The Expansion of POMALYST Data: A decade of data supports pomalidomide-containing regimens, as early as first relapse.

Hello, I'm Dr David Siegel, Chief of the Myeloma Division at The John Theurer Cancer Center at Hackensack University Medical Center, and the Founding Director of the Institute for Multiple Myeloma.

I treat patients with multiple myeloma, including many whose disease has progressed while taking REVLIMID (known generically as lenalidomide) and a proteasome inhibitor.

When their disease begins to progress on REVLIMID, this is when I consider a different regimen for my patients. I often choose to begin these patients on another immunomodulatory drug (or IMiD): POMALYST, in combination with an anti-CD38 such as daratumumab, and dexamethasone. I will refer to this combination as DPd.

A decade of data supports my choice to use a POMALYST-containing regimen in this patient population. In this video, I will review four trials that studied POMALYST as early as first relapse and in later line therapy.

In 2013, MM-003 established the efficacy and safety for the POMALYST and low-dose dexamethasone (or Pd) doublet in relapsed/refractory multiple myeloma patients. This was the pivotal trial for POMALYST and was the basis for FDA approval.

In 2017, EQUULEUS was the pivotal trial for the approval of the DPd triplet.

In 2021, APOLLO validated the DPd combination using a subcutaneous administration of daratumumab, which I'll refer to as Pd + dara SC.

And in 2022, MM-014 provided further data for DPd in first and second relapse.

Before we go over the details of each of these trials, let's review some Important Safety Information.

POMALYST® (pomalidomide) is a thalidomide analogue indicated, in combination with dexamethasone, for adult 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 adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

POMALYST + dexamethasone + daratumumab and hyaluronidase-fihj is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.

Limitations of Use:
Daratumumab and hyaluronidase-fihj is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.

Information about DPd and Pd + dara SC does not appear in the POMALYST Prescribing Information (PI). Please see the daratumumab and dara SC full PIs for a complete discussion of Important Safety Information at www.darzalexhcp.com/iv and www.darzalexhcp.com/faspro, respectively.

POMALYST Boxed WARNINGS: EMBRYO-FETAL TOXICITY, A RESTRICTED DISTRIBUTION PROGRAM – the POMALYST REMS, and VENOUS AND ARTERIAL THROMBOEMBOLISM.

CONTRAINDICATIONS FOR DARATUMUMAB AND DARA SC

Daratumumab and dara SC are contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab, hyaluronidase, or any of the components of the formulation.

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.**

Please see Important Safety Information throughout this video and full Prescribing Information for POMALYST, including Boxed WARNINGS, at www.POMALYSTHCP.com.

The Expansion of POMALYST Data.

MM-003 Phase 3 Trial.

POMALYST + dexamethasone, referred to as Pd.

In this section of the video, I am going to review the first trial that led to FDA approval for POMALYST: MM-003.

MM-003 studied Pd vs high-dose dexamethasone in patients with relapsed/refractory multiple myeloma.

Let's look at the MM-003 study design.

Patients in the Pd arm received 4 mg of POMALYST orally on Days 1 to 21 of 28-day cycles with 40 mg low-dose of dexamethasone once daily on specified days in the cycle.

Patients in the high-dose dexamethasone arm received 40 mg of dexamethasone once daily on specified days in each 28-day cycle, as seen here.

The enrolled patients had received at least 2 prior treatment regimens and demonstrated disease progression on or within 60 days from the last therapy.

Patients receiving Pd and patients with a history of DVT or PE were required to receive prophylaxis or anti-thrombotic treatment.

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.

In the study, the majority of patients were refractory to REVLIMID, bortezomib, or both.

Now, let's review the MM-003 efficacy and safety profile.

For the primary endpoint, Pd doubled median progression-free survival to 3.6 months from 1.8 months with high-dose dexamethasone.

The Pd doublet had a well-established safety profile. 8% of patients discontinued Pd due to adverse reactions. Other key safety data to note include:

- The most common hematologic any-grade treatment-emergent adverse event, or TEAE, was neutropenia (51%)
- The most common non-hematologic any-grade TEAE was fatigue and asthenia (47%)
- The asterisk indicates serious adverse reactions were reported in at least 3 patients in the POM + low-dose dex arm; AND were at least 1% higher than the high-dose dex arm percentage

The results of MM-003 were pivotal for the approval of POMALYST. For me, the results influenced my decision to start prescribing POMALYST-containing regimens to appropriate patients whose multiple myeloma has progressed on REVLIMID and have received a PI.

The Expansion of POMALYST Data.

EQUULEUS Trial.

POMALYST + dexamethasone + daratumumab, referred to as DPd.

In this section of the video, I am going to review the 2017 EQUULEUS trial which studied the DPd triplet.

Pd was studied in combination with daratumumab in a single-arm trial of 103 patients.

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 each week.

In addition to Pd, patients received 16 mg/kg of daratumumab as an infusion based on the schedule shown on-screen.

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. Adjustments made for patients on reduced doses of dexamethasone are shown here.

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

The results of the EQUULEUS trial established that DPd is an effective treatment option for patients whose MM has progressed on REVLIMID.

For more information on the efficacy and safety data for DPd, please visit pomalysthcp.com.

Before we continue on to discuss the APOLLO trial, let's review important safety information about daratumumab.

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 DARATUMUMAB

- **Infusion-Related Reactions:** Daratumumab can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported. 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.
- **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.
- **Neutropenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding daratumumab until recovery of neutrophils.
- **Thrombocytopenia:** Monitor complete blood cell counts periodically during treatment. Consider withholding daratumumab until recovery of platelets.
- **Interference With Determination of Complete Response:** Daratumumab can interfere with the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception.

Information about DPd 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.darzalexhcp.com/iv.

Please see Important Safety Information throughout this video and full Prescribing Information for POMALYST, including Boxed WARNINGS, at www.POMALYSTHCP.com.

The Expansion of POMALYST Data.

APOLLO Trial.

POMALYST + dexamethasone + dara SC, referred to as Pd + dara SC.

In this section of the video, I am going to review the 2021 APOLLO trial that included subcutaneous daratumumab as part of the DPd combination.

Let's take a look at the study design.

Pd was studied in combination with dara SC and compared to Pd doublet. Treatment continued until disease progression or unacceptable toxicity.

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 dexamethasone each week.

In addition to Pd, patients received 1800 mg of dara SC, first weekly, then every 2 weeks, and then every 4 weeks, as shown here.

For the Pd-only arm, 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 dexamethasone on days 1, 8, 15, and 22.

80% of the patients enrolled in the trial were refractory to REVLIMID, 48% were refractory to a proteasome inhibitor, and 42% were refractory to both.

Let's take a look at the efficacy endpoints. The primary endpoint was progression-free survival.

Pd + dara SC prolonged the median progression-free survival time from 6.9 months with Pd to 12.4 months with the triplet.

For the secondary endpoint, overall response rate, 69% of the patients treated with the Pd and dara SC triplet had a response, which ranged from partial response to greater than complete response, versus 46% of the patients on the doublet.

Information about Pd + dara SC does not appear in the POMALYST Prescribing Information.

Now, let's review the APOLLO study safety data.

This chart highlights adverse reactions reported in at least 10% of patients and with at least a 5% greater frequency in the Pd + dara SC arm versus Pd alone.

Key safety data to note include:

- Serious adverse reactions occurred in 50% of patients who received Pd + dara SC
- Neutropenia was the most common hematologic grade 3/4 TEAE at 68%
- Pneumonia was the most common non-hematologic grade 3/4 TEAE at 23%
- 2% of patients permanently discontinued Pd + dara SC due to adverse reactions
- Fatal adverse reactions occurred in 7% of patients

To conclude, the APOLLO trial reinforces why using the DPd combination could be a treatment option for your appropriate patients whose MM has progressed as early as first relapse.

Here is some important safety information for dara SC before we move onto the final trial, MM-014.

CONTRAINDICATIONS FOR DARA SC

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

WARNINGS AND PRECAUTIONS FOR DARA SC

- **Hypersensitivity and Other Administration Reactions:** Daratumumab and hyaluronidase-fihj can cause systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions. Fatal reactions have been reported with daratumumab-containing products, including daratumumab and hyaluronidase-fihj. Permanently discontinue daratumumab and hyaluronidase-fihj for life-threatening reactions.
- **Cardiac Toxicity in Patients With Light Chain (AL) Amyloidosis:** Monitor patients with cardiac involvement more frequently for cardiac adverse reactions and administer supportive care as appropriate.
- **Neutropenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding daratumumab and hyaluronidase-fihj to allow recovery of neutrophils.
- **Thrombocytopenia:** Monitor complete blood cell counts periodically during treatment. Consider withholding daratumumab and hyaluronidase-fihj to allow recovery of platelets.

- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception.
- **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 administration. Type and screen patients prior to starting treatment. Inform blood banks that a patient has received daratumumab and hyaluronidase-fihj.
- **Interference With Determination of Complete Response:** Daratumumab can interfere with the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Information about Pd + dara SC does not appear in the POMALYST Prescribing Information (PI). Please see the dara SC full PI for a complete discussion of Important Safety Information at www.darzalexhcp.com/faspro.

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%), fatigue and asthenia (47%), upper respiratory tract infection (31%), thrombocytopenia (30%), pyrexia (27%), dyspnea (25%), diarrhea (22%), constipation (22%), back pain (20%), cough (20%), pneumonia (19%), bone pain (18%), edema peripheral (17%), peripheral neuropathy (17%), muscle spasms (15%), 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%), thrombocytopenia (22%), and pneumonia (16%).

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%).

ADVERSE REACTIONS FOR POMALYST + dexamethasone + dara SC.

The most common adverse reactions (≥20%) included fatigue (46%), pneumonia (38%), upper respiratory tract infection (36%), and diarrhea (22%). Grade 3 or 4 hematology laboratory abnormalities included: decreased neutrophils (84%), decreased leukocytes (64%), decreased lymphocytes (59%), decreased platelets (19%), and decreased hemoglobin (16%).

DRUG INTERACTIONS FOR POMALYST

Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. If concomitant use of a strong CYP1A2 inhibitor is unavoidable, reduce POMALYST dose to 2 mg.

Please see Important Safety Information throughout this video and full Prescribing Information for POMALYST, including Boxed WARNINGS, at www.POMALYSTHCP.com.

The Expansion of POMALYST Data.

MM-014 Phase 2 Trial.

POMALYST + dexamethasone + daratumumab, referred to as DPd.

The MM-014 trial provides additional DPd efficacy and safety data.

Results from MM-014 are not included in the Prescribing Information for POMALYST or daratumumab.

But before we look into the study design, let's review some of the key study limitations:

- All data are observational in nature.
- MM-014 was a Phase 2 single-arm study with no comparator arm.
- The majority of patients received 1 prior line of therapy (69 of 112 patients; 62%).
- Not all patients received a PI, though 80% of patients did.
- Differences in outcomes could be due to differences in baseline characteristics or previous lines of therapy.
- PFS and OS were secondary endpoints of MM-014 and were not statistically tested in the setting of this single-arm trial. PFS and OS data are not in the Prescribing Information and should be interpreted with caution in a single- arm trial. The statistical significance of PFS and OS is not known.

Now let's look at the MM-014 study design.

DPd was studied in a Phase 2, open-label, single-arm trial. The multicenter trial included 112 patients divided into 3 cohorts. The cohorts were designed to investigate the outcomes of sequencing a regimen with POMALYST in early relapse and immediately after treatment failure with a REVLIMID regimen.

Results from Cohort B are presented here.

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 dexamethasone each week. Patients older than 75 years received 20 mg of dexamethasone.

In addition to POMALYST and dexamethasone, patients received 16 mg/kg of daratumumab first weekly, then every 2 weeks, then every 4 weeks, as an infusion as shown here.

62% of patients enrolled in the trial had been treated with 1 prior line of therapy, while 38% received 2 prior lines.

All patients had received REVLIMID in the immediate prior line of treatment.

76% of the patients enrolled in the trial were refractory to REVLIMID. 24% of patients had relapsed after REVLIMID.

Now, let's look at the overall response rates (ORR), progression-free survival (PFS), and overall survival (OS) efficacy endpoints.

ORR was the primary endpoint.

- ORR in the intention-to-treat population was 78.6%:
- Complete response was 26.8%,
- Very good partial response: 25.9%
- And partial response was 25.9%

Patients who relapsed after or were refractory to REVLIMID had an ORR of 81.5% and 77.6%, respectively.

Median time to response was 1 month.

Median PFS was a secondary endpoint.

- After a follow-up of 41.9 months, the median PFS was 23.7 months in the intent-to-treat population

Median OS was another secondary endpoint.

- After a follow-up of 41.9 months, the median OS was 56.7 months in the intent-to-treat population. There were 40 patients at risk at the 56.7-month data point.
- Patients were followed for OS, subsequent treatment, and secondary primary malignancy for up to 5 years after the last patient was enrolled

Now let's move to the safety results.

The adverse event profile for DPd was consistent with the known toxicities of the individual agents.

- Nearly all patients (97.3%) had a TEAE of any grade.
- The most common hematologic grade 3/4 TEAE was neutropenia.
- Other common hematologic grade 3/4 TEAEs were anemia, thrombocytopenia, febrile neutropenia, and leukopenia.
- Any-grade infusion-related reactions were reported in 34 patients (30.4%).
- The most common non-hematologic any-grade TEAE was infections and infestations, including upper respiratory tract infection.
- The most common non-hematologic grade 3/4 TEAE was pneumonia.
- Other common non-hematologic Grade 3/4 TEAEs were neutrophil count decreased, hypertension, dyspnea, back pain, fatigue, white blood cell count decreased, sepsis, chronic obstructive pulmonary disease, hyperglycemia, hypokalemia, atrial fibrillation, and insomnia
- 8.9% of patients discontinued due to adverse events.
- At a median follow-up of 41.9 months, 97 patients (86.6%) had discontinued treatment, most commonly due to disease progression.
- TEAEs leading to discontinuation of POMALYST, dex, or dara occurred in 7 (6.3%), 9 (8.0%), and 6 (5.4%) patients, respectively.
- 31 (27.7%) and 38 (33.9%) patients experienced TEAEs leading to POMALYST and dex reduction, respectively, while 55 (49.1%), 17 (15.2%), and 65 (58.0%) experienced TEAEs leading to POMALYST, dex, and dara interruption, respectively
- Neutropenia was the most common TEAE leading to dose modification of POMALYST and dara.
- Insomnia was the most common TEAE leading to dose modification of dex.

Median duration of treatment was 15.7 months for POMALYST, 13.7 months for dex, and 15.2 months for dara.

At a median follow-up of 41.9 months, 97 patients (86.6%) discontinued treatment, most commonly due to disease progression. At follow-up, 75 patients (67%) had discontinued from the study, most commonly due to death. Of the 50 patients who died, 47 died off treatment, during the long-term follow-up.

The data for POMALYST has expanded over the last decade. In appropriate patients, proceed to a POMALYST-containing regimen as early as first-relapse.

The National Comprehensive Cancer Network® (NCCN®) recommends triplet regimens over doublet regimens for previously treated multiple myeloma patients.

The DPd triplet is an NCCN Category 1 preferred regimen for patients with multiple myeloma after one prior therapy, including lenalidomide and a PI.

And the DPd triplet is the number one prescribed second-line regimen.

So, the next time you are faced with a decision about which regimen to prescribe after your patients have progressed on REVLIMID, consider the evidence supporting the POMALYST-containing triplet DPd.

Now, let's review Important Safety Information for POMALYST.

POMALYST® (pomalidomide) is a thalidomide analogue indicated for the treatment of adult patients:

- 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 adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

POMALYST + dexamethasone + daratumumab and hyaluronidase-fihj is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.

Limitations of Use:
Daratumumab and hyaluronidase-fihj is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.

Information about DPd and Pd + dara SC does not appear in the POMALYST Prescribing Information (PI). Please see the daratumumab and dara SC full PIs for a complete discussion of Important Safety Information at www.darzalexhcp.com/iv and www.darzalexhcp.com/faspro, respectively.

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 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 severe 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.

CONTRAINDICATIONS FOR DARA SC.

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

WARNINGS AND PRECAUTIONS FOR POMALYST.

- Embryo-Fetal Toxicity & Females of Reproductive Potential: See Boxed WARNINGS for POMALYST.
  - 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.pomalystrems.com** or by telephone at 1-888-423-5436.
- Venous and Arterial Thromboembolism: See Boxed WARNINGS for POMALYST. 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 or 4 adverse reaction, 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 with POMALYST. 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 POMALYST interruption or discontinuation for Grade 2 or 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 (SPMs):**
    - Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.
    - Monitor patients for the development of SPMs.
- **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.

WARNINGS AND PRECAUTIONS FOR DARATUMUMAB

- **Infusion-Related Reactions:** Daratumumab can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported. 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.
- **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.
- **Neutropenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding daratumumab until recovery of neutrophils.
- **Thrombocytopenia:** Monitor complete blood cell counts periodically during treatment. Consider withholding daratumumab until recovery of platelets.

- **Interference With Determination of Complete Response:** Daratumumab can interfere with the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception.

WARNINGS AND PRECAUTIONS FOR DARA SC

- **Hypersensitivity and Other Administration Reactions:** Daratumumab and hyaluronidase-fihj can cause systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions. Fatal reactions have been reported with daratumumab-containing products, including daratumumab and hyaluronidase-fihj. Permanently discontinue daratumumab and hyaluronidase-fihj for life-threatening reactions.
- **Cardiac Toxicity in Patients With Light Chain (AL) Amyloidosis:** Monitor patients with cardiac involvement more frequently for cardiac adverse reactions and administer supportive care as appropriate.
- **Neutropenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding daratumumab and hyaluronidase-fihj to allow recovery of neutrophils.
- **Thrombocytopenia:** Monitor complete blood cell counts periodically during treatment. Consider withholding daratumumab and hyaluronidase-fihj to allow recovery of platelets.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception.
- **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 administration. Type and screen patients prior to starting treatment. Inform blood banks that a patient has received daratumumab and hyaluronidase-fihj.
- **Interference With Determination of Complete Response:** Daratumumab can interfere with the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

ADVERSE REACTIONS FOR POMALYST.

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%), fatigue and asthenia (47%), upper respiratory tract infection (31%), thrombocytopenia (30%), pyrexia (27%), dyspnea (25%), diarrhea (22%), constipation (22%), back pain (20%), cough (20%), pneumonia (19%), bone pain (18%), edema peripheral (17%), peripheral neuropathy (17%), muscle spasms (15%), 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%), thrombocytopenia (22%), and pneumonia (16%).

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%).

ADVERSE REACTIONS FOR POMALYST + dexamethasone + dara SC.

The most common adverse reactions (≥20%) included fatigue (46%), pneumonia (38%), upper respiratory tract infection (36%), and diarrhea (22%). Grade 3 or 4 hematology laboratory abnormalities included: decreased neutrophils (84%), decreased leukocytes (64%), decreased lymphocytes (59%), decreased platelets (19%), and decreased hemoglobin (16%).

DRUG INTERACTIONS FOR POMALYST.

Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. If concomitant use of a strong CYP1A2 inhibitor is unavoidable, reduce POMALYST dose to 2 mg.

USE IN SPECIFIC POPULATIONS FOR POMALYST.

- **Pregnancy: See Boxed WARNINGS for POMALYST.** 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 the REMS Call Center 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:** For patients with severe renal impairment requiring dialysis, reduce POMALYST dosage to 3 mg orally daily. Take dose of POMALYST following hemodialysis on hemodialysis days.
- **Hepatic Impairment:** For patients with mild to moderate hepatic impairment, reduce POMALYST dosage to 3 mg orally daily and to 2 mg orally daily in patients with severe hepatic impairment.
- **Smoking Tobacco:** Advise patients that smoking may reduce the efficacy of POMALYST. Cigarette smoking reduces pomalidomide AUC due to CYP1A2 induction.

Please see full Prescribing Information for POMALYST, including Boxed WARNINGS, at www.POMALYSTHCP.com.

Information about DPd and Pd + dara SC does not appear in the POMALYST Prescribing Information (PI). Please see the daratumumab and dara SC full PIs for a complete discussion of Important Safety Information at www.darzalexhcp.com/iv and www.darzalexhcp.com/faspro, respectively.

Thank you for your time in reviewing these important data for POMALYST-containing regimens. For more information, please visit www.POMALYSTHCP.com or contact your local POMALYST representative.

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11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines.) for Multiple Myeloma V.3.2023. National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed December 8, 2022. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
12. Data on file. Bristol-Myers Squibb Co; January 2023.