNINGS
  - Prescribers and pharmacies must be certified with the **POMALYST REMS** program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive POMALYST. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.
  - Further information about the **POMALYST REMS** program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.
- Venous and Arterial Thromboembolism: **See Boxed WARNINGS.** Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.
- Increased Mortality with Pembrolizumab: In clinical trials in patients with multiple myeloma, the addition of pembrolizumab 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.
- Hematologic Toxicity: Neutropenia (46%) was the most frequently reported Grade 3/4 adverse reaction in patients taking POMALYST in clinical trials, followed by anemia and thrombocytopenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification.
- Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor liver function tests monthly. Stop POMALYST upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
- Severe Cutaneous Reactions: Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These reactions can be fatal. Consider POMAYLST interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue POMALYST for Grade 4 rash, exfoliative or bullous rash, or any other severe cutaneous reactions such as SJS, TEN or DRESS.
- Dizziness and Confusional State: In patients taking POMALYST in clinical trials, 14% experienced dizziness (1% Grade 3 or 4) and 7% a confusional state (3% Grade 3 or 4). Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.
- Neuropathy: In patients taking POMALYST in clinical trials, 18% experienced neuropathy (2% Grade 3 in one trial) and 12% peripheral neuropathy.
- Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.
- Tumor Lysis Syndrome (TLS): TLS may occur in patients treated with POMALYST. Patients at risk are those with high tumor burden prior to treatment. These patients should be monitored closely, and appropriate precautions taken.
- Hypersensitivity: Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to POMALYST have been reported. Permanently discontinue POMALYST for angioedema or anaphylaxis.

ADVERSE REACTIONS FOR POMALYST + dexamethasone

The most common adverse reactions for POMALYST (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain, and pyrexia.

In the phase III trial, nearly all patients treated with POMALYST + low-dose dex experienced at least one adverse reaction (99%). Adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥2% higher than control) included neutropenia (51.3%), fatigue and asthenia (46.7%), upper respiratory tract infection (31%), thrombocytopenia (29.7%), pyrexia (26.7%), dyspnea (25.3%), diarrhea (22%), constipation (21.7%), back pain (19.7%), cough (20%), pneumonia (19.3%), bone pain (18%), edema peripheral (17.3%),

peripheral neuropathy (17.3%), muscle spasms (15.3%), and nausea (15%). Grade 3 or 4 adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥1% higher than control) included neutropenia (48.3%), thrombocytopenia (22%), and pneumonia (15.7%).

ADVERSE REACTIONS FOR POMALYST + dexamethasone + daratumumab
The most common adverse reactions (≥20%) included neutropenia (95%), lymphopenia (94%), thrombocytopenia (75%), anemia (57%), infusion reactions (50%), fatigue (50%), upper respiratory tract infection (50%), cough (43%), diarrhea (38%), constipation (33%), dyspnea (33%), nausea (30%), muscle spasms (26%), pyrexia (25%), back pain (25%), insomnia (23%), arthralgia (22%), vomiting (21%), dizziness (21%), and chills (20%). Grade 3 or 4 hematology laboratory abnormalities included: neutropenia (82%), lymphopenia (71%), anemia (30%), and thrombocytopenia (20%).

DRUG INTERACTIONS FOR POMALYST
Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce POMALYST dose by 50%.

USE IN SPECIFIC POPULATIONS FOR POMALYST

- **Pregnancy: See Boxed WARNINGS:** If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a POMALYST pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALYST during pregnancy as well as female partners of male patients who are exposed to POMALYST. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.
- **Lactation:** There is no information regarding the presence of pomalidomide in human milk, the effects of POMALYST on the breastfed child, or the effects of POMALYST on milk production. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in a breastfed child from POMALYST, advise women not to breastfeed during treatment with POMALYST.
- **Pediatric Use:** Safety and effectiveness have not been established in pediatric patients.
- **Geriatric Use:** No dosage adjustment is required for POMALYST based on age. Patients >65 years of age were more likely than patients ≤65 years of age to experience pneumonia.
- **Renal Impairment:** Reduce POMALYST dose by 25% in patients with severe renal impairment requiring dialysis. Take dose of POMALYST following hemodialysis on hemodialysis days.
- **Hepatic Impairment:** Reduce POMALYST dose by 25% in patients with mild to moderate hepatic impairment and 50% in patients with severe hepatic impairment.
- **Smoking Tobacco:** Advise patients that smoking may reduce the efficacy of POMALYST. Cigarette smoking reduces the AUC of pomalidomide by 32% by CYP1A2 induction.

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I hope you have found the information in this video valuable. As a reminder, please visit POMALYST.com for more information or contact your local Celgene representative.

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