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CLEAR CELL SARCOMA: CASE STUDY

Unusual Clinical Presentation of Clear Cell Sarcoma in a Young Woman

DRUG SHORTAGES: INTERVIEW

Lucio N. Gordan, MD

Price Gouging Among Shortages "Significantly Affects" Drug Supply

Multiple Myeloma: Case Study

Secondary Pure Red Cell Aplasia During Daratumumab/Hyaluronidase Therapy for Multiple Myeloma

CME:

Neoadjuvant Immunotherapy in Melanoma: Where We Are, and Where We Aren't

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DARZALEX® (daratumumab) injection for intravenous infusion 100 mg/5 mL, 400 mg/20 mL | DARZALEX *Faspro*® (daratumumab and hyaluronidase-fihj) Injection for subcutaneous use | 1,800mg/30,000units

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma[1]:

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

Help your patients live longer than Rd alone with DRd, an established frontline treatment proven to significantly extend overall survival[1]

After 56 months: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).*[1]

*Median follow-up was 56 months in the DRd group (range: 53.0-60.1 months) and in the Rd group (range: 52.5-59.4 months)[1,2]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

DARZALEX® and DARZALEX *FASPRO*® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX *FASPRO*®), or any of the components of the formulations.

DARZALEX®: Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions.

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX *FASPRO*® on adjacent pages.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DARZALEX® (daratumumab) + Rd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma.

Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) and OS was a secondary endpoint.[1]

Powerful efficacy to start the treatment journey[1,3]

At follow-up of 28 months, **median progression-free survival (mPFS) was not reached** with DARZALEX® + Rd vs 31.9 months (95% CI, 28.9 to not reached) with Rd alone*

- **70.6% of patients had not progressed** with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0-75.4; Rd: 95% CI, 49.5-61.3)†

44% **reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.56; 95% CI, 0.43-0.73; *P*<0.0001)

Efficacy results in long-term follow-up[1,4]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, not evaluable) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm

45% **reduction in the risk of disease progression or death** with DARZALEX® + Rd vs Rd alone (HR=0.55; 95% CI, 0.45-0.67)

Secondary endpoint of overall survival (OS)[1,2]
After 56 months of follow-up:

- 66% of patients were still alive with DRd vs 53% with Rd alone (DRd: 95% CI, 60.8-71.3; Rd: 95% CI, 47.2-58.6)†
- Median OS was not reached for either arm

32% **reduction in the risk of death** in patients treated in the DRd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013)

Demonstrated safety profile
(median treatment duration of 25.3 months)[1]

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

Safety results in long-term follow-up
(median follow-up of 64.5 months)[4]

This information is not included in the current Prescribing Information and has not been evaluated by the FDA.

- Most frequent TEAEs for DRd occurring in ≥30% of patients were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms‡
- Grade 3/4 infections were 43% for DRd vs 30% for Rd‡
- Grade 3/4 TEAEs occurring in ≥10% of patients were neutropenia (54% for DRd vs 37% for Rd), pneumonia (20% vs 11%), and anemia (17% vs 22%)‡

Treatment-emergent adverse events are reported as observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[1,3]
†Kaplan-Meier estimate.[3]
‡Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after the start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

See the rolled-out data.
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IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj): Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX *FASPRO*®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX *FASPRO*® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX *FASPRO*® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX® and DARZALEX *FASPRO*®.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX *FASPRO*®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX *FASPRO*® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX *FASPRO*®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX *FASPRO*® on adjacent pages.

cp-248517v3

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(11):1582-1596. doi:10.1016/s1470-2045(21)00466-6 **3.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249 **4.** Kumar SK, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA.

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DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported *[see Adverse Reactions]*.

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision *[see Adverse Reactions]*.

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX can cause fetal harm when administered to a pregnant woman. DARZALEX may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

The combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion-related reactions *[see Warning and Precautions]*.
- Neutropenia *[see Warning and Precautions]*.
- Thrombocytopenia *[see Warning and Precautions]*.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA *[see Clinical Studies (14.1) in Full Prescribing Information]*. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).

Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

Body System Adverse Reaction	DRd (N=364)			Rd (N=365)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders						
Diarrhea	57	7	0	46	4	0
Constipation	41	1	<1	36	<1	0
Nausea	32	1	0	23	1	0
Vomiting	17	1	0	12	<1	0
Infections						
Upper respiratory tract infection[a]	52	2	<1	36	2	<1
Bronchitis[b]	29	3	0	21	1	0
Pneumonia[c]	26	14	1	14	7	1
Urinary tract infection	18	2	0	10	2	0
General disorders and administration site conditions						
Infusion-related reactions[d]	41	2	<1	0	0	0
Peripheral edema[e]	41	2	0	33	1	0
Fatigue	40	8	0	28	4	0
Asthenia	32	4	0	25	3	<1
Pyrexia	23	2	0	18	2	0
Chills	13	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Back pain	34	3	<1	26	3	<1
Muscle spasms	29	1	0	22	1	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[f]	32	3	<1	20	1	0
Cough[g]	30	<1	0	18	0	0
Nervous system disorders						
Peripheral sensory neuropathy	24	1	0	15	0	0
Headache	19	1	0	11	0	0
Paresthesia	16	0	0	8	0	0
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	15	<1	<1
Hyperglycemia	14	6	1	8	3	1
Hypocalcemia	14	1	<1	9	1	1
Vascular disorders						
Hypertension[h]	13	6	<1	7	4	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[b] Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

[c] Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

[d] Infusion-related reaction includes terms determined by investigators to be related to infusion

[e] Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

	DRd (N=364)			Rd (N=365)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	90	30	5	82	20	4
Neutropenia	91	39	17	77	28	11
Lymphopenia	84	41	11	75	36	6
Thrombocytopenia	67	6	3	58	7	4
Anemia	47	13	0	57	24	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX *[see Clinical Studies (14.2) in Full Prescribing Information]*. Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 3: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

Adverse Reaction	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Infections						
Upper respiratory tract infection[a]	65	6	< 1	51	4	0
General disorders and administration site conditions						
Infusion-related reactions[b]	48	5	0	0	0	0
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[b] Infusion-related reaction includes terms determined by investigators to be related to infusion

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Lymphopenia	95	42	10	87	32	6
Neutropenia	92	36	17	87	32	8
Thrombocytopenia	73	7	6	67	10	5
Anemia	52	13	0	57	19	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products may be misleading.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction, IRR (including deaths)
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

Risk Summary

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use

Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients *[see Adverse Reactions]*. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing, itching, and blurred vision *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding *[see Warnings and Precautions]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions]*.

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, pomalidomide, or thalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Hereditary Fructose Intolerance (HFI)

DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol *[see Description (11) in Full Prescribing Information]*.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com

cp-271933v4

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation *[see Warnings and Precautions* and *Adverse Reactions].*

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO *[see Adverse Reactions].*

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Dosage and Administration (2.5) in Full Prescribing Information].* Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions *[see Dosage and Administration (2.5) in Full Prescribing Information].*

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone *[see Adverse Reactions].* Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations].*

The combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO *[see Dosage and Administration (2.1) in Full Prescribing Information].*

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions].* This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions *[see Warnings and Precautions].*
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis *[see Warnings and Precautions].*
- Neutropenia *[see Warnings and Precautions].*
- Thrombocytopenia *[see Warnings and Precautions].*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (14.2) in Full Prescribing Information].* Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Adverse Reaction	DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)	
	All Grades (%)	Grades ≥3 (%)
General disorders and administration site conditions		
Fatigue[a]	52	5[#]
Pyrexia	23	2[#]
Edema peripheral	18	3[#]
Gastrointestinal disorders		
Diarrhea	45	5[#]
Constipation	26	2[#]
Nausea	12	0
Vomiting	11	0
Infections		
Upper respiratory tract infection[b]	43	3[#]
Pneumonia[c]	23	17
Bronchitis[d]	14	2[#]
Urinary tract infection	11	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	31	2[#]
Back pain	14	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	22	3
Cough[f]	14	0
Nervous system disorders		
Peripheral sensory neuropathy	17	2[#]
Psychiatric disorders		
Insomnia	17	5[#]
Metabolism and nutrition disorders		
Hyperglycemia	12	9[#]
Hypocalcemia	11	0

[a] Fatigue includes asthenia, and fatigue.
[b] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c] Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
[d] Bronchitis includes bronchitis, and bronchitis viral.
[e] Dyspnea includes dyspnea, and dyspnea exertional.
[f] Cough includes cough, and productive cough.
[#] Only Grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Lenalidomide and Dexamethasone[a]	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	94	34
Decreased lymphocytes	82	58
Decreased platelets	86	9
Decreased neutrophils	89	52
Decreased hemoglobin	45	8

[a] Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 812 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision *[see Warnings and Precautions]*.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion *[see Warnings and Precautions]*.

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Manufactured by:
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For patent information: www.janssenpatents.com

cp-267681v3

PUBLISHER'S NOTE

OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

Judd W. Moul, MD, FACS
Prostate Cancer Editorial Board Member
Moul, recently published research titled "Application of next-generation imaging in biochemically recurrent prostate cancer", of which he was the lead author. The study found that there was improved detection and selectivity of next-generation imaging compared with current modalities. You can read the full article in *Prostate Cancer and Prostatic Diseases*.

Davis A. Reardon, MD
Neuro-oncology Editorial Board Member
Reardon is currently leading a phase 1 clinical trial (NCT05698199) evaluating ITI-1001, a plasmoid DNA vaccine, for patients with glioblastoma multiforme. The trial will analyze the safety, tolerability, and efficacy of giving 8 mg of ITI-1001 to these patients. Topline data is expected are read out in 2025.

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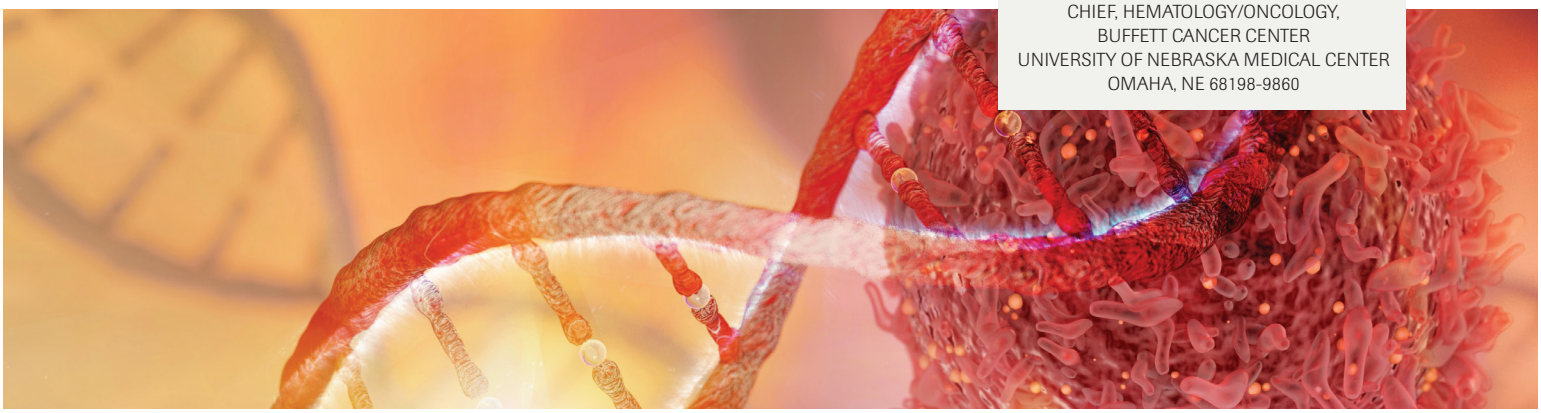

Multidisciplinary Team Approach Is Integral to Oncology Care

Treating and caring for patients with cancer can require a complex team of medical professionals who work together toward a common goal. This type of approach emerged in the 1980s with the addition of chemotherapy to radiotherapy and/or surgery to improve survival outcomes for patients with cancer. In addition to the medical, surgical, and radiation oncologists, many other team members are needed to assist with more complex treatments. Other key members of the multidisciplinary team may include a nurse case manager/navigator, dietitian, physical therapist, social worker, psychologist, palliative care staff, onco-geriatrician, oncology pharmacists, and financial counselor.[1,2] Unfortunately, not all patients who need this support are able to receive it due to a lack of resources or ancillary support in some clinical settings.

The majority of malignancies demonstrate an increased incidence with age. The use of a multidisciplinary geriatric assessment in older patients can be beneficial in planning for treatments in this population.[1] For example, gastrointestinal cancers represent a challenge for older adults who may need multimodality treatments such as surgery, chemotherapy, and radiation therapy. Surgery complications can lead to nutritional issues such as malabsorption and delayed gastric emptying. Adverse effects of narcotics and polypharmacy issues are also frequent problems. A multidisciplinary geriatric assessment can uncover issues to be addressed before treatment starts, such as the need for nutritional support, physical therapy, pharmacy evaluation, and medication education.[2]

Another example is the expanded use of novel agents and alternative donors for hematopoietic stem cell transplantation for older patients with blood cancers. A multidisciplinary team is important in caring for these patients and assessing their needs prior to and during their treatment, including physical therapy, nutrition consultations, and psychological evaluation. Early identification and interventions can mitigate some of these risk factors.

As we become more successful in our oncology treatments, cancer survivors are living longer and facing many challenges created by the cancer or the therapies. Therefore, our multidisciplinary care does not end when their active cancer treatment has been completed. Issues such as fatigue, pain, osteoporosis, cardiac toxicity, nutritional challenges, neuropathy, and cognitive decline are only a subset of potential long-term issues they may face.

Our multidisciplinary care must continue far beyond the actual treatment. Addressing survivorship issues requires a coordinated team and the use of survivorship care plans that include key information on the treatment and assessment of ongoing toxicities, education on potential long-term toxicities, and overall health and wellness counseling. Survivorship education should include tailored individual information for the patient, the treatment received, and strategies to boost their health and wellness. ■

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2. Taberna M, Gil Moncayo F, Jané-Salas E, et al. The multidisciplinary team (MDT) approach and quality of care. *Front Oncol.* 2020;10:85. doi:10.3389/fonc.2020.00085

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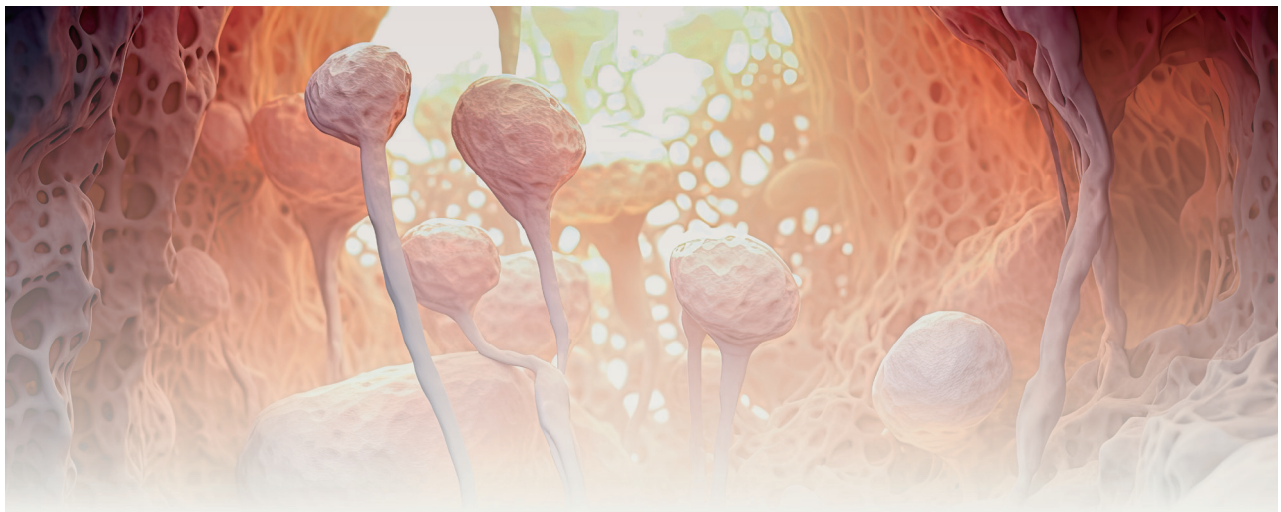

VIDEO

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Unusual Clinical Presentation of Clear Cell Sarcoma in a Young Woman

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BACKGROUND

Clear cell sarcoma (CCS) is a rare but aggressive malignancy that typically occurs in young adults and is characterized by soft tissue tumors of the extremities. CCS can be difficult to distinguish from metastatic melanoma based solely on histology and immunohistochemistry (IHC) because of the significant overlap between them. However, it is imperative to get an accurate clinical diagnosis, as it informs disease staging and treatment options for patient care. Present in approximately 75% of CCS cases, the *EWSR1* gene rearrangement detected by fluorescence in situ hybridization (FISH) can help with establishing a diagnosis; the underlying reciprocal translocation has never been reported in cutaneous melanoma.

CASE DESCRIPTION

We reviewed a case of a young woman who presented with a confusing picture of widespread lymphadenopathy, cutaneous metastases, and electrolyte derangements and was subsequently diagnosed with metastatic CCS.

CONCLUSIONS

This case suggests possible value in performing molecular testing when a clinical picture does not correspond with what is expected for melanoma. It also raises the question of whether CCS cases may be underreported. This case highlights an uncommon presentation that may not be recognized as a manifestation of CCS by an oncologist who is not a sarcoma specialist. It is unclear how COVID-19 vaccination contributed to her clinical presentation, and it is also unclear whether an early diagnosis would have changed her clinical outcome.

Introduction

Clear cell sarcoma (CCS) is commonly seen in adolescents and young adults, with most patients aged 20 to 40 years at the time of diagnosis.[1] It commonly develops in the deep soft tissue of the extremities, usually in proximity to tendons and aponeuroses.[2]

CCS can be difficult to differentiate from malignant melanoma due to their histological and clinical similarities. In fact, CCS has historically been referred to in literature as "malignant melanoma of soft parts."[3] Like malignant melanoma, CCS demonstrates melanocytic differentiation, and they share similar immunohistochemical markers such as S100, HMB-45, and melanin.[4-6] CCS also has a propensity for repeated local recurrences, regional nodal metastases, in-transit metastases, and distant disease.[7] However, in CCS, as with other soft tissue sarcomas, pulmonary metastases are the most commonly reported distant metastases.[7]

CCS typically presents as a slow-growing mass that may be painful. In a study by Kuiper et al, they reported an 18-month interval between a swelling first being noticed by a patient and a physician consultation.[2] In advanced stages, patients may also exhibit systemic symptoms such as weight loss, anorexia, and malaise.[8]

Here, we present a case of an unusual clinical presentation of CCS in a young patient with predominant cutaneous and lymph node involvement and rapid clinical deterioration.

Case Presentation

A 26-year-old woman with no pertinent medical history presented in July 2021 to the emergency department (ED) with painless lumps in her left groin 5 days after receiving a second monovalent Moderna COVID-19 vaccine. On physical examination, left inguinal lymphadenopathy without overlying skin changes was noted. This was suspected to be reactive adenopathy from her recent immunization, and follow-up with her primary care provider was advised.

She was reevaluated in the ED 6 weeks later for persistent left inguinal

lymphadenopathy, now associated with left lateral hip pain. Tenderness to palpation over the left lateral hip was noted during the examination. A bilateral pelvis plain radiograph showed no acute or healing fracture. She was discharged home with a diagnosis of left trochanteric bursitis. Subsequently, an outpatient ultrasound of the left inguinal region was performed due to persistent lymphadenopathy. It demonstrated multiple abnormal inguinal lymph nodes, suggestive of a malignant process. A CT scan of the chest, abdomen, and pelvis was planned, but she presented to the ED again with worsening symptoms.

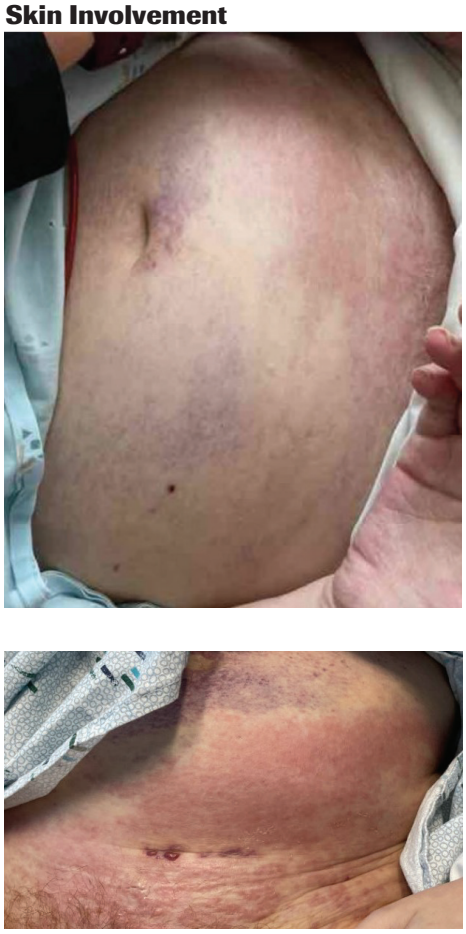
She now reported bilateral hip and lower abdominal pain, persistent left inguinal lymphadenopathy, constipation, nausea and vomiting, fatigue, abdominal skin discoloration, and a 15-lb weight loss. A physical examination revealed hard ecchymosis over the pubis and erythema over the left flank (**Figure 1**) with nontender, firm lymphadenopathy in the left inguinal area. Initial laboratory test results were remarkable for an elevated lactate dehydrogenase level of 1097 U/L (normal range, 98-192 U/L), a uric acid level of 9.1 mg/dL (normal range, 3.0-6.8 mg/dL), an elevated serum creatinine level of 1.18 mg/dL (normal range, 0.44-1.03 mg/dL), and hypercalcemia with a serum calcium level of 1.7 mg/dL (normal range, 8.6-10.4 mg/dL).

A CT scan of the abdomen and pelvis with intravenous contrast demonstrated conglomerates of cardiophrenic, retroperitoneal, bilateral iliac chain, and bilateral inguinal lymph nodes, with the largest node being in the left iliac chain and measuring 7.4 cm. Additional findings included moderate left hydronephrosis, diffuse lytic osseous lesions, a left adnexal 5.1-cm soft tissue lesion suspected to be of ovarian etiology, a large indeterminate lesion measuring 9.3×4.3 cm in the left flank that infiltrated the abdominal muscles, and external compression of the left iliac veins. She was subsequently admitted for obstructive uropathy and hematologic consultation due to concerns about a possible lymphoproliferative disorder.

A fluorodeoxyglucose F18 (FDG)–PET/CT scan revealed multifocal FDG-avid lymphadenopathy, lytic osseous lesions, and a left lower quadrant abdominal wall mass; overall radiographic findings were most suspicious for lymphoma (**Figure 2**). Hydronephrosis and left ovarian enlargement with mild FDG uptake were also noted, suggestive of a possible complex cyst rather than malignant involvement. An MRI of the brain revealed a right frontal bone lesion suspicious for metastasis but no intraparenchymal lesions.

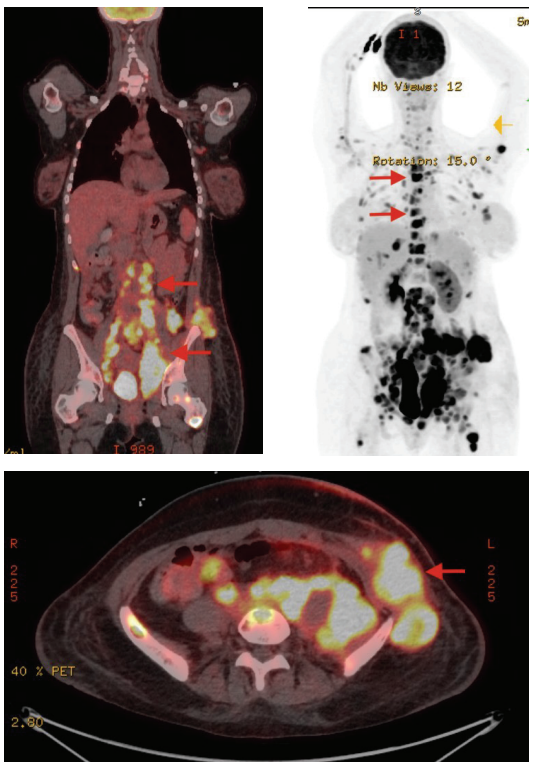
A core biopsy of the left inguinal lymph node was obtained. On histopathology, numerous cohesive clusters of large and monotonous tumor cells were noted. Singly scattered tumor cells were also detected. These tumor cells had a high nucleus-to-cytoplasmic ratio, round nuclei with fine chromatin, 1 to 3 nucleoli, and clear to

FIGURE 1. **Clear Cell Sarcoma Skin Involvement**



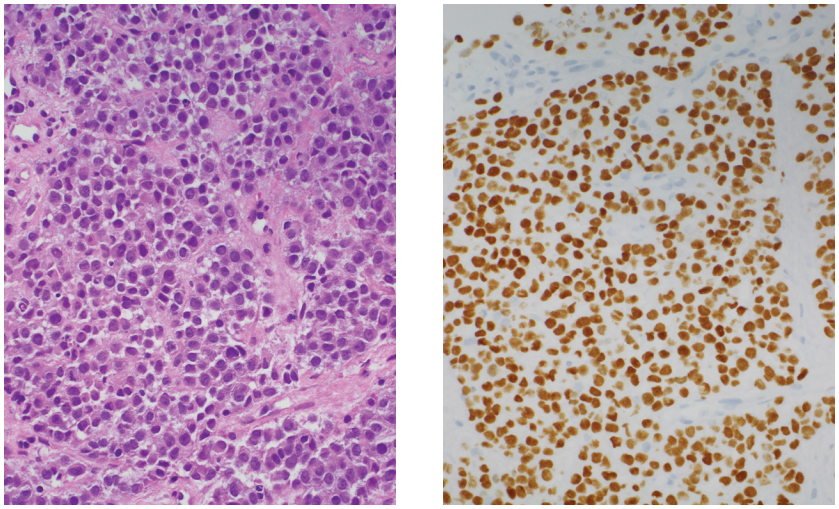
(A) Left lower abdomen **(B)** Left inguinal area

FIGURE 2. **FDG-PET/CT Imaging**



(A) Multifocal lymphadenopathy **(B)** Lytic osseous lesions **(C)** Left lower quadrant abdominal wall mass
FDG, fluorodeoxyglucose F 18.

FIGURE 3. **Core Biopsy Results of the Left Inguinal Lymph Node**



(A) Note the monotonous round cells with prominent nucleoli and the clear to eosinophilic cytoplasm arranged in nests and sheets in this biopsy from the left groin mass lesion (hematoxylin and eosin stains; original magnification ×400).
(B) Note the strong positive staining for SOX10 that is seen in both malignant melanoma and clear cell sarcoma (SOX10 immunostain; original magnification ×400).

eosinophilic cytoplasm. Ki-67 expression was 40%. On immunostaining, tumor cells were positive for HMB-45, Melan-A, SOX10, and CD99 and negative for S100, AE1/AE3, desmin, SALL4, and Oct3/4. On flow cytometry, a lymphoma cell population was not identified, and both T cells and natural killer cells appeared normal via antigen profiling. Based on this biopsy, the diagnosis was reported as malignant melanoma (**Figure 3**).

A bone marrow aspiration and biopsy of the left iliac crest had been obtained simultaneously with the lymph node biopsy due to high suspicion of a lymphoproliferative disorder and to expedite treatment initiation. This revealed normocellular marrow (70%) with focal involvement by a nonhematopoietic metastatic tumor (20%).

The patient was treated for hypercalcemia and hyperuricemia with intravenous hydration, pamidronate disodium, rasburicase, and allopurinol. Hypercalcemia was attributed to diffuse osteolytic metastases, and hyperuricemia and acute kidney injury were suspected to be from obstructive uropathy rather than tumor lysis syndrome. The urology team placed a left ureteral stent.

She was discharged to outpatient follow-up with a diagnosis of metastatic melanoma. Additional immunostains for melanoma were requested on her bone marrow aspiration/biopsy sample because of the atypical disease course and the lack of previous history of superficial melanoma; these tumor cells were strongly positive for HMB-45 and SOX10 and weakly positive for S100. Samples were also sent for additional analysis using cytogenetics, including fluorescence in situ hybridization (FISH), and next-generation sequencing. A melanoma-specific molecular analysis on the lymph node biopsy sample was negative for variants in *BRAF*, *GNA11*, *GNAQ*, *HRAS*, *KIT*, and *NRAS*. Initiation of treatment was planned with the combination immunotherapy ipilimumab and nivolumab.

Prior to her scheduled first dose of immunotherapy, the patient was brought to the ED with altered mental status and increased somnolence. Laboratory work-up demonstrated recurrent hyperuricemia and hypercalcemia with renal impairment, hyponatremia, and lactic acidosis. A CT scan of the head with contrast revealed no intraparenchymal metastases. Pamidronate and rasburicase were administered again. She was also given broad-spectrum antibiotics and fluid resuscitation. A percutaneous nephrostomy tube was placed because of the acute kidney injury. An extensive work-up for infectious etiologies was performed and was essentially negative.

Because of the rapid decline in her clinical condition, the first cycle of treatment with ipilimumab and nivolumab was administered while she was an inpatient. Approximately a week later, she developed fever and hypotension, requiring transfer to the intensive care unit and, eventually, mechanical ventilation and inotropic support. Broad-spectrum antibiotics were initiated again, and a repeat infectious work-up remained unrevealing. An increased confluence of her abdominal rash was also noted, prompting a biopsy of the skin rash. The possibility of cytokine release syndrome in the setting of dual immunotherapy was considered. Her IL-6 level was checked and elevated at 11.5 pg/mL (normal range, ≤ 2 pg/mL). However, she subsequently improved with supportive care alone without steroid initiation or anti–IL-6 therapy and was extubated and weaned off vasopressor support.

At this time, results from the additional testing performed on the prior

biopsy specimens became available. Cytogenetics revealed an abnormal karyotype with an *EWSR1-ATF1* gene fusion identified by FISH and copy number losses in *CDKN2A*, *CDKN2B*, and *MTAP*. Although this tumor was previously reported as melanoma, due to the presence of the *EWSR1-ATF1* gene fusion, the diagnosis was updated per pathology to CCS. Additionally, a skin punch biopsy revealed anastomosing cords and fascicles of pleomorphic cells throughout the mid- and deep dermis, diffusely positive for SOX-10 and also consistent with CCS.

After the oncology team consulted with a sarcoma expert at our institute, the University of Nebraska Medical Center, the decision was made to continue with combination immunotherapy after optimization of her acute medical issues. However, she developed acute renal failure accompanied by worsening encephalopathy. Our nephrology service recommended urgent hemodialysis initiation. After multidisciplinary family meetings, the patient and her family elected to proceed with comfort measures, and the patient died later the same day.

Discussion

CCS is an uncommon malignancy, comprising approximately 1% of all soft tissue sarcomas.[9] It is commonly seen in young adults with no specific gender predilection. The most common site of involvement is the lower extremities, especially the foot and ankle.[10] Although primary cutaneous CCS has been reported, cutaneous metastasis from a deep-seated CCS is an uncommon phenomenon.[5] In reported cutaneous cases of CCS, superficial dermis is involved and epidermal involvement by CCS is a rare occurrence.[11] Hypercalcemia is seen frequently among patients with malignancies, but it is rarely reported in patients with soft tissue sarcoma.[12] Only 1 prior case of CCS with hypercalcemia has been reported in which hypercalcemia was attributed to the presence of osteolytic metastases.[13]

The majority of patients with CCS are diagnosed with early-stage disease. In a Surveillance, Epidemiology, and End Results Program database study by Li et al, 57.7% and 33.7% of patients had localized and regional CCS, respectively, whereas only 8.6% of patients had distant or metastatic disease. Of these cases, 74.3% involved lower extremities. Based on this study, 5-year disease-specific survival was 62.9%. As expected, patients with localized stage had better 5-year disease-specific survival than those with regional stage (82.4% vs 44%, respectively). None of the patients with distant disease survived at 5 years; in fact, survival at 2 years was only 6.7%.[9]

In a small retrospective review of patients with CCS by Finley et al, patients with large primary tumors (> 5 cm) were noted to have an increased risk of disease recurrence and progression to metastatic disease despite optimal surgical management. The median survival for these patients was 3 months after progression to metastatic disease.[14]

Due to its rare nature and histological similarities, CCS can easily be mistaken for malignant melanoma. However, the need to distinguish between the 2 entities remains crucial due to the differences in their clinical course and management options. As witnessed in our case, differentiating between them based on histology alone can be a diagnostic challenge. Cutaneous CCS in particular may be confused with cutaneous spindle cell melanoma or metastatic melanoma based solely on histology and immunohistochemistry.[6]

Despite the histological commonalities of these 2 cancers, their molecular landscapes vary substantially. In as many as 75% of CCS cases, the cytogenetic analysis revealed the reciprocal translocation t(12;22)(q13;q12) involving the *EWSR1* gene and the *ATF1* gene.[15,16] Four types of *EWSR1/ATF1* chimeric transcripts have been noted in CCS.[1,17] This translocation has not been described in malignant melanoma and, therefore, can help distinguish between the 2 diagnoses. A t(2:22)(q34;q12) translocation resulting from the fusion of the *EWSR1* and *CREB1* genes has been reported in CCS that arises in the gastrointestinal tract.[18] Notably, CCS is marked by the absence of mutations in *BRAF* that are commonly noted in malignant melanoma.[17]

Other chromosomal abnormalities that may be observed in CCS include additional copies of chromosomes 2, 7, and 8.[19] Luzar et al presented a series of 4 cases (3 primary cutaneous CCS, 1 CCS with metastases to skin).[5] Three cases demonstrated a rearrangement of *EWSR1* and 1 showed *ESWR1-ATF1* translocation. Hence, FISH analysis is crucial to distinguish cases of CCS in which cutaneous involvement mimics that of malignant melanoma.

The rarity of this disease also limits the availability of information regarding its optimal management. Management of CCS should involve a multidisciplinary team.[8] For patients with localized disease, wide local excision is the treatment of choice. The utility of sentinel lymph node biopsy or elective lymph node dissection in the management of localized CCS is unclear.[8,10] A reexcision can be considered to achieve tumor-free margins, whereas adjuvant radiation therapy is recommended for close resection margins. For local recurrences or oligometastatic recurrences, surgery resection is usually recommended.[8]

Management of locally advanced or metastatic disease remains challenging. There is no clear effective or preferred treatment regimen due to the limited data from studies reviewing outcomes for a small number of patients with CCS.

Conventional chemotherapy has limited efficacy in CCS. Jones et al evaluated the role of palliative chemotherapy in patients with CCS, most of whom received anthracycline-based chemotherapy either as a single agent or in combination with ifosfamide and/or a platinum agent.[20] Other regimens included cisplatin; cisplatin in combination with vinblastine, dacarbazine, and interferon alfa 2B; vincristine as a single agent; or temozolomide with thalidomide, sorafenib, sirolimus, and IGF1R antibody.[20] Findings from this study showed only a 4% response rate to palliative chemotherapy.[20] The median progression-free survival with first-line chemotherapy was 11 weeks, and the median overall survival after initiation of chemotherapy was 39 weeks.[20] Similarly, in a study by Kawai et al of 75 patients with CCS receiving cisplatin-based chemotherapy regimens, the objective tumor response was low (23%).[21]

Because CCS responds poorly to chemotherapy and is histologically and clinically similar to malignant melanoma, the use of immune checkpoint inhibitors (ICIs) to treat CCS is of ongoing interest. In a case reported by Marcrom et al, a young woman with a bulky chest wall recurrence of mediastinal CCS had a complete clinical response after she was treated with pembrolizumab in combination with standard fractionated radiation.[22] Additionally, Tawbi et al noted some clinical responses to ICIs in patients with soft tissue sarcomas, with response varying based on tumor type.[23] Additional studies with larger sample sizes and randomized settings are needed to further evaluate the role of immunotherapy in treatment of CCS.

Although targeted therapies have revolutionized care for melanoma and other cancers, the role of targeted therapies in CCS has yet to be determined. In an observational study by investigators at The University of Texas MD Anderson Cancer Center comparing outcomes of ICIs and targeted therapy with standard chemotherapy, Jones et al reported finding no significant difference in overall survival between those receiving an ICI (15.9 months) or a targeted therapy (16.9 months) and those receiving chemotherapy (17.1 months).[24] Moreover, in CCS with a *MET* alteration, crizotinib has shown similar efficacy as doxorubicin-based chemotherapy.[25] The VEGFR inhibitor pazopanib is also being investigated in patients with advanced or metastatic CCS.[26] Again, further investigations are needed to determine optimal targeted therapies for advanced CCS.

Conclusion

Because of the difficulty in differentiating CCS from malignant melanoma based solely on histology and immunohistochemistry, our case suggests that there may be value in performing molecular testing if a clinical picture does not correspond with what is clinically expected for melanoma. It also raises the question about whether CCS cases may be underreported due to the difficulty in differentiating them histologically from melanoma. This case particularly highlights an uncommon presentation with hypercalcemia and cutaneous metastases that may not be recognized as a manifestation of CCS by an oncologist who does not specialize in sarcomas.

It is unclear how COVID-19 vaccination contributed to this patient's clinical presentation; these vaccines have been noted to cause transient lymphadenopathy, which was the "red herring" that led to the delayed diagnosis of cancer. It is also unclear whether an early diagnosis would have changed her clinical outcome, given the aggressive nature of the disease. The optimal systemic treatment for CCS has yet to be determined, and the rarity of CCS limits the information available via randomized control trials. The role of ICIs in the management of CCS remains an exciting avenue for future research, and participation in clinical trials under the care of sarcoma specialists should be encouraged. ■

SA drafted the discussion section, and BH drafted the case presentation sections of the manuscript; both reviewed and edited the manuscript. SH reviewed the manuscript. SL contributed pathology images and reviewed the manuscript. BS provided supervision and final review and editing of the manuscript. All the authors have read and approved the final version of this manuscript.

DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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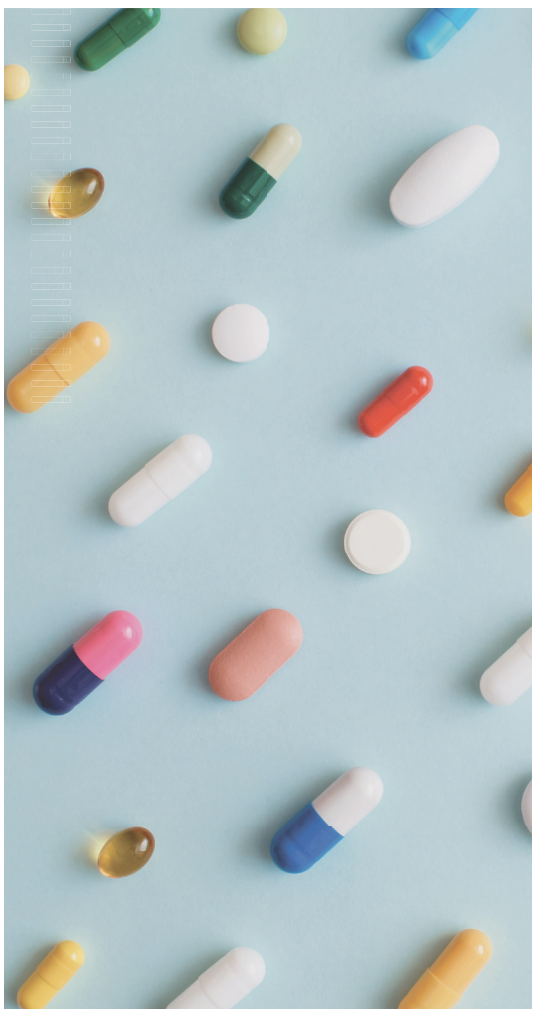
For references visit
cancernetwork.com/Sarcoma_10.23

MEET OUR EXPERT

Lucio N. Gordan, MD, president and managing physician at Florida Cancer Specialists & Research Institute

Price Gouging Among Shortages "Significantly Affects" Drug Supply

"There are just not enough studies to allow us to replace carboplatin [and] cisplatin with another class of drugs with the same level of comfort, from a scientific standpoint."



Shortages of cisplatin and carboplatin have had been felt across various institutions and communities as clinicians have to switch or adjust treatment to conserve the supply. Increases in pricing of almost 1700% from baseline have been observed, according to Lucio N. Gordan, MD.

Gordan went on to discuss how small institutions may have trouble acquiring the drugs because of price gouging, and patients will not be able to receive the treatment. He also discussed how certain organizations are trying to enact legislation to prevent a shortage like this from happening again.

Q: How has price gouging, because of the chemotherapy shortages, affected institutions across the United States?

GORDAN: Price gouging does not happen with a major group of purchase organizations or distributors in the country, like AmerisourceBergen, or Cardinal [Health]. There's not a level of concern there. However, there are smaller buyers that would acquire these drugs…and then release them when there is a [shortage]. We have seen a price [increase] up to 1700% from baseline. A drug that costs $30 per unit is going up to almost $400. This affects the shortage significantly.

Q: How has your institution responded to this situation?

GORDAN: We have allowed the purchase of some amount of drugs even at a higher price because we thought it was important to keep the patients on treatment with these lifesaving drugs. They're the backbone of several chemotherapy regimens, and many of these patients are receiving these treatments to improve cure rates. Essentially, the practice absorbs the cost, and we did invest the cost [in] the patient. We can do this for a while, but if the price increases or gouging is allowed to go unchecked—if a drug costs $1000 or $10,000, if you have price gouging of 200%, 300%, 1000%, or more—then it's impossible to stay in business and to get the drug to the patients.

The problem is that with some of these drugs that are in shortage—specifically, the platinum agents carboplatin and cisplatin—it is a financial problem because the price of these drugs got so low that it is not feasible for a manufacturer to produce these drugs. Most of us would be reasonable and…pay

a slightly higher price than the current [price] to allow improved supplies.

Q: Looking on a national scale, what should institutions be doing to compensate for these price increases?

GORDAN: It's very important that the large practices and institutions in the country stay united. The Community Oncology Alliance, the American Society of Clinical Oncology, and others are pushing legislation that would protect the consumer, the patients, and us to make sure that we have a proven supply. We have to make efforts to bring manufacturing back to the United States so we can make sure the quality is top-notch. If it stays overseas, there are ways to monitor quality as well. We need to make sure that we have a sustainable approach.

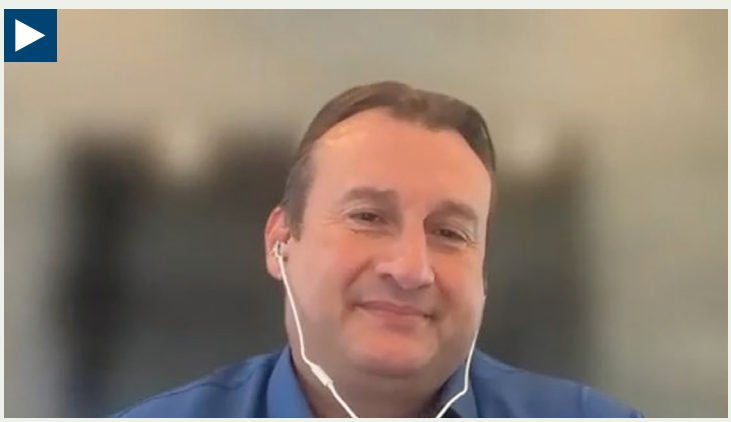
If there are ways that a drug can be replaced, we try to do drug replacement for another potential best second drug, but it's frequently a problem. There are just not enough studies to allow us to replace carboplatin [and] cisplatin with another class of drugs with the same level of comfort, from a scientific standpoint. Essentially, we need to stick together and try to work with the federal government and state governments to make sure that they understand the magnitude of the problem.

Q: What do you hope to see changed to avoid shortages and price gouging from happening again?

GORDAN: From a shortage standpoint, we need to make sure that we understand the mechanisms that bring the prices of the drugs down. It's important that Congress understand that. From a brand-drug standpoint, we understand there's enormous pressure on pharmaceutical companies to keep the prices under control; [it is] certainly a reasonable ask to help patients and consumers afford them. However, for generic drugs and other classes of drugs like biosimilars, there is a very profound erosion of pricing because these drugs are commoditized. The financial value goes down over time, quarter over quarter. Eventually, it gets to the point that it's not worth it for a manufacturer to produce such drugs to bring to us. The No. 1 [priority] is to fix that.

Without the financials working, there's no way we can force anybody to produce more drugs at a loss. How can we fix this? One is to stabilize and get to the bottom of pricing for specific drugs. Of course, there has to be a multitasking force that understands the problem and makes sure we find a fair number. The other way of doing this is [implementing] potential tax benefits for manufacturers that produce generics or some form of subsidizing the production of such drugs.

That's the most important part because, in my opinion, it's mostly a financial problem. We live in a very capitalist world, and it boils down to having a good end point for the manufacturer to [be willing to] bring the drug to the patients. ■



Watch: Strategies for Stabilizing Chemotherapy Prices During Ongoing Drug Shortage

Implementing tax benefits for manufacturers who produce chemotherapy drugs may be one solution to increase drug production in the United States, according to Lucio N. Gordan, MD.

To view the full video series with Gordan, visit:
https://www.cancernetwork.com/authors/lucio-gordan-md

Secondary Pure Red Cell Aplasia During Daratumumab/Hyaluronidase Therapy for Multiple Myeloma

Ludovic Saba, MD[1*]; Kevin S. Landau, MD[1*]; Silvia Bunting, MD[2]; Chakra P. Chaulagain, MD[1]

ABSTRACT

Predominantly autoimmune in origin, severe normochromic, normocytic anemia with reticulocytopenia in the setting of the normal production of leukocytes and megakaryocytic lineages is known as pure red cell aplasia (PRCA), which is unlike aplastic anemia in which all lineages are affected due to a stem cell defect. PRCA can be primary (such as autoimmune) or acquired, which can be an acute self-limited illness or a chronic disease that may be induced by medications, including immunotherapy such as monoclonal antibodies (mAbs). Daratumumab is a mAb directed against CD38 used for the treatment of multiple myeloma and systemic amyloid light-chain amyloidosis. The intravenous formulation of daratumumab received initial FDA approval, and later approval was received for the subcutaneous formulation daratumumab and hyaluronidase-fihj. The subcutaneous version increases patient convenience and has become the preferred route of administration since its approval. We herein present the case of a patient with multiple myeloma who developed acquired DNMT3A-positive PRCA while transitioning to daratumumab/hyaluronidase after initial treatment with daratumumab.

Anemia can take many forms, and like other diseases, the acquired or secondary cases can be induced by medications, including immunotherapy with monoclonal antibodies (mAbs). Pure red cell aplasia (PRCA) is a type of anemia that is predominantly autoimmune in origin; it is characterized by the presence of severe normochromic, normocytic anemia with reticulocytopenia (< 1%) and marked reduction of erythroblasts in the bone marrow (< 5%) in the setting of normal production of leukocytic and megakaryocytic lineages.[1] PRCA can be primary or secondary. It can sometimes be a transient self-limited illness or a chronic disease. Gérard et al reported a case of PRCA associated with nivolumab use for the treatment of metastatic melanoma.[2] PRCA shares myeloid neoplasm–associated gene mutations, such as the *DNMT3A* mutation that has been described as a driver for PRCA in patients with myeloid malignancies.[3] Located on chromosome 2p23.3, *DNMT3A* encodes DNA methyltransferase 3 alpha and is believed to be involved in de novo methylation. Additionally, *DNMT3A* is the most frequently mutated gene involved in clonal hematopoiesis of indeterminate potential, followed by mutations in *TET2* and *ASXL1*. It is not yet known whether *DNMT3A* mutation plays a role in the development of PRCA. This mutation could be an incidental finding, especially in the older population.[4]

CD38 is highly expressed on myeloma cells but has a relatively low expression on normal immune cells, making it an attractive target for treatment in patients with multiple myeloma (MM). Daratumumab is a humanized IgGκ mAb targeting a unique epitope of CD38 and has been approved in patients with MM and amyloid light-chain amyloidosis.[5] Due to reports of PRCA acquired from the use of other types of mAbs (**Table 1**[2,6-11]), cases of

PRCA occurring around the time of daratumumab use should be investigated as a potential etiology. Conversely, daratumumab has been shown to be the most effective treatment for PRCA after allogeneic stem cell transplant–induced PRCA (**Table 2**[12-21]).[6] In this manuscript, we are discussing an older patient who developed PRCA during daratumumab-based treatment for MM.

Case Presentation

THE CASE

An 83-year-old female patient with more than a decade-long history of pernicious anemia was referred to a hematologist in June 2013 because of worsening fatigue despite treatment with parenteral vitamin B^{12}. At the time, her laboratory results were as follows:

- **Serum IgG level:** 2060 mg/dL (range, 586-1602)
- **IgA level:** 74 mg/dL (range, 70-400)
- **IgM level:** 47 mg/dL (range, 40-230 mg/dL)
- **Monoclonal spike:** 1.69 g/dL (range, 0-0.001)
- **Free κ/λ ratio:** 0.5 (range, 0.26-1.65)
- **Total free λ level:** 26.3 mg/L (range, 5.7-26.3)

Serum immunofixation showed IgGλ monoclonal gammopathy. Her β_2-microglobulin level was 2.3 mg/L (range, < 2.16). Bone marrow showed less than 5% plasma cells, translocation t(11;14), and hyperdiploidy, as well as a gene expression risk stratification profile score of 22. However, no lytic lesions were present. She was diagnosed with monoclonal gammopathy of undetermined significance and was followed expectantly.

Starting in April 2018, the patient had multiple fractures, including her thoracolumbar vertebra, ribs, and jaw, for which a pathologic fracture was deemed a possibility. Hemoglobin and calcium levels were 9.8 g/dL (range, 11.5-15.5) and 11.8 mg/dL (range, 8.4-10.2), respectively, and her serum creatinine level was normal. A bone marrow biopsy in September 2018 revealed 20% involvement by clonal plasma cells and again the translocation t(11;14) that was detected in 2013, supporting the diagnosis of active MM requiring therapy.

Antimyeloma therapy was initiated in September 2019 with intravenous (IV) daratumumab at 16 mg/kg weekly, lenalidomide orally at 25 mg for 21 days on and 7 days off, and dexamethasone orally 20 mg weekly (DRd). Cycle 1 of DRd therapy was complicated by diarrhea and pancytopenia—with a white blood cell (WBC) count of 1380 K/μL (range, 3.70-11), a hemoglobin level of 7.8 g/dL (range, 11.5-15.5), and an absolute neutrophil count of 480 K/μL (range, 1.45-7.50)—requiring red blood cell transfusion and use of filgrastim. Therapy was held for 2 weeks and reintroduced with cycle 2 and cycle 3 with lenalidomide at a lower dose of 10 mg.

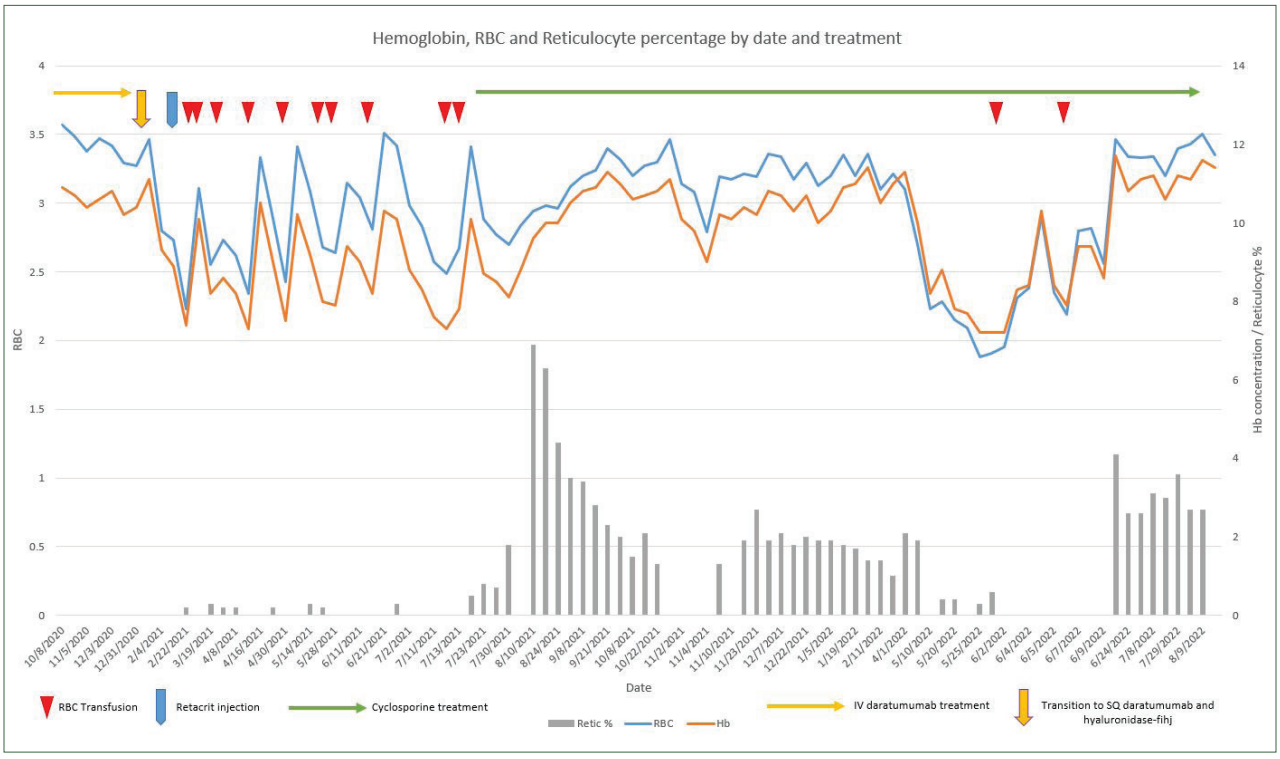
In December 2019, despite thromboprophylaxis with aspirin given at 81 mg daily, she experienced an acute deep venous thrombosis of the right lower extremity and was started on anticoagulation with rivaroxaban. Lenalidomide was discontinued permanently in December 2019 due to anemia, neutropenia, diarrhea, and acute deep venous thrombosis, and therapy was continued with IV daratumumab and dexamethasone. By June 2020, she achieved a very good partial response after daratumumab plus bortezomib and dexamethasone (DVd) was added to the regimen with the goal of achieving complete hematologic response. DVd therapy was given every 2 weeks due to her frailty and the multiple adverse effects (AEs) she had with the DRd regimen.

She tolerated the DVd therapy very well, and by December 2020, she achieved complete response. In January 2021, it was decided to switch from IV daratumumab to the subcutaneous (SQ) daratumumab and hyaluronidase-fihj for patient convenience; the goal was to use the SQ formulation once every 4 weeks as maintenance therapy. At the time of the transition, her WBC count was 9630 K/μL with normal differential counts, her hemoglobin level was 11.1 g/dL, and her platelet count was 239,000 (range, 150-400 K/μL).

Two weeks after the transition to the SQ formulation, her hemoglobin level dropped to 9.3 g/dL, but her platelet and WBC counts remained normal. Four weeks from the time of transition, the patient required 2 units of blood after a reticulocyte count of less than 0.2% (range, 0.6%-2.6%) and a further drop in hemoglobin level to 7.4 g/dL. **Figure 1** illustrates the trends in hemoglobin, red blood cell count, and reticulocyte levels over time, showcasing the impact of treatment. The levels of vitamin B_{12}, iron, folate, zinc, and copper were normal. Daratumumab/hyaluronidase therapy was discontinued, and she was monitored without any further anti–plasma cell therapy.

Parvovirus B19 DNA polymerase chain reaction test results were negative, and serology reported remote infection (normal immunoglobulin [IgM], elevated IgG). A bone marrow biopsy showed normal trilineage hematopoiesis, megakaryopoiesis, granulocytic maturation, and absent erythropoiesis consistent with PRCA (**Figure 2**). No clonal plasma cells were detected by flow cytometry, and immunohistochemistry reported rare CD38+ cells. A myeloid next-generation sequencing panel of 54 genes came back normal except for a clinically significant *DNMT3A* variant at

FIGURE 1. **Hb, RBC, and Reticulocyte Trend as a Function of Time and Treatment**



Hb, hemoglobin; IV, intravenous; RBC, red blood cell; reti, reticulocyte; SQ, subcutaneous.

splice acceptor site c.1475-1G>C.

A 60,000-unit dose of epoetin alfa injection was started weekly in May 2021. In June 2021, prednisone 1 mg/kg was added and given for 4 weeks without improvement in the patient's hemoglobin level. Cyclosporine 100 mg twice daily was then added for the treatment of PRCA. With the dual immunosuppressive therapy of prednisone and cyclosporine, her hemoglobin level improved to 10 g/dL, making her transfusion independent by week 4. Prednisone was dose reduced by 50%, and cyclosporine continued at the same dose.

By January 2022, she remained transfusion-dependent on a reduced dose of prednisone 10 mg daily and cyclosporine 50 mg twice daily. By the end of January, the patient was instructed to reduce cyclosporine to 25 mg twice daily and to continue prednisone at 10 mg daily. In June 2022, the patient was admitted to the hospital for 10 days for new-onset atrial fibrillation with rapid ventricular response. At that time, the patient's hemoglobin level had dropped to 7.2 g/dL. The patient had recurrent hypoproliferative anemia that required transfusion, consistent with recurrent PRCA. Hence, the cyclosporine dose was increased to 100 mg twice daily in addition to 60 mg of prednisone that was tapered to 40 mg over a 2-week period. Because her hemoglobin level rose to 11.1 g/dL in August 2022, prednisone was reduced to 20 mg and cyclosporine to 100 mg once daily, and she remained transfusion independent.

In early August 2022, the patient exhibited improvements in her anemia status. Nevertheless, despite her enhanced anemia condition and newfound independence from transfusions, she experienced a relapse later in the same month. A whole-body PET scan from September 2022 showed new fluorodeoxyglucose F18–avid myeloma lesions at T4 and the right first rib, indicative of relapsed myeloma. A restaging bone marrow aspiration/biopsy reported up to 15% λ light-chain restricted plasma, and a MM fluorescence in situ hybridization panel reconfirmed translocation t(11;14). She started venetoclax and dexamethasone in October 2022 and tolerated 1 cycle well. Unfortunately, 1 month later, the patient presented to the emergency department with acute abdominal pain. A CT scan showed pneumoperitoneum, highly suggestive of large-bowel perforation likely at the transverse colon from ischemic colitis. A subtotal colectomy with end ileostomy was performed. She was admitted to the intensive care unit for refractory septic shock that required support. Her course was complicated by multiorgan failure including shock liver and severe

TABLE 1. **mAbs Identified in Literature to Date That Induce PRCA2,[6-11]**

Authors	Year	mAbs inducing PRCA	Diagnosis	Title
Bennett et al[6]	2021	Atezolizumab	Unknown	"Atezolizumab-Induced Pure Red Cell Aplasia"
Meri-Abad et al[7]	2021	Pembrolizumab	Melanoma	"Unexpected Pure Red Series Aplastic Anemia Secondary to Pembrolizumab Treatment: A Case Report and Literature Review"
Gérard et al[2]	2020	Nivolumab	Melanoma	"Case Report: Successful Treatment of Steroid-Refractory Immune Checkpoint Inhibitor–Related Pure Red Cell Aplasia With Cyclosporin"
Isoda et al[8]	2020	Pembrolizumab	Hodgkin lymphoma	"Pembrolizumab-Induced Pure Red Cell Aplasia Successfully Treated With Intravenous Immunoglobulin"
Yuki et al[9]	2017	Nivolumab	Melanoma	"A Case of Pure Red Cell Aplasia During Nivolumab Therapy for Cardiac Metastatic Melanoma"
Elimelakh et al[10]	2007	Alemtuzumab and daclizumab	Post transplant of pancreas	"Red Cell Aplasia and Autoimmune Hemolytic Anemia Following Immunosuppression With Alemtuzumab, Mycophenolate, and Daclizumab in Pancreas Transplant Recipients"
Thachil et al[11]	2007	Alemtuzumab	Chronic lymphatic leukemia	"Campath-1H Induced Pure Red Cell Aplasia in a Patient With Chronic Lymphatic Leukaemia"

mAb, monoclonal antibody; PRCA, pure red cell aplasia.

metabolic encephalopathy coupled with anoxic brain injury. These events led to the patient's death.

Discussion

PRCA is an extremely rare condition that can be primary or secondary. It can be congenital, but most cases are acquired. The primary PRCA is an idiopathic autoimmune disorder in which an immune attack of erythroid precursor cells leads to underproduction anemia. Rarely, primary PRCA can be the initial presentation of a myelodysplastic syndrome.[12] The patient described in this case report developed hypoproliferative anemia in the setting of *DNMT3A* positivity, which may have a few potential etiologies. Although PRCA can be present congenitally, such as in infancy cases of Diamond-Blackfan anemia, it may also be acquired, such as during parvovirus B19 infection. For the latter, the patient should test positive for parvovirus B19 DNA and/or IgM, which was not the case for our patient. PRCA cases have been reported in association with hepatitis A, B, and C; HIV; Epstein-Barr virus; cytomegalovirus; and SARS-CoV-2/COVID-19.[3] All these serologies were negative in this patient.

Other associations of PRCA include immune disorders (autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, and ABO-incompatible hematopoietic stem cell transplant), hematologic neoplasms (chronic lymphocytic leukemia, large granular leukemia, Hodgkin and non-Hodgkin lymphoma, plasma cell neoplasms, chronic myeloid leukemia, primary myelofibrosis, and thymoma).

Finally, secondary PRCA can also be due to drugs (recombinant erythropoietin, mycophenolate, phenytoin, trimethoprim and sulfamethoxazole, and various mAbs) (**Table 1**). Drug-induced PRCA is a rare condition in which certain medications trigger immune responses, bone marrow suppression, alteration of growth factors, or autoimmune mechanisms that lead to a decrease or absence of red blood cell precursors in the bone marrow, resulting in anemia. These drugs can form immune complexes or directly interact with bone marrow cells, leading to immune-mediated destruction. Additionally, they can disrupt growth factors or trigger autoimmune reactions that target red blood cell precursors.[22]

The possibility of mAb-induced PRCA[1] crossed our minds, prompting us to request a bone marrow aspiration and biopsy that confirmed the diagnosis.

The 7 cases outlined in Table 1 represent mAbs reported in literature that induce PRCA. At the time of writing, the literature reports no cases of SQ

TABLE 2. **mAbs Identified in Literature to Date That Treat PRCA[12-21]**

Authors	Year	mAbs treating PRCA	Diagnosis	Title
Gangat et al[13]	2022	Daratumumab	Idiopathic PRCA	"Daratumumab for Treatment-Refractory Acquired Idiopathic Pure Red Cell Aplasia"
Sato et al[14]	2022	Alemtuzumab	Autoimmune polyendocrine syndrome type 1	"The Efficacy of Alemtuzumab for Pure Red Cell Aplasia Associated With Autoimmune Polyendocrine Syndrome Type 1"
Martino et al[15]	2021	Daratumumab	Post allogeneic hematopoietic stem cell transplantation	"Daratumumab May Be the Most Effective Treatment for Post-Engraftment Pure Red Cell Aplasia Due to Persistent Anti-Donor Isohemagglutinins After Major ABO-Mismatched Allogeneic Transplantation"
Jeyaraman et al[16]	2021	Daratumumab	Post allogeneic hematopoietic stem cell transplantation	"Daratumumab for Pure Red Cell Aplasia Post ABO Incompatible Allogeneic Hematopoietic Stem Cell Transplant for Aplastic Anemia"
Nieto-Benito et al[17]	2020	Ixekizumab	Psoriatic disease	"Anemia in a Psoriatic Patient Treated With Ixekizumab"
Rautenberg et al[12]	2020	Daratumumab	Acute myeloid leukemia	"Daratumumab for Treatment of Pure Red Cell Aplasia After Allogeneic Stem Cell Transplantation"
Bathini et al[18]	2019	Daratumumab	Myelodysplastic syndrome with refractory anemia with excess blasts type 2	"Refractory Postallogeneic Stem Cell Transplant Pure Red Cell Aplasia in Remission After Treatment With Daratumumab"
Chapuy et al[19]	2018	Daratumumab	Myelodysplastic syndrome	"Daratumumab for Delayed Red-Cell Engraftment After Allogeneic Transplantation"
Au et al[20]	2005	Alemtuzumab	T-cell large granular lymphocytic leukemia	"Alemtuzumab Induced Complete Remission of Therapy-Resistant Pure Red Cell Aplasia"
Zecca et al[21]	2001	Rituximab	Autoimmune hemolytic anemia with PRCA	"Anti-CD20 Monoclonal Antibody for the Treatment of Severe, Immune-Mediated, Pure Red Cell Aplasia and Hemolytic Anemia"

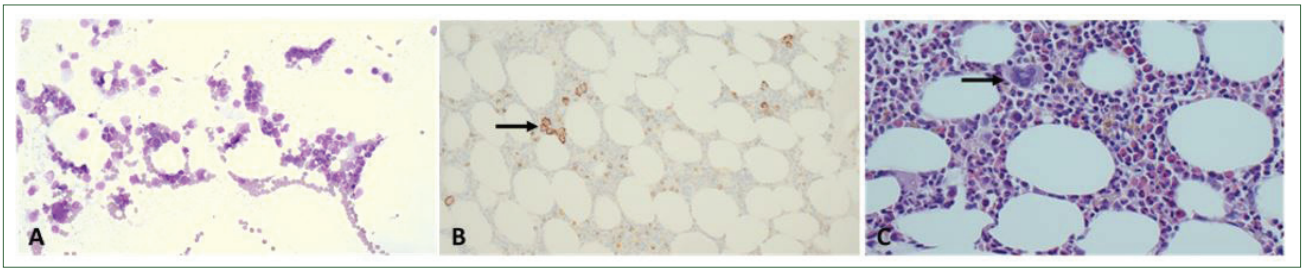
mAb, monoclonal antibody; PRCA, pure red cell aplasia.

daratumumab/hyaluronidase causing PRCA. The exact mechanism by which SQ daratumumab and hyaluronidase-fihj might induce PRCA is not fully understood, but we suggest a few potential explanations. First, daratumumab targets CD38, which is expressed in various cell types, including immune cells.[5] The immune response against CD38-expressing cells might inadvertently affect red blood cell precursors in the bone marrow, leading to PRCA. Another theory is immune-complex formation. Daratumumab could potentially form immune complexes with CD38 or other molecules in the bone marrow, leading to an immune response that damages red blood cell precursors. Lastly, the immune system—triggered by the daratumumab interaction with CD38-expressing cells—might mistakenly recognize red blood cell precursors as foreign due to their expression of CD38 or other related factors.[23] This could result in an autoimmune reaction against these cells.

In contrast, the 10 cases outlined in Table 2 represent mAbs reported in the literature that treat PRCA. Interestingly, 6 of 10 of the reported cases were treated with IV daratumumab, so it is with great interest that we further investigate why the patient presented here had induction of PRCA from daratumumab upon transitioning from the IV formulation to the SQ daratumumab/hyaluronidase formulation.

The transition from IV to SQ administration of daratumumab may lead to certain changes in drug exposure, pharmacokinetics, or immune interactions that could potentially contribute to the development of PRCA. The shift from IV to SQ administration might alter the interaction of daratumumab with immune cells, particularly those present in the SQ tissue. Changes in the immune cell activation or distribution could contribute to an immune response against red blood cell precursors. In addition, some patients might be more sensitive to changes in drug administration route or

FIGURE 2. **(A) Bone Marrow Aspirate, (B) CD138 Immunohistochemical Staining, (C) Core Biopsy**



(A) The bone marrow aspirate shows predominance of granulocytic lineage cells in different stages of maturation. No erythroid precursors are seen.
(B) This immunohistochemical stain for CD138 highlights the plasma cells in small clusters (arrow).
(C) The bone marrow core biopsy shows erythroid aplasia with absence of erythroid precursors and a predominance of granulocytic lineage cells and eosinophils. A single megakaryocyte is observed (arrow).

pharmacokinetics. Individual variability in immune responses also could contribute to the development of PRCA in response to the change in administration.[24]

It's important to note that the development of PRCA after transitioning from IV to SQ daratumumab is rare. We suggest that patients undergoing this transition be closely monitored by their health care providers for any signs of AEs, including anemia or changes in blood counts. If PRCA or any other concerning AE is suspected, appropriate medical intervention and management should be pursued promptly.

Conclusion

PRCA is a primary or secondary disorder that can be induced by drugs, including mAbs. Several mAbs used for various disorders have been reported to cause PRCA. However, at the time of writing, there are no reports in the literature of PRCA induced by the SQ form of daratumumab in a patient with myeloma who tolerated IV daratumumab well. We hope this case report can raise awareness to providers that the SQ daratumumab/hyaluronidase formulation has a potential association with secondary PRCA in patients with plasma cell neoplasms. ■

Ludovic Saba, MD; and Kevin S. Landau, MD, contributed equally to the creation of this manuscript.

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Neoadjuvant Immunotherapy in Melanoma: Where We Are and Where We Aren't

FACULTY

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Surgery is the definitive treatment approach for the majority of patients with cutaneous melanoma.[1] For patients with high-risk, resectable melanoma, adjuvant therapy with immune checkpoint inhibitors has been shown to improve recurrence-free survival and distant metastasis-free survival.[2-4] Now adjuvant immunotherapy has become a standard treatment option for patients with stage IIB-IIC, III, or IV melanoma.

This work has led to further exploration of immunotherapy as a neoadjuvant treatment approach. In this article, Sapna P. Patel, MD, chair of SWOG Melanoma Committee in Houston, Texas, provides insights into recent trials and future directions for neoadjuvant treatment of resectable melanoma.

Q: Can you describe what makes neoadjuvant therapy an attractive treatment approach for melanoma?

PATEL: We know that resection is definitive therapy for primary melanoma and even melanoma that might have spread to lymph nodes. But there has been this longstanding hypothesis that if you educate the immune system while the tumor is macroscopic and visible in the body, you will get a stronger immune response[5] than if you just take out the tumor outright, leaving behind only microscopic cancer, which is harder for the immune system to see. We know the traditional approach to stage III melanoma of surgery followed by adjuvant immunotherapy still leads to melanoma recurrence. And the reason there are recurrences is that, at that point, the immunotherapy is really working with an immune system that's having to look hard for the cancer. The cancer is at a microscopic level, and the immune system has to find that microscopic cancer and then become activated for the immunotherapy to be of any real benefit.

On the other hand, if you leave the tumor in place for a short period of time, specifically if you can feel that tumor, if you can measure it radiographically or see it (eg, clinically detectable), now the immune system is also more likely to see it. And when you give immunotherapy at that point it's going to prime an immune response against cancer that it can actually see and not invisible, microscopic cancer that it cannot see. Leaving the tumor in place for a period of time we believe educates the immune system better.

And that was demonstrated in a pilot study by Christian Blank, MD, PHD, called the OpACIN study [NCT02437279] where they treated 10 patients with traditional surgery then adjuvant immunotherapy, and 10 patients got preoperative immunotherapy, then surgery, and then postoperative [immunotherapy].[6] And what they found was that in the group that received preoperative immunotherapy, they had a numerical expansion of circulating T cells in the bloodstream, and they had a numerical increase of new clones from baseline. [There were] more diverse, more numerous T cells. The belief was you actually gave these patients a richer antitumor immune response.

We put that into practice with THE PHASE 2 SWOG S1801 [NCT03698019] where we randomly assigned patients with resectable, clinically detectable melanoma.[7] Participants with stage IIIB-IV melanoma were randomly assigned to the traditional removal followed by a year of adjuvant pembrolizumab or 3 doses of preoperative pembrolizumab [Keytruda], then surgery, and then 15 doses of adjuvant pembrolizumab. Importantly, both arms of the study received numerically the same amount of pembrolizumab: 18 doses. There's sometimes a slide I see going around that says it's standard of care adjuvant therapy plus 3 doses preoperative. The neoadjuvant-adjuvant arm was not numerically more pembrolizumab; it's the same number of doses. We did that for a reason…to make both arms cost-neutral because we know around the world, globally, some health care systems are funded at a national level. We didn't want to make one regimen more expensive than the other.

Additionally, the surgery was the same in both arms. Before a participant was randomly assigned, the surgeon had to say, "My plan is to do… this type of lymph node dissection and/or wide local excision of the primary melanoma." And even if the patient experienced an excellent response to neoadjuvant therapy, the surgeon could not de-escalate their procedure, they were required to do the same surgery they planned from the outset. And, hats off to these surgeons, I would say by and large that's exactly what they did. They followed the rules. If anything, they escalated surgery [as needed]. So one of the key takeaways with neoadjuvant immunotherapy is you're receiving preoperative therapy and you're still going to surgery. We've not demonstrated that you can remove or even minimize surgery at this time, and you're still ideally going to receive some form of adjuvant therapy.

We've not proven that you can take away or de-escalate surgery or adjuvant therapy. Those are all future initiatives that we hope to prove with randomized studies. To date, the trials that are testing de-escalation have been non-randomized, so it is unclear if the approach is superior to another approach. The other thing to remember is if you give neoadjuvant immunotherapy and the patient's cancer grows, that's not a failure of treatment. It's not a failure if you're still able to go to surgery. Remember in the adjuvant setting, everybody's going to surgery and then getting some adjuvant therapy. In

that period of time before you go to surgery, there might be some growth. We don't call that "failure due to waiting," "failure due to scheduling." We still go to surgery and put our heads down and prescribe adjuvant therapy. As long as the tumor can come out, the immunotherapy may still have done its job stimulating the immune system and clonally expanding more T cells. There is no requirement that a short course of neoadjuvant immunotherapy shrinks the cancer. You just want to be able to still have operable disease. Reduction of the tumor with a short course of treatment is not the goal. The goal is priming of the immune system with intact tumor in situ. In this short period, the immune system may very well have begun expanding, but it may not yet have trafficked to the tumor/lymph node to begin active immune-mediated cell killing. So reduction of tumor size or major effect on the histopathology of the tumor is not a requirement for neoadjuvant immunotherapy success (at this time). Once we begin comparing neoadjuvant regimens in a randomized fashion, we might establish that these are indicators of a more optimal outcome, but the absence of these clinical biomarkers [eg, radiographic or pathologic response] is not an indication of immunotherapy treatment failure in the neoadjuvant setting.

Q: In SWOG S1801, what made you choose to move only 3 doses of pembrolizumab into the neoadjuvant setting?

PATEL: I hate to tell you this, [but] it's arbitrary, not evidence-based…If you go back to the International Neoadjuvant Melanoma Consortium, they will say it's this amount of neoadjuvant treatment, but nobody compared different durations head-to-head. It's not that somebody gave 1 dose to 50 patients, then they gave 2 doses to 50 patients, then they gave 3 doses and compared outcomes. Nobody's done that. It's somewhat arbitrary.

If you go back to the receptor occupancy data with nivolumab, 4 of these every-2-week doses at 0.1, 1.0, 3.0, and 10.0 mg/kg, receptor occupancy was around 70%. So nivolumab was blocking about 70% of the PD-1/PD-L1 interaction after 8 weeks. We know that it sits on that receptor a long time, with a half-life of about 25 days. How much is occupied after 1 dose of nivolumab? There are many believers, and a University of Pennsylvania [study] suggested,…that a single dose [of pembrolizumab] was effective, and it may be that the majority of receptor occupancy is happening after that single dose.[8] Then doses 2, 3, and 4 (or however many you're giving) may just give the patient more toxicity because the receptors are already adequately blocked. Back to your original question, how did we decide on 3? It's fairly arbitrary. There have been no head-to-head studies. We tried to align ourselves with the International Neoadjuvant Melanoma Consortium, but there is certainly room to do a head-to-head study of the optimal duration of neoadjuvant therapy, randomized, and powered for efficacy.

Q: For the small (n = 4) proportion of patients with mucosal melanoma, outcomes appeared to be impressive. How do you interpret these findings in the context of historically disappointing results with immunotherapy?

PATEL: The honest academic in me should tell you that we cannot draw any conclusions. It's 4 patients. They were all randomly assigned to neoadjuvant immunotherapy. I really cannot tell you that neoadjuvant is better than adjuvant for this population because we had no mucosal participants in the adjuvant-only arm. In the real world, if we have these patients show up in clinic with what we think is a resectable mucosal melanoma, it seems reasonable to consider this neoadjuvant-adjuvant approach.

Q: What do the SWOG study results indicate for using neoadjuvant immunotherapy in contemporary practice?

PATEL: It's randomized phase 2 data, and the pure statistical analysis would say this was a striking result. It was powered on a small sample size, so we could be making a sample size error in believing the study result. However, the difference was strikingly statistically significant at a *P* value of .004. It seems like we're not making a major leap to assume neoadjuvant is better based on the study results; it is a strongly positive result for a phase 2 study. But it does not meet the level of FDA approval, which requires randomized phase 3 data or a confirmatory study after a positive phase 2 finding. It does, however, meet the approval standard for Australia's regulatory agency and pharmaceutical benefits administration. They are the first regulatory authority in the world to recognize these data as practice changing, and now patients in Australia with stage III melanoma can get neoadjuvant pembrolizumab covered. That's huge. That's thousands and thousands of [Australian patients with] melanoma patients where tens of thousands of them in the US still don't necessarily have a reimbursement option.

What I think it says for Americans is that we need to consider this, and I think guidelines will get updated. EORTC [European Organisation for Research and Treatment of Cancer] and NCCN [National Comprehensive Cancer Network] guidelines will suggest neoadjuvant immunotherapy as a high-level treatment option,

but ultimately if we want regulatory approvals in these more traditional countries (eg, Europe, United Kingdom, United States) we're going to have to do a randomized phase 3 study or we're going to have to move on and say, we're going to try something else in a randomized phase 3 fashion, and neoadjuvant pembrolizumab simply broke the mold.

Q: We continue to see small signals that patients with a complete response (CR) may be able to safely forgo surgery, as happened with 1 patient in S1801. What would we need to see to make this an approach that can be routinely offered to patients achieving a CR?

PATEL: I think we have to do a randomized trial. I think we need a study that randomly assigns patients with a pathologic CR on index node removal to either a therapeutic lymph node dissection or no further surgery. There are some clever surgeons in our field who are actually designing that. Then we can move forward and say we can now de-escalate surgery in these individuals. Let's say we have a neoadjuvant therapy that is far more clinically effective than single-agent pembrolizumab…, and you start to see a higher radiographic response rate. Then you can design a study that takes that group of patients who've had radiographic responses, and you randomly assigned them. Half of them still have to go to the surgery that was planned, and half of them can forgo it or minimize it…Is the recurrence rate different in those [who] de-escalated surgery? That's what we learned in breast cancer. When they used neoadjuvant chemotherapy and de-escalated surgery, there were more in-breast recurrences in the group that did a lesser surgery, so maybe you should have done neoadjuvant [therapy] but [combined with] the big surgery all along. Chemotherapy is a different animal than immunotherapy. There's no memory that's being formed, but maybe that's a study we need to do. When a patient exhibits a radiographic response, they get randomly assigned to no surgery (or less surgery) versus the traditional surgery.

Q: Given the reduced number of events in the neoadjuvant arm during adjuvant therapy, should we still be giving a full year of adjuvant pembrolizumab?

PATEL: That is really asking if the benefit of neoadjuvant-adjuvant immunotherapy is driven by the neoadjuvant portion or the first few doses of adjuvant therapy or the full regimen (neoadjuvant + adjuvant). [What] you're referring to [in the question] regarding the reduced number of events is the lollipop plot that we presented and published in the supplementary appendix of the S1801 manuscript where it shows [when] in the treatment period the events occurred. And in the adjuvant arm, of course, some of them are happening even before the initiation of adjuvant therapy. It's the first time we've ever been able to count those [events] in an adjuvant group. [From the patient's perspective:] You thought you were disease-free: You went to surgery that was supposed to remove all the melanoma, and just before you [started] your adjuvant treatment, the melanoma has already recurred. We can now quantify that number or frequency. Those patients are not counted in any of our sentinel adjuvant therapy clinical trials where all patients were free of disease at the time they started the treatment. Now, we can quantify what percentage that is, and it is slightly more than 10% of the [population with]resected stage III.

The majority of events on S1801 happened in the adjuvant period in the adjuvant arm. By comparison, less than half of the events in the neoadjuvant-adjuvant group are happening in that adjuvant period. If that's the case, do you need that full year of therapy? Where is the benefit coming from? Again, [we] probably have to go slow and be methodical and design a study of neoadjuvant-adjuvant, just like S1801, compared with neoadjuvant and 6 months of adjuvant or neoadjuvant alone. Those are boring and unsexy studies, but we can do them, and there is enthusiasm for these safely designed studies in community oncology.

Q: If neoadjuvant therapy were a standard option you could routinely offer patients, how would you decide when to offer this perioperative approach vs adjuvant only?

PATEL: The conversation at tumor board now goes like this. I've got a [patient with stage III disease], but I'm not sure if I want to give them neoadjuvant immunotherapy. Because I'm in an academic center, the conversation [generally goes like this]: I'm not sure if I want to give them neoadjuvant pembrolizumab…or nivolumab/ipilimumab or nivolumab/relatlimab. But regardless, my answer is this. If the patient had gone to surgery first and had then shown up in your clinic, were you going to give them adjuvant therapy? And if the answer is "Yes, I was going to give them adjuvant therapy," then based on S1801, you swing a few of those doses before surgery, and you give it to them preoperatively. If you were already thinking of adjuvant therapy, then I believe you need to give this patient neoadjuvant immunotherapy, since S1801 suggests neoadjuvant-adjuvant does better than adjuvant only…[If] a patient were to come to you preoperatively, [and] there's no way you would touch [give the patient] adjuvant therapy because

they have some medical contraindication, [then] of course you wouldn't want to give them neoadjuvant, either.

[There is also this question] of which neoadjuvant immunotherapy would you give them: single agent or combination. That's not really a discussion that's ready for clinical, reimbursable practice right now. [What] has to be studied [in a clinical trial is whether a] single agent vs a combination neoadjuvant immunotherapy gives [patients a] different survival benefit. Pathologic CR is a really cool biomarker, [but] that's not a clinical trial end point for community practices. That's an end point where you want to flesh out some nuances academically. A pathologist in routine practice is not going to take the time to perform a nuanced pathologic assessment because it is not the current standard of care, nor are they reimbursed for the extra time it takes to do this type of assessment. They're going to do their normal assessment and tell you if there's tumor present, period. They're not going to give you the percentage of pathologic response. As a medical oncologist, the outcome you care about is whether the melanoma came back, and did the patient die from their melanoma? Those are clinical end points you're following with physical examination and scans, not poring over pathology reports for percentage of pathologically viable tumor vs necrosis, fibrosis, etc.

Determining the optional neoadjuvant regimen is within our grasp. We need to design a study of single agent vs combination immunotherapy, and look at 2 years, 5 years, and 10 years at the event-free survival and recurrence-free survival. You don't decide based on whether there is massive shrinkage or more pathological response. As I said at the beginning, focusing on tumor reduction in the perioperative period is wrong. We're not asking the immunotherapy to shrink these cancers. We never do that with immunotherapy. Immunotherapy is focused on boosting the immune system side of the tumor–T-cell equation. When you're giving immunotherapy, the immune system takes time to be primed and educated, and the tumors might actually grow during the early period. As long as a tumor remains resectable and there is no distant spread, the clinical end point of melanoma-free survival is the most facile for clinical practice. We are looking at correlatives in S1801 to demonstrate this immune cell priming did in fact occur. And with a follow-up study of single agent vs combination therapy, maybe a less toxic regimen will emerge, on par for survival with toxic combination therapy. The financial impact is not only in drug costs but also in [lower] health care costs with a less toxic regimen. And this has implications globally for national health care systems. I think we just don't know the optimal neoadjuvant regimen at this point. All we know is single-agent pembrolizumab. If you're planning to give adjuvant anti–PD-1, consider giving it neoadjuvant-adjuvant.

Q: What other trials are you watching in the neoadjuvant space? Will there be further readouts in the next year?

PATEL: The phase 3 NADINA [NCT04949113] trial is the next study we're really excited about. It's neoadjuvant inverted dosing of ipilimumab/nivolumab [for] 2 doses followed by surgery versus the adjuvant approach, which is surgery and then adjuvant PD-1. In the NADINA study, in the neoadjuvant group, after you take neoadjuvant immunotherapy and go to surgery, based on the pathologic response, you can then either forgo adjuvant therapy or continue with some adjuvant therapy, and [if you have a *BRAF* mutation], you have the choice of moving to targeted therapy. So there are a few more variables in the NADINA study, but the fact that it investigates neoadjuvant combination immunotherapy is good, and eventually we'll end up doing these cross-trial comparisons, which are going to be invalid statistically, comparing [the neoadjuvant arm of] S1801 with the NADINA neoadjuvant arm. Ultimately, we're going to have to look at 2-year event-free survival, 2-year recurrence-free survival, and overall survival.

If those end points are not that different, it really doesn't matter what's happening pathologically or radiographically, but then the impetus would be to do a trial solely comparing these 2 neoadjuvant regimens, taking survival end points and also cost and toxicity into account.

As far as other readouts for S1801, we will be presenting pathological response data shortly. Not every [patient with neoadjuvant melanoma] is the same. Maybe there are some groups that benefit more from this approach than others. And we are trying to design neoadjuvant studies in other kinds of melanoma and nonmelanoma skin cancer spaces. ■

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