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ONCOLOGY®

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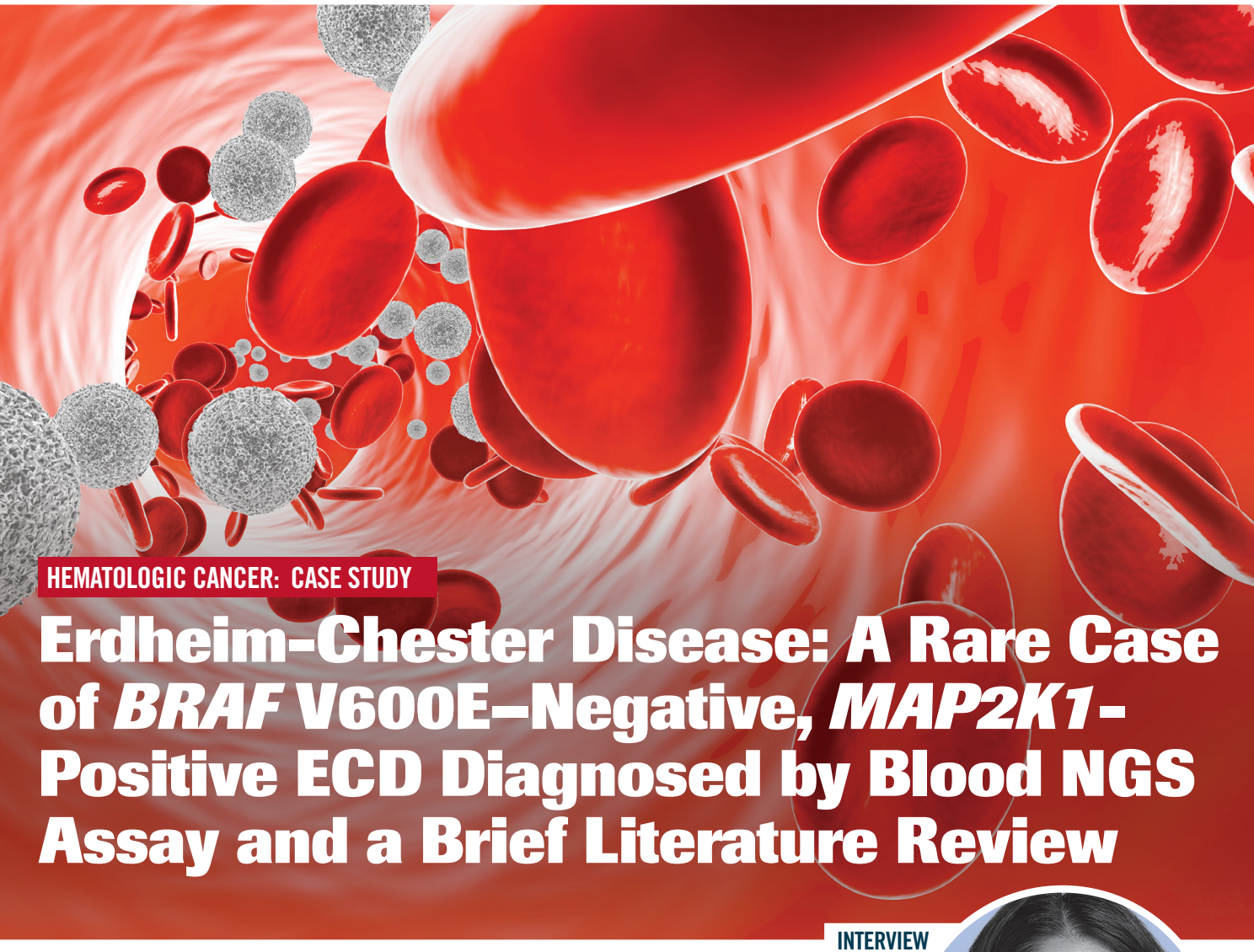

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RYBREVANT®
(amivantamab-vmjw)
Injection for IV Use | 350 mg/7 mL (50 mg/mL)

ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of *EGFR*+ mNSCLC, few challenges have been tougher to navigate than *EGFR* exon 20 insertion mutations.[1-10]

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with ***EGFR* exon 20 insertion mutations,** as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[11]

INDICATION

RYBREVANT® (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions

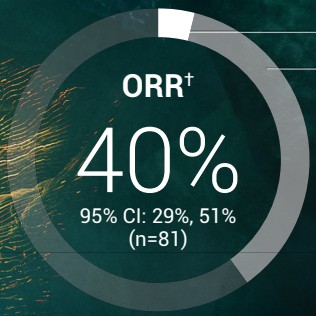
RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

In a multicenter, open-label, multicohort study[11]*

Results for tough-to-treat disease



- 3.7% of patients achieved a CR
- 36% of patients achieved a PR

- Efficacy was evaluated by ORR† and DOR[11]

MEDIAN DOR WAS 11.1 MONTHS[11]‡
(95% CI: 6.9, NE)[11]

*CHRYSALIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBREVANT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had *EGFR* exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBREVANT® was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.[11]

†According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).[11]

‡Based on Kaplan-Meier estimates.[11]

The safety of RYBREVANT® was evaluated in the CHRYSALIS* study (n=129)[11]:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity[11]
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%)[11]
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%)[11]
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion[11§]

§Based on the safety population, N=302.

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CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non-small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT®.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Please see Brief Summary of full Prescribing Information for RYBREVANT® on subsequent pages.

References: 1. Clinical Test Report: Oncomine™ Dx Target Test US. Thermo Fisher Scientific. Accessed October 13, 2021. https://tools.thermofisher.com/content/sfs/brochures/oncomine-dx-target-test-sample-report.pdf **2.** Chiang AC. *BMC Cancer*. 2020;20(1):356. **3.** Robichaux JP. *Nat Med*. 2018;24(5):638-646. **4.** Riess JW. *J Thorac Oncol*. 2018;13(10):1560-1568. **5.** FoundationOne®CDx. Technical specifications. Foundation Medicine. Accessed October 13, 2021. https://assets.ctfassets.net/w98cd481qyp0YqqKHaqQmFeqc5ueQk48w/0a34fcdaa3a71dbe460cdcb01cebe8ad/F1CDx_Technical_Specifications_072020.pdf **6.** Arcila ME. *Mol Cancer Ther*. 2013;12(2):220-229. **7.** Oxnard GR. *J Thorac Oncol*. 2013;8(2):179-184. **8.** Naidoo J. *Cancer*. 2015;121(18):3212-3220. **9.** Chen D. *Onco Targets Ther*. 2016;9:4181-4186. **10.** Girard N. Presented at: IASLC 2020 World Conference on Lung Cancer; January 28-31, 2021; Singapore. **11.** RYBREVANT® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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cp-213274v2

RYBREVANT (amivantamab-vmjw) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in Full Prescribing Information]*, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population *[see Adverse Reactions]*, IRR occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Interstitial Lung Disease/Pneumonitis

RYBREVANT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population *[see Adverse Reactions]*, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Dermatologic Adverse Reactions

RYBREVANT can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population *[see Adverse Reactions]*, rash occurred in 74% of patients treated with RYBREVANT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients *[see Adverse Reactions]*.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Ocular Toxicity

RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population *[see Adverse Reactions]*, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT. *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions]*
- Ocular Toxicity *[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.

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash and paronychia.

The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

Table 1 summarizes the adverse reactions in CHRYSALIS.

Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

Adverse Reactions	RYBREVANT (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue[b]	33	2.3
Edema[c]	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia[d]	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[f]	37	2.3
Cough[g]	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis[h]	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain[i]	11	0.8
Vascular disorders		
Hemorrhage[j]	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy[k]	13	0
Dizziness	12	0.8
Headache[l]	10	0.8

[a] Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis

[b] Fatigue: asthenia, fatigue

[c] Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling

[d] Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis

[e] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[f] Dyspnea: dyspnea, dyspnea exertional

[g] Cough: cough, productive cough, upper airway cough syndrome

[h] Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis

[i] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[j] Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage

[k] Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy

[l] Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

RYBREVANT™ (amivantamab-vmjw) injection

Table 2 summarizes the laboratory abnormalities in CHRYSALIS.

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT+ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

+ The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

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 amivantamab products may be misleading.

In CHRYSALIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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.

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in

multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivantamab-vmjw in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

Pediatric Use

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

Geriatric Use

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions *[see Warnings and Precautions]*.

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions]*.

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT *[see Warnings and Precautions]*. Advise patients to apply alcohol free emollient cream to dry skin.

Ocular Toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions]*.

Paronychia

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. *[see Warnings and Precautions, Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose *[see Use in Specific Populations]*.

Product of Ireland

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

cp-213278v1

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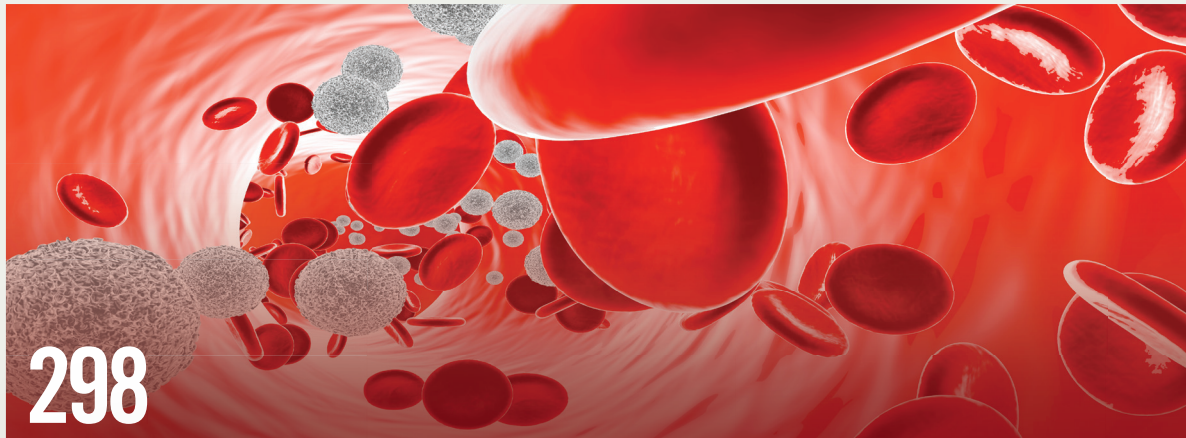

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Ankita Aggarwal, MD[1]; Mackenzie Taychert, DO[1]; MHD Louay Hasanin, MD[2]; Donald Doll, MD[3]; Mira Gabrielle Basuino,BS[1]; Hassan Hasanein, MD[3]

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PUBLISHER'S NOTE

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

William J. Gradishar, MD, FACP
Breast Cancer Editorial Board Member
In April, Gradishar, chair of the National Comprehensive Cancer Network's Guidelines Panel for Breast Cancer, helped to publish new guidelines for patients with inflammatory breast cancer. These new guidelines outline systemic therapy treatment to shrink the tumor, surgery options to remove the breast and lymph nodes, and radiation therapy.

Shubham Pant, MD, MBBS
Gastrointestinal Cancer Editorial Board Member
At the 2023 American Society of Clinical Oncology Annual Meeting, Pant presented results from the phase 2 HERIZON-BTC-01 trial (NCT04466891). This study analyzed zanidatamab in patients with HER2-positive biliary tract cancer. Topline results included a median duration of response of 12.9 months and a median follow-up of 12.4 months. Additionally, 49% of responders had an ongoing response, and 82% had a response for longer than 16 weeks.

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PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

JULY 2023 ▪ VOL. 37 ▪ NO. 7

PROSPECT: A Study Whose Time Is Past

Howard S. Hochster, MD
ASSOCIATE DIRECTOR FOR CLINICAL RESEARCH,
RUTGERS CANCER INSTITUTE OF NEW JERSEY
DIRECTOR OF ONCOLOGY RESEARCH,
RWJBARNABAS HEALTH

First of all, kudos to Deb Schrag, MD, MPH, and all the investigators of the phase 2/3 PROSPECT trial (NCT01515787) for achieving and completing this landmark study.[1] In appreciating its significance, it is helpful to turn back the hands of time to the 1980s. At this time the Gastrointestinal Tumor Study Group performed a 4-arm randomized study in adjuvant therapy of rectal cancer, showing for the first time that both radiation and chemotherapy were better than surgery alone but that the combination of both had the best outcome.[2] This study set the stage for an era of surgery, followed by adjuvant chemotherapy and radiation, with radiation sandwiched in the middle 2 months of the 6-month adjuvant program. We also note that, at this time, the standard 5-fluorouracil (5FU)-leucovorin treatment was the "Mayo regimen" with 5 days of bolus of 5FU.

The next major advance in rectal cancer therapy came with the concept of preoperative chemoradiation therapy. Over time, physicians realized that a major long-term toxicity of the postoperative approach described above was many patients having the late adverse effects (AEs) of significant rectal strictures. These patients, after being cured, lived a life with bowel dysfunction. Many of them eventually required colostomy to function relatively normally at work and in daily activities.

This led to the German randomized trial of preoperative chemoradiation (with adjuvant chemotherapy) vs the standard of care, postoperative therapy, whose results demonstrated better local control and equal survival but, importantly, fewer long-term AEs.[3] This changed the rectal cancer paradigm to preoperative chemoradiation followed by surgery, followed by 4 to 6 months of adjuvant chemotherapy. Additionally, at the same time, emerging data on rectal surgery suggested that local recurrence in the pelvis could be reduced using a more technically complete surgical approach of total mesorectal excision (TME). This approach, using sharp dissection along the natural tissue planes, and keeping the mesorectal fascia intact, was superior to the prior technique of blunt dissection, using the surgeon's fingers to mobilize the rectum. With the use of TME, the need for radiation for local control was called into question once more.

It is in this context that the PROSPECT trial was framed about 12 years ago (opening to accrual in 2012), asking the question: Does every patient need chemoradiation after neoadjuvant chemotherapy, in the setting of better surgery and good response to chemotherapy? This was a groundbreaking study, attempting to show that we are overtreating some patients who do not require it. In this study, the "neoadjuvant" therapy functions like a biomarker test for responsive patients with 20% or greater shrinkage as marking a good prognosis with chemotherapy and not needing radiation.

The PROSPECT study unequivocally showed, using a large noninferiority design of 1200 patients, that radiation is not always necessary. For patients with radiographic T2-3 and/or N1 rectal cancers, those who respond to the "chemotherapy test" with more than 20% shrinkage have the same outcome for local recurrence and survival when treated with chemotherapy and surgery as those who received the standard chemoradiation followed by surgery and adjuvant chemotherapy—as proved by noninferior outcomes. We offer a huge "bravo!" to those investigators and patients who participated in the study, and to study leadership in showing we can reduce the amount of toxic therapy.

More recently, progress in the treatment of rectal cancer is focused on the total neoadjuvant therapy (TNT) approach. In this treatment paradigm, chemotherapy and chemoradiation are moved up front and surgery is performed last, and only if necessary. Most importantly, this approach maximizes the number of patients with a clinical complete response (CR) and pathologic complete response (pCR) who may be spared surgical resection. This is particularly important for low-lying cancers, which would otherwise require an abdominoperineal resection. The nonoperative management (NOM) approach was first documented by Angelita Habr-Gama, MD, PhD, in Brazil.

Most recently, findings from the phase 2 OPRA trial (NCT02008656), led by Julio Garcia-Aguilar, MD, PhD, at Memorial Sloan Kettering Cancer Center, showed a high NOM rate and an improved pCR status for patients treated with chemoradiation followed by chemotherapy, compared with the opposite sequence.[4] The TNT approach is now favored by the US community in an attempt to spare patients from rectal surgery.

In many respects, the PROSPECT trial has been superseded by advances in therapy for rectal cancer, particularly with the TNT and NOM approaches that eliminate some surgeries rather than radiation. Nonetheless, the PROSPECT trial was a massive undertaking with a 1200-patient sample size. Such a large sample size for a rectal cancer trial has never been achieved in the United States previously. With this noninferiority approach, we can accept the fact that it is safe to treat responding patients without rectal radiation using the chemotherapy-first approach. However, in 2023 the field has moved on from this to the use of TNT and NOM. We do note, though, that there are no large comparative trials to demonstrate the equal efficacy of TNT vs conventional therapy as of this date. We again express our gratitude to the PROSPECT leadership and investigators for showing us an undisputed path to reducing debilitating cancer treatments by adapting treatment to response. ■

For references visit
cancernetwork.com/7.23_LTR

MEET OUR EXPERT

Sara M. Tolaney, MD, MPH, is the chief of the Division of Breast Oncology and the associate director of the Susan F. Smith Center for Women's Cancer; senior physician at Dana-Farber Cancer Institute; associate professor of medicine at Harvard Medical School in Boston, MA; and faculty on the 21st Annual Meeting of the School of Breast Oncology®, hosted by Physicians' Education Resource®, LLC (PER).

T-DXd Has Revolutionized the Standard of Care in Breast Cancer

"I'd love to see us figure out a way to optimize treatment and personalize care. Biomarkers will help us get there, but we also need to be bold in our clinical trial designs."

Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) has been at the forefront of the breast cancer community since the positive readout of the phase 3 DESTINY-Breast04 trial (NCT03734029) at the 2022 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois. These results ultimately led the FDA to approve this treatment in patients with unresectable or metastatic HER2-low breast cancer who received prior chemotherapy in the metastatic setting or experienced disease recurrence within 6 months of treatment.[1]

Sara M. Tolaney, MD, MPH, sat down with *ONCOLOGY* to discuss how T-DXd has affected the current standard of care and where future efforts are focused to improve treatment options. She also examined unmet needs in the breast cancer space and advocated for more clinical trials involving biomarkers to help optimize therapy.

Q: Are there any treatments on the horizon that can affect the standard of care?

TOLANEY: There are some treatments coming along that could [affect] our standard of care. One such drug is T-DXd. We've already seen, in the metastatic setting, the tremendous benefits of T-DXd; head to head, it's better than T-DM1 [trastuzumab emtansine; Kadcyla]. That raises the question: Could T-DXd replace T-DM1 in early-stage disease? The phase 3 DESTINY-Breast05 trial [NCT04622319] is currently studying this [question].

The question comes up of [whether] T-DXd could replace all the preoperative chemotherapy. For example, there's a trial that's looking at replacing AC [doxorubicin and cyclophosphamide] plus THP [docetaxel, trastuzumab, and pertuzumab (Perjeta)] with T-DXd, or replacing half of it, so replacing the AC with 4 cycles of T-DXd and following up with THP. That agent does seem very promising given what we've seen in the metastatic setting. There are some toxicity concerns that come up, particularly the risk of interstitial lung disease. We will have to look at the efficacy data from these trials and balance them with potential toxicity to figure out how [they] fit in. [T-DXd] has the potential to change the standard [of care].

Q: Can you speak to the importance of the multidisciplinary approach in the breast cancer space?

TOLANEY: Multidisciplinary care in breast cancer is so critical right now. Patients [who come to] Dana-Farber with a new breast cancer diagnosis are seen in combination with our surgical oncologists and sometimes a radiation oncologist up front with the medical oncologist. The reason for this is that these decisions are complicated. Does it make sense for the patient to get systemic therapy before surgery? What about additional tests that need to be done before preoperative therapy? Do they need a lymph node biopsy? What if there's an area on the imaging that concerns

the surgeon and they want a biopsy to understand [whether the patient] will be a candidate for breast conservation? Even more complicated is this whole issue of nodal evaluation at the time of surgery. Can they get away with [evaluating] the sentinel node alone? Do they need an x-ray dissection? Will that influence decisions regarding radiation? Could that change systemic therapy recommendations? It's so complicated, and it's nice to be able to have these multidisciplinary discussions with our colleagues so that we make the right decisions for each individual patient.

Q: Looking ahead, what are some unmet needs in the space that you hope are overcome?

TOLANEY: We've been successful in early-stage HER2-positive disease. We're curing more and more patients, and we're doing so in a way in which toxicities are thoughtfully considered. We are giving some patients too much therapy and some [patients] too little therapy. I'd love to see us figure out a way to optimize treatment and personalize care. Biomarkers will help us get there, but we also need to be bold in our clinical trial designs. We're learning how to design de-escalation studies, but they're tricky because you don't want to undertreat a curable patient and leave them with a recurrence. [These clinical trials] have to be conducted thoughtfully.

We always want to get patient advocates involved in such designs as well. The optimal duration of HER2-directed therapy is still not known. We've done multiple trials, but we're still giving a year of trastuzumab-based treatment. Does everyone need that? Can some [patients] get away with less? Who's going to need T-DXd in the time to come? We're going to need to figure that out because there are some potential toxicities. [We want to know whether] some patients can get away with fewer toxic regimens. Who can get away with no chemotherapy? There are patients who can get away with [no] chemotherapy at all, who can just receive antibody-[drug conjugates]. We don't have predictors [that are] robust enough, and we need to get there. So we'll continue to see things evolve as we learn how to integrate biomarkers into the early-disease setting.

Q: What do you find most exciting about the *21st Annual* School of Breast Oncology meeting?

TOLANEY: One thing I love about the School of Breast Oncology meeting is not only that there are experts who know the field so well and provide the most up-to-date educational sessions on the data but [also that] Joyce O'Shaughnessy, MD, does a phenomenal job of bringing tough case discussions to the forefront. These are the cases we struggle with in the clinic, and it's helpful to get guidance from the very thoughtful clinicians [in attendance]. The discussions [about these cases] are probably one of my favorite parts of the meeting. ■

Reference

1. FDA approves fam-trastuzumab deruxtecan-nxki for HER2-low breast cancer. FDA. August 5, 2022. Accessed May 17, 2022. https://bit.ly/3BAS4NQ

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with mCSPC or nmCRPC.[1]

HE NEVER THOUGHT HE'D SEE THE DAY. HELP HIM BE THERE™.

Some of his best moments may not have happened yet.
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INDICATIONS

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA® and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA® and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and 1% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA®, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Severe Cutaneous Adverse Reactions — Fatal and life-threatening cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) occurred in patients receiving ERLEADA®.

Monitor patients for the development of SCARs. Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy). If a SCAR is suspected, interrupt ERLEADA® until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other Grade 4 skin reactions, permanently discontinue ERLEADA® *[see Dosage and Administration (2.2)]*.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® *[see Use in Specific Populations (8.1, 8.3)]*.

ADVERSE REACTIONS

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)

- **Hematology —** In the TITAN study: white

Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

TITAN dual primary endpoint, final analysis

ERLEADA® + ADT demonstrated **SUPERIOR OS** in men with mCSPC vs ADT alone[1-3]

35%

REDUCTION IN THE RISK OF DEATH IN MEN WITH mCSPC*

HR=0.65; 95% CI: 0.53, 0.79

- Median OS was not reached in the ERLEADA® + ADT arm compared with 52.2 months in the ADT arm. Median follow-up time was 44.0 months[1,2]
- TITAN primary analysis results: Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; *P*=0.0053. Median follow-up time was 22.7 months[1,2]

Visit erleadahcp.com for more information about

STARTING EARLY WITH ERLEADA® TO HELP HIM LIVE LONGER.[1]

blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)

- **Chemistry —** In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1.0%); hypertriglyceridemia ERLEADA® 67% (1.6%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (1.9%), placebo 22% (0.5%)

Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability *[see Dosage and Administration (2.2)]*.

Effect of ERLEADA® on Other Drugs

CYP3A4, CYP2C9, CYP2C19, and UGT Substrates — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure.
Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

cp-50507v6

***Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival and rPFS.[1,4]

ADT, androgen deprivation therapy; CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; mCSPC, metastatic castration-sensitive prostate cancer; NE, not estimable; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival; TITAN, Targeted Investigational Treatment Analysis of Novel Anti-androgen.

References: 1. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*. 2021;39(20):2294-2303. **3.** A study of apalutamide (JNJ-56021927, ARN-509) plus androgen deprivation therapy (ADT) versus ADT in participants with mCSPC (TITAN). ClinicalTrials.gov identifier: NCT02489318. Updated October 26, 2022. Accessed November 23, 2022. https://clinicaltrials.gov/ct2/show/NCT02489318 term=apalutamide&cond=prostate+cancer&draw=4&rank=22 **4.** Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. Protocol. *N Engl J Med*. 2019;381(1):13-24. Accessed March 15, 2022. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1903307/suppl_file/nejmoa1903307_protocol.pdf

Janssen Oncology

Brief Summary of Prescribing Information for ERLEADA® (apalutamide)
ERLEADA® (apalutamide) tablets, for oral use
See package insert for Full Prescribing Information

INDICATIONS AND USAGE
ERLEADA is indicated for the treatment of patients with

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events
Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA and 1% of patients treated with placebo *[see Adverse Reactions]*. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures
Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 2.7% of patients treated with ERLEADA and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 1.5%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls
Falls occurred in patients receiving ERLEADA with increased frequency in the elderly *[see Use in Specific Populations]*. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure
Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Severe Cutaneous Adverse Reactions
Fatal and life threatening cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), occurred in patients receiving ERLEADA *[see Adverse Reactions]*.

Monitor patients for the development of SCARs. Advise patients of the signs and symptoms of SCARs (e.g., a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

If a SCAR is suspected, interrupt ERLEADA until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other grade 4 skin reactions, permanently discontinue ERLEADA *[see Dosage and Administration (2.2) and Adverse Reactions]*.

Embryo-Fetal Toxicity
The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA *[see Use in Specific Populations and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:

- Cerebrovascular and Ischemic Cardiovascular Events *[see Warnings and Precautions]*.
- Fractures *[see Warnings and Precautions]*.
- Falls *[see Warnings and Precautions]*.
- Seizure *[see Warnings and Precautions]*.
- Severe Cutaneous Adverse Reactions (SCARs) *[see Warnings and Precautions]*.

Clinical Trial 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 most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2.3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

	ERLEADA N=524		Placebo N=527	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Musculoskeletal and connective tissue disorders				
Arthralgia[a]	17	0.4	15	0.9
Skin and subcutaneous tissue disorders				
Rash[b]	28	6	9	0.6
Pruritus	11	0.2	4.6	0.2
Vascular disorders				
Hot flush	23	0	16	0
Hypertension	18	8	16	9

[a] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

[b] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3.1% versus 1.9% on placebo), dysgeusia (3.2% versus 0.6% on placebo), and hypothyroidism (3.6% versus 0.6% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

	ERLEADA N=524		Placebo N=527	
Laboratory Abnormality	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Hematology				
White blood cell decreased	27	0.4	19	0.6
Chemistry				
Hypertriglyceridemia[a]	17	2.5	12	2.3

[a] Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥ 2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3.2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3.4%) in the ERLEADA arm and urinary retention (3.8%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions				
Fatigue[a,b]	39	1.4	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia[b]	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash[c]	25	5.2	6	0.3
Metabolism and nutrition disorders				
Decreased appetite[d]	12	0.1	9	0
Peripheral edema[e]	11	0	9	0
Injury, poisoning and procedural complications				
Fall[b]	16	1.7	9	0.8
Fracture[f]	12	2.7	7	0.8
Investigations				
Weight decreased[b]	16	1.1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1.1	15	0.5
Nausea	18	0	16	0

[a] Includes fatigue and asthenia

[b] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

[c] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

[d] Includes appetite disorder, decreased appetite, early satiety, and hypophagia

[e] Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

ERLEADA® (apalutamide) tablets

[f] Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, and tibia fracture

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (6% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
Laboratory Abnormality	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Hematology				
Anemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	1.8	21	1.6
Chemistry				
Hypercholesterolemia[a]	76	0.1	46	0
Hyperglycemia[a]	70	2	59	1.0
Hypertriglyceridemia[a]	67	1.6	49	0.8
Hyperkalemia	32	1.9	22	0.5

[a] Does not reflect fasting values

Rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of patients treated with ERLEADA and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 4.9% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted *[see Drug Interactions]*.

Post-Marketing Experience

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

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability *[see Dosage and Administration (2.2) in Full Prescribing Information]*. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on ERLEADA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose *(see Data)*.

Data

Animal Data

In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s), and small, incomplete ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients.

Lactation

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA *[see Use in Specific Populations]*.

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in Full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over.

No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Cerebrovascular and Ischemic Cardiovascular Events

- Inform patients that ERLEADA has been associated with cerebrovascular and ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular or a cerebrovascular event occur *[see Warnings and Precautions]*.

Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures *[see Warnings and Precautions]*.

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure *[see Warnings and Precautions]*.

Severe Cutaneous Adverse Reactions (SCARs)

- Inform patients that ERLEADA has been associated with SCARs (including SJS/TEN and DRESS), which can be life-threatening or fatal. Advise patients to stop taking ERLEADA and contact their healthcare provider or seek medical attention right away if they experience signs or symptoms of SCARs *[see Warnings and Precautions]*.

Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash *[see Adverse Reactions]*.

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole. Do not crush or split tablets *[see Dosage and Administration (2.1) in Full Prescribing Information]*.
- Instruct patients who cannot swallow tablets whole to follow the instructions for the prescribed strength of ERLEADA tablets for alternate methods of administration *[see Dosage and Administration (2.3) in Full Prescribing Information]*.
- Instruct patients on administration of the ERLEADA 240 mg tablet through a feeding tube *[see Dosage and Administration (2.3) in Full Prescribing Information]*.
- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman *[see Warnings and Precautions]*.

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA *[see Use in Specific Populations]*.

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De-Escalation Treatment for Human Papillomavirus–Related Oropharyngeal Cancer: Questions for Practical Consideration

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ABSTRACT

Human papillomavirus (HPV)–positive oropharyngeal squamous cell carcinoma (SCC), which accounts for an increasing proportion of all head and neck cancers, represents a specific entity with distinct clinical and molecular characteristics. It is now firmly established that patients with HPV-positive oropharyngeal SCC have a significantly improved prognosis because this variant has exquisite radiosensitivity compared with HPV-negative oropharyngeal SCC; thus, it can be targeted with de-escalated approaches using reduced doses of radiation and/or chemotherapy. The overriding goal of de-escalation is to maintain the high cure and survival rates associated with traditional approaches while reducing the incidence of both short- and long-term toxicity. Although the exact reason for the improved radiosensitivity of HPV-positive oropharyngeal carcinoma is unclear, prospective studies have now been published demonstrating that de-escalated radiation can successfully maintain high rates of cure and preserve the quality of life for appropriately selected patients with this disease. However, these studies have been complicated by such factors as the relatively limited sample sizes, as well as the variability in treatment, inclusion criteria, and follow-up. How treatment paradigms will evolve, particularly in the era of precision medicine, is a provocative question and is the subject of this review.

Data have accumulated to demonstrate that patients with human papillomavirus (HPV)–positive oropharyngeal squamous cell carcinoma (SCC) have a significantly improved prognosis because this variant has exquisite radiosensitivity compared with HPV-negative oropharyngeal SCC.[1-4] These tumors have been shown to shrink briskly and robustly in both preclinical laboratory models and in actual patients. **Table 1** illustrates data from prospective trials that have shown the favorable prognostic significance of HPV status. The recognition that HPV-positive oropharyngeal SCC responds favorably to radiation has prompted investigators to suggest that patients with these tumors might be overtreated and unnecessarily subjected to the toxicity of intensive chemoradiotherapy with excessively high radiation doses. Indeed, data from axial imaging studies obtained serially during the course of radiation to observe in vivo patterns of tumor response showed that HPV-positive oropharyngeal SCC tends to regress early during treatment, reaching a plateau by week 5 to 6, providing illustrative evidence that the intensity of treatment can possibly be reduced (**Figure 1**).[5,11] As a result, prospective trials have been conducted investigating the role of treatment de-escalation with the goal of reducing adverse effects (AEs), particularly those related to swallowing and salivary function, while maintaining the high rates of cure historically observed.[6-11]

Why Is De-escalation Biologically Feasible?

Multiple theories have been proposed as to how HPV mediates an enhanced radiation response of oropharyngeal SCC.[12-20] The most direct explanation is that HPV infection and the subsequent downstream pathways initiated

TABLE 1. **Subset Analysis of Prospective Trials Demonstrating Improved Prognosis With HPV-Positive Oropharyngeal SCC**

First Author	N	Dose	Induction	Concurrent	Outcomes
Fakhry[3]	96	70 Gy	Carboplatin/paclitaxel × 2	Paclitaxel	86% vs 53%, 2-y PFS; *P* = .02
Rischin[64]	172	70 Gy	None	Cisplatin +/– tirapazamine	87% vs 72%, 2-y PFS; *P* = .01 93% vs 86%, 2-y LRC; *P* = .09
Ang[2]	323	70-72 Gy	None	Cisplatin	74% vs 43%, 3-y PFS; *P* <.001 86% vs 65%, 3-y LRC; *P* <.001
Lassen[4]	331	66-68 Gy	None	+/– Nimorazole	61% vs 35%, 5-y LRC; *P* <.001
Lassen[4]	794	66-68 Gy	None	None	78% vs 64%, 5-y PFS; *P* = .001 69% vs 57%, 5-y LRC; *P* = .004
Worden[65]	66	70 Gy	Carboplatin/cisplatin + 5-FU × 1	Carboplatin/cisplatin	85% vs 37%, 3-y PFS; *P* = .001
Seiwert[66]	110	72 Gy	Carboplatin/paclitaxel/cetuximab × 2	Cetuximab/5-FU/ hydroxyurea or cetuximab/cisplatin	84% vs 66%, 5-y PFS; *P* <.01

5-FU, 5-fluorouracil; HPV, human papillomavirus; LRC, local-regional control; PFS, progression-free survival; SCC, squamous cell carcinoma

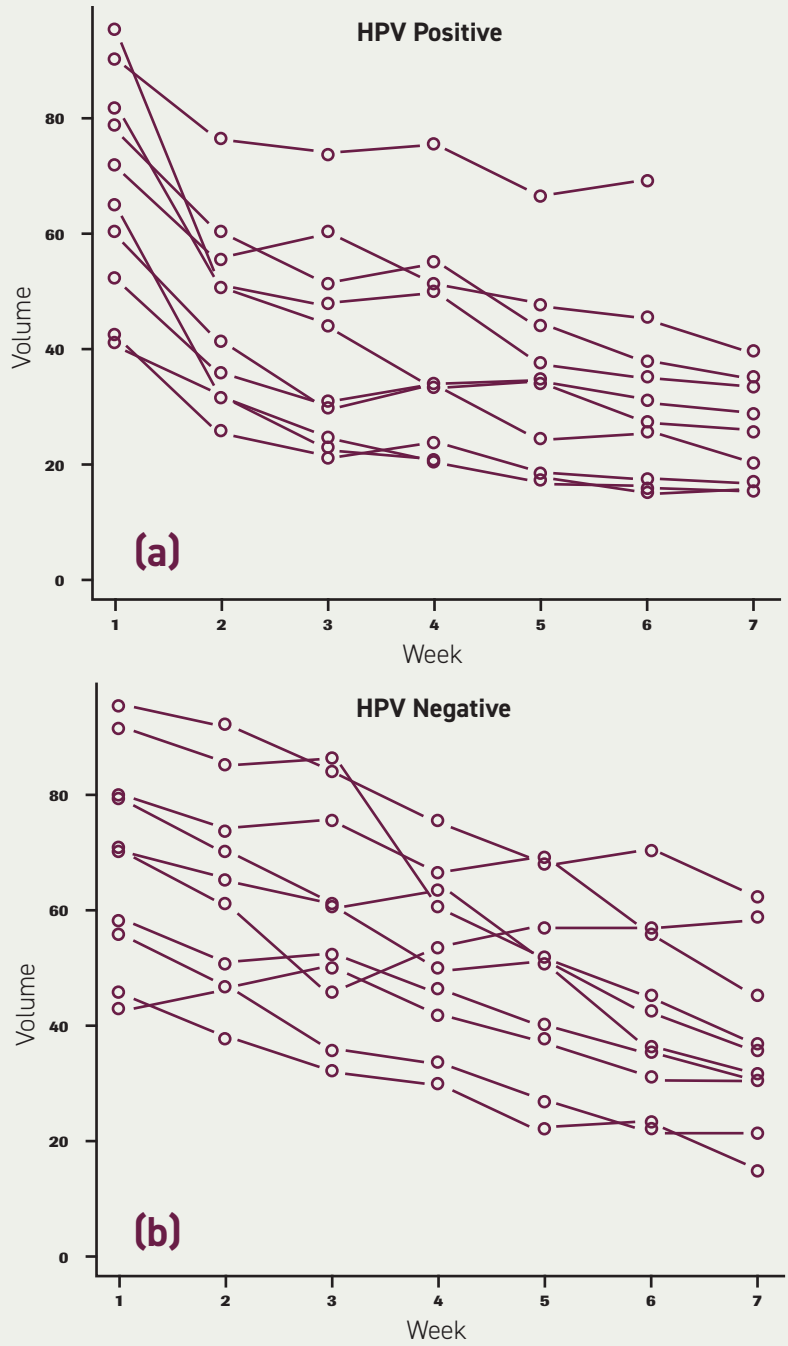
by the degradation of the p53 and pRb proteins through the viral products E6 and E7 lead to the deregulation of cell cycle checkpoints, downregulation of cell cycle regulatory proteins, and increased genomic instability, somehow rendering the host tumor cell more susceptible to radiation-induced apoptosis. Other studies have suggested that radiation enhances the host's immune response to the viral antigens that are expressed in the cancer.[14,15] For instance, it has been demonstrated that the degree of tumor-infiltrating lymphocytes was associated with outcomes among patients treated with radiation for HPV-positive oropharyngeal SCC.[16] Researchers have also demonstrated that the presence of regulatory T lymphocytes and PD-1–positive T lymphocytes, and the levels of PD-1–positive cells, were positively correlated with a favorable clinical outcome in HPV-positive compared with HPV-negative head and neck cancers.[17-19] These studies suggest that the tumor microenvironment plays a large role in mediating the differential effects of radiation between HPV-positive and HPV-negative oropharyngeal SCC. Alternatively, Vlashi et al showed that the improved radiosensitivity of HPV-positive (vs HPV-negative) head and neck cancer might be due to the lower frequency of cancer stem cells and their decreased capacity to engage in radiation-induced dedifferentiation.[20]

Who Might Be Eligible for De-escalation?

Patients with newly diagnosed HPV-positive SCC localized to the head and neck and originating from the oropharynx (ie, the tonsils, base of tongue, or uvula) are potential candidates for de-escalation. The exact type of de-escalation treatment may vary depending on the extent and location of the disease. However, given the strong link between HPV and radiation response, the American Joint Committee on Cancer (AJCC) created a new staging system in 2016 (**Figure 2**)[21] specifically for patients diagnosed with HPV-positive oropharyngeal SCC to reflect its favorable prognosis vs HPV-negative disease.[21] Notably, many HPV-positive tumors that had been previously categorized as stage IV were significantly "downstaged" to stage II or even stage I cancers. This new staging system has prompted many investigators to question historical treatment paradigms.[22] Published data have also suggested that the favorable impact of HPV positivity on prognosis is particularly strong for those deemed "never smokers" or even those with a minimal smoking history, thereby suggesting that these patients might benefit the most from de-escalation.[23]

Lastly, it is important to recognize that the AJCC staging system, similar to most clinical trials, has considered p16 positivity to be equivalent to HPV positivity. However, the possibility of discordance needs to be considered since p16 positivity can occur in the absence of HPV and is better suited as a screening tool due to its high sensitivity. This is relevant because it is likely that p16-positive/HPV-negative SCCs do not have the same favorable prognosis as p16-positive/HPV-SCCs.

FIGURE 1. **Differences in Regression Velocity Among Patients Treated for Oropharyngeal Cancer Based on HPV Status[5,11]**



Reduction in gross tumor volume during a course of definitive radiation therapy for head and neck cancer among (a) 10 patients with human papilomavirus (HPV)-positive and (b) 10 patients with HPV-negative oropharyngeal squamous cell carcinomas who were matched based on clinical and disease characteristics.

Why Is De-escalation Studied?

The incidence of HPV-positive oropharyngeal SCC has increased dramatically in recent years, reaching epidemic-like proportions. For many patients, radiation therapy is recommended as initial treatment, because of the excellent cure rates generally observed. Historically, this regimen has consisted of 7 weeks of daily radiation utilizing relatively high doses, often combined with cisplatin chemotherapy. However, this treatment can be difficult to tolerate and also incurs significant posttreatment sequelae: A significant proportion of patients develop long-term toxicity, including swallowing dysfunction, dry mouth, and/or neck stiffness.[24] Unfortunately, these AEs can be severe, life altering, and permanent. Indeed, the detrimental effect of treatment on quality of life (QOL), psychosocial health, and overall functional capacity has been well established.[25] Because patients with HPV-positive oropharyngeal SCC most often present at a relatively young age and can potentially survive for decades after treatment, the focus on decreasing long-term complications and optimizing QOL is particularly germane. In short, de-escalation is about trying to maximize the potential for a cure while also focusing on preserving QOL. Given the plethora of data that now exist showing that patients with HPV-positive oropharyngeal SCC respond robustly to treatment and have tumors that are extremely sensitive to radiation, the concept of de-escalation makes the most sense in this population.

What Can De-escalation Accomplish for Patients?

The major AEs of standard treatment with high-dose radiation (often combined with concurrent chemotherapy) in both the short and long term pertain to difficulty with swallowing and are directly related to incidental exposure of normal tissue to radiation. Indeed, the

FIGURE 2. **American Joint Commission on Cancer Staging System for p16-Positive Oropharyngeal Cancer (Eighth Edition)[21]**

T category
T0 No primary tumor
T1 Tumor size ≤2 cm in greatest dimension
T2 Tumor size >2 cm but ≤4 cm in greatest dimension
T3 Tumor size >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced tumor invading larynx, extrinsic tongue muscles, medial pterygoid, hard palate, or mandible or beyond

Clinical N category
NX Regional nodes cannot be assessed
N0 No regional nodal metastasis
N1 Metastasis to ≥ 1 ipsilateral nodes, ≤6 cm
N2 Metastasis to contralateral or bilateral nodes, ≤6 cm
N3 Metastasis in any cervical lymph node, >6 cm

Pathologic N category
NX Regional nodes cannot be assessed
pN0 No regional nodal metastasis
pN1 Metastasis to ≤ 4 lymph nodes
pN2 Metastasis to ≥ 5 lymph nodes

M category
M0 Absence of distant metastasis
M1 Presence of distant metastasis

Stage group
I T0-3; N0-1; M0
II T0-2; N2; M0 *OR* T3N1
III Any T3 or any T4 and M0
IV Any M1

reported rates of feeding tube dependence, aspiration pneumonia, severe dehydration, and malnutrition are not insignificant among patients completing treatment.[26-29] The disruption of salivary production, which can often be permanent, also leads to challenges with chewing and speaking. Because studies have shown that the likelihood and severity of AEs increase with radiation dose, it has been hypothesized that by effectively reducing radiation to the normal structures of the head and neck, there will be a consequent decrease in AEs—particularly related to swallowing and salivation—resulting in improved QOL.[30-33] Additionally, biological models have shown that reducing radiation should also decrease the incidence of radiation injuries, some of which can be debilitating, to the bone, nerves, and soft tissue.[34] From a practical standpoint, reducing the intensity of treatment has the potential to eliminate or ameliorate many commonly observed AEs.

Does This Mean De-escalation Can Improve QOL?

Given that the probability of developing most radiation-induced complications can be decreased by reducing the radiation dose exposure to healthy tissue, the potential of de-escalation to improve the QOL for patients undergoing treatment for head and neck cancer is profound. By potentially decreasing toxicity without lowering cure rates, de-escalation of radiation dose for HPV-positive tumors has the potential to improve QOL for survivors and to allow them to live more functional and productive lives. Since basic functions such as speaking, eating, chewing, and tasting are recognized as critical to maintaining a social life, any disruption of these abilities can dramatically affect one's sense of well-being.

The potential of de-escalation to reduce psychosocial distress, such as symptoms of depression and anxiety, has also begun to be recognized.[35] In fact, one recent study showed that de-escalation significantly reduced the proportion of survivors who are dependent on pain medications and opioids after treatment for HPV-positive oropharyngeal SCC.[36]

Is It Possible to Reduce the Radiation Dose?

Over the past decade, several prominently published prospective trials (**Table 2**) have demonstrated promising outcomes with de-escalated radiation regimens using doses that are lower than those conventionally accepted.[5-10] Although the trial designs have varied, the results have consistently shown that de-escalated radiation for HPV-positive oropharyngeal SCC can maintain the historically high rates of cure while significantly decreasing toxicity and improving QOL, thus largely validating the premise for which de-escalation was proposed.

Our group from the University of California performed a multicenter, phase 2 trial, treating 45 patients with locally advanced, HPV-positive oropharyngeal SCC. They received 2 cycles of induction chemotherapy given 21 days apart, followed by de-escalated radiation. At 2 years, the reported rates of disease control and overall survival were 92% and 98%, respectively, which compared favorably with historical controls treated without de-escalation.[5] Just as important, at 6 months post radiation, the incidence of both gastrostomy-tube dependence and severe swallowing dysfunction was zero. A prospective analysis of end points related to the QOL and pre- and posttherapy swallow studies

showed that de-escalation dramatically improved function with respect to every variable analyzed—including weight loss, depression, and opioid usage—compared with contemporary control participants who opted not to be treated with de-escalation.[35,36] A survey of perspectives and attitudes of the patients treated on the University of California de-escalation trial showed that nearly all individuals were satisfied with their decision and had virtually no regrets about their treatment choice.[37]

While some research teams have helped validate the paradigm of induction chemotherapy prior to de-escalated radiation for HPV-positive oropharyngeal SCC, others have investigated different approaches. For instance, the use of up-front concurrent chemoradiation using de-escalated radiation with weekly cisplatin has also been shown to lead to excellent outcomes.[6] As a result, when de-escalated radiation is considered in the setting of chemoradiation, 2 different strategies have generally been proposed: One utilizes concurrent chemotherapy, and the other utilizes induction chemotherapy.[38]

Is It Possible to Modify the Chemotherapy or Eliminate It Altogether?

The purpose of chemotherapy, when given together with radiation, is widely accepted as a means to make radiation more effective. In the setting of head and neck cancer, it is considered a "radiosensitizer." Given the exquisite sensitivity of HPV-positive oropharyngeal SCC to radiation, a logical question is whether chemotherapy is needed. Because biological models have suggested that the addition of chemotherapy is equivalent to approximately 3 to 5 extra radiation sessions, a strategy of intensifying treatments seems to be paradoxical to the premise of de-escalation.[39] One way to approach this dilemma is to change the way that chemotherapy is delivered. For instance, studies have now shown that weekly delivery of attenuated doses of cisplatin might be just as effective and better tolerated as administering the chemotherapy every 3 weeks using larger doses, as is traditionally done.[40] Although attempts have been made to replace cisplatin with a targeted systemic agent, cetuximab, the results of prospective trials have suggested that this may lead to inferior outcomes.[41-43] Studies analyzing whether immunotherapy can be utilized as an alternative are also ongoing.[44]

The evidence in favor of radiation alone for appropriately selected patients with HPV-positive oropharyngeal SCC is provocative. Based on historic data from the University of California – Davis and Princess Margaret Hospital in Toronto, Ontario, Canada, showing that radiation alone can be curative for many patients with HPV-positive oropharyngeal SCC, investigators from Japan recently published findings from a phase 2 trial showing positive outcomes and a 2-year overall survival rate of 100%.[45-47] For another phase 2 study, University of North Carolina investigators further reported on patients with lower tumor volumes who were treated with de-escalated radiation alone.[5] Although the phase 2 NRG HN02 study (NCT02254278) results showed that the addition of concurrent cisplatin to de-escalated radiation reduced the 2-year local failure rate from 9% to 3%, it was unclear which patients benefited the most.[10] When the 2-year disease control and overall

TABLE 2. **Prospective Clinical Trials Evaluating De-escalated Radiation as Initial Treatment for HPV-Positive Oropharyngeal SCC[5-10]**

First author (year)	N	Dose	Chemotherapy	PFS	OS	Time
Chen (2017)	45	54-60 Gy	Induction carboplatin/paclitaxel Concurrent paclitaxel	95%	98%	2 years
Chera (2019)	114	60 Gy	Concurrent cisplatin or none	86%	95%	2 years
Marur (2017)	51	54 Gy	Induction cisplatin/paclitaxel/cetuximab Concurrent cisplatin	80%	94%	2 years
Misiukiewicz (2019)	12	56 Gy	Induction docetaxel/cisplatin/5-FU Concurrent carboplatin	83%	83%	3 years
Seiwert (2019)	62	45-75 Gy	Induction carboplatin/paclitaxel	95%	98%	2 years
Yom (2021)	150	60 Gy	None	88%	97%	2 years
Yom (2021)	158	60 Gy	Concurrent cisplatin	91%	97%	2 years

5-FU, 5-fluorouracil; HPV, human papillomavirus; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

survival rates were analyzed, no differences were observed between patients treated with de-escalated radiation with or without chemotherapy. These studies suggest that some patients with HPV-positive oropharyngeal SCC can be treated with de-escalation and achieve excellent outcomes. The explanation for the lack of benefit associated with cetuximab might be because HPV-related tumors are less driven by underlying alterations in cell signaling pathways due to the oncogenic properties of HPV-oncoproteins E6 and E7. In other words, compared with HPV-negative carcinoma, HPV-positive oropharyngeal SCC harbors mutational landscapes that are more devoid of driver mutations or alterations such as EGFR overexpression. Although the eligibility criteria varied between studies, both studies have suggested that cisplatin should continue to be the standard when chemotherapy is utilized with radiation in the definitive treatment of HPV-positive oropharyngeal cancer. Although the results do not truly address the question of which patients require chemotherapy for this disease, they nonetheless demonstrate the need for caution with ongoing attempts to pursue de-escalation. It must also be recognized that HPV confirmation with in situ hybridization was not standardly performed, which raises the possibility that some patients with p16-positive disease actually did not have HPV-related disease. Given the historically high rates of toxicity associated with chemotherapy, the use of radiation alone can be considered an attractive option for appropriate patients.

Is Transoral Robotic Surgery Considered De-escalation?

Minimally invasive operative techniques using transoral robotic surgery (TORS) have also been proposed as a means of de-escalating treatment for HPV-positive oropharyngeal SCC.[48,49] However, the treatment by itself is not considered de-escalation because it is a type of surgery. In select patients with low-volume disease, TORS, combined with a surgical neck dissection, may actually serve as a replacement for radiation, eliminating its necessity entirely. However, although TORS has been shown to be a reasonable initial option for select patients with HPV-positive oropharyngeal SCC, it must be recognized that a substantial proportion of patients will ultimately require postoperative radiation.[50] Although published studies have investigated whether lower radiation doses or smaller target volumes can be delivered after TORS, these strategies are still not considered standard.[51-53] Enthusiasm for the use of TORS also may have been dampened by the results of the phase 2 ORATOR trial (NCT01590355), which randomly assigned patients with newly diagnosed HPV-positive oropharyngeal SCC to either initial TORS or to primary radiation.[54] Although survival and cure rates were the same in the 2 arms, patients randomized to TORS had significantly decreased swallowing function at 1 year.[54]

Why Is De-escalation So Popular?

De-escalation for HPV-positive oropharyngeal SCC is a form of precision medicine: using the biological characteristics of a tumor to drive treatment decision-making. Given that HPV-positive tumors have been shown to be innately sensitive to radiation, investigators have proposed that a "one size fits all" approach to treating oropharyngeal SCC no longer makes sense. The popularity of this de-escalation approach has been driven by both the increasing recognition that HPV-positive oropharyngeal SCC is exquisitely sensitive to radiation and the desire of patients to avoid short- and long-term AEs. Now that prospective trials have been published demonstrating its feasibility, de-escalation continues to be investigated as a curative treatment for patients with HPV-positive oropharyngeal SCC.

Is De-escalation Ready to Become Standard Treatment?

Given the preponderance of evidence attesting to the sensitivity of HPV-positive oropharyngeal SCC to radiation, a tremendous amount of attention has focused on investigating whether patients with locally advanced HPV-positive oropharyngeal SCC should be treated differently than those with HPV-negative tumors. The concept of de-escalation encompasses a variety of different strategies intended to make treatment gentler, such as reductions in radiation, alterations in chemotherapy regimens, and/or full elimination of either modality. However, how to best offer this approach to patients is uncertain, and the question of whether de-escalation is even ready for use outside a clinical trial is hotly debated.

The overriding goal of de-escalation is to maintain the high survival rates associated with traditional approaches while reducing the incidence of both short- and long-term toxicity by lessening the intensity of treatment. Even so, it is still not considered a standard of care, because the published data are still relatively preliminary and they are complicated by such factors as variability in treatment, inclusion criteria, and follow-up. However, the reality of clinical decision-making for HPV-positive oropharyngeal SCC has evolved to the point where patients are now routinely demanding de-escalated radiation, and it has become increasingly offered to patients with HPV-positive oropharyngeal SCC as standard treatment, a testament to the concept's popularity.[55] Although the strategy is seemingly well supported by the depth and breadth of data that have been published, we nonetheless

believe that at this time, attempts to offer de-escalation outside a clinical trial should be avoided.

Where Is Future Research Headed?

Continued efforts to better refine selection criteria and to dynamically monitor treatment response will define the evolution of de-escalation for HPV-positive oropharyngeal SCC. At present, the only factor (other than AJCC cancer stage) used for risk stratification is smoking history. Future advances in de-escalation will need to incorporate a combination of clinical, radiological, and biological data—helping to apply principles of precision medicine to this approach. For instance, considerable interest has arisen in using HPV DNA levels from the blood—obtained before, during, and after treatment—to monitor de-escalation.[56-58] Another approach involves using special imaging techniques, often combined with machine learning and/or artificial intelligence algorithms, to predict response to de-escalation.[59-63] The explosion of radiomic information also has the potential to identify who may or may not be eligible for de-escalation, both at diagnosis and midway through radiation. For instance, investigators recently used a radiomics signature of intratumoral and peritumoral regions to predict which patients might benefit from the addition of chemotherapy to radiation for HPV-positive oropharyngeal SCC.[59] Although these approaches hold promise for the future, exactly how to utilize such strategies remains uncertain and the subject of ongoing research.

Conclusions

Given its demonstrated ability to dramatically preserve QOL and functioning while maintaining high rates of cure, de-escalation has come to light as an attractive option in the management of HPV-positive oropharyngeal SCC. Although data continue to emerge suggesting that treatment should be individualized for the subgroup of patients with HPV-positive oropharyngeal SCC, exactly how to do so remains uncertain. Some patients can likely be effectively treated with de-escalated radiation alone, but it is possible that others with higher-risk disease might benefit from the addition of chemotherapy to de-escalated radiation. However, these paradigms continue to evolve as studies contribute to an improved understanding of HPV-positive oropharyngeal SCC. While proponents argue that the data robustly support the integration of de-escalation into contemporary practice, skeptics note that the published data are still relatively preliminary, making definitive recommendations difficult. Based on the emerging evidence, as well as on the explosion in interest from patients and physicians alike, well-designed clinical trials are urgently needed to better refine selection criteria for de-escalation and to stratify patients with newly diagnosed oropharyngeal SCC into the appropriate means of treatment. ■

DISCLOSURE: The author has no financial disclosures or conflicts of interest to report.

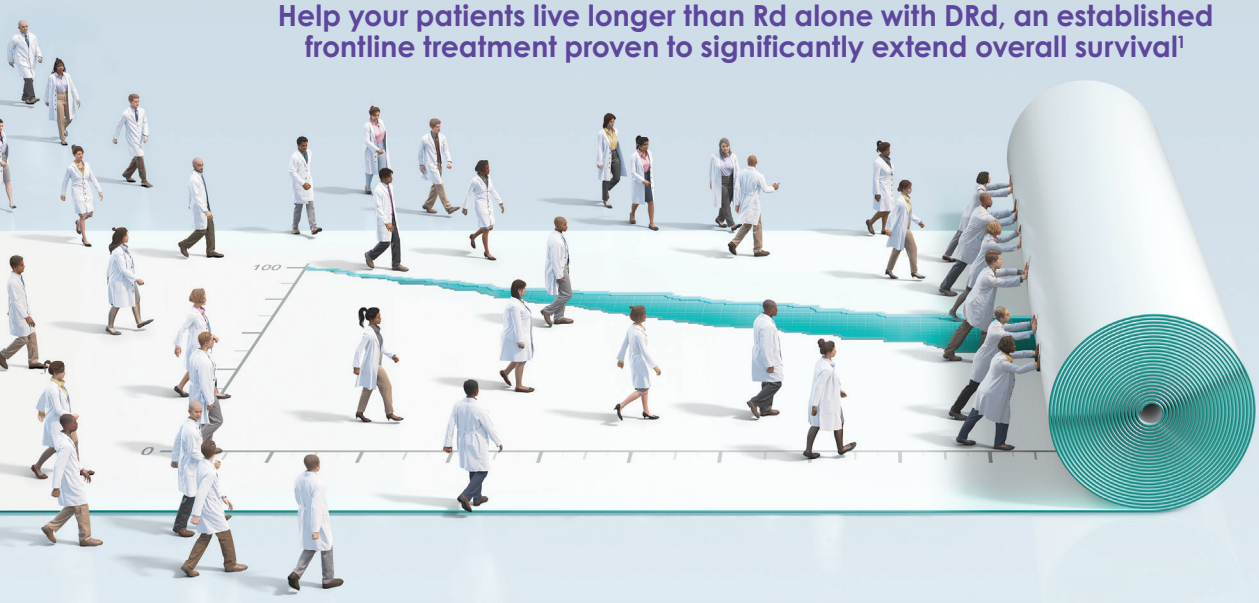
For references visit
cancernetwork.com/7.23_H&N

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]



At ~5 years: 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]

DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

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

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.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (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 and OS was a secondary endpoint.[1]

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

At follow-up of ~30 months*, **median progression-free survival (mPFS) was not reached** with **DARZALEX® (daratumumab) + 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)

Secondary endpoint of overall survival (OS)[1,2]

At ~5 years (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 follow-up was 56 months. 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[1]

(median treatment duration of 25.3 months)

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, vomiting, 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%)

Efficacy results in long-term follow-up[2]

At ~5 years (56 months)‡ of follow-up, **mPFS was not reached** with DRd vs 34.4 months with Rd alone.

- **52.5% of patients had not progressed** after ~5 years of treatment with DRd vs 28.7% with Rd alone (DRd, 95% CI: 46.7, 58.0; Rd, 95% CI: 23.1, 34.6)†

47% **reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information (PI). No conclusions should be drawn.

Safety results in long-term follow-up[2]

(median treatment duration of 47.9 months)

At median ~5 years of follow-up:

- Most frequent TEAEs§ for DRd ≥30% 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 41% for DRd vs 29% for Rd
- Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (18% vs 10%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5 year analyses are not in the current PI. 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); HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

*Range: 0.0-41.4 months.[3]

†Kaplan-Meier estimate.

‡Range: 0.03-69.52 months.[2]

§TEAEs are defined as any adverse event (AE) that occurs after 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 drug 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. Visit darzalexhcp.com

IMPORTANT SAFETY INFORMATION (CONTINUED)

DARZALEX®: Infusion-Related Reactions

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

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.

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

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11/22 cp-352216v1

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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
U.S. License Number 1864

cp-271933v3

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]*.

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cp-267681v2

Erdheim–Chester Disease: A Case Report of *BRAF* V600E–Negative, *MAP2K1*-Positive ECD Diagnosed by Blood Next-Generation Sequencing Assay and a Brief Literature Review

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ABSTRACT

Erdheim-Chester disease (ECD) is a rare type of non-Langerhans cell histiocytosis. However, its prevalence has increased significantly the past few years due to increased awareness about the disorder, and 1500 cases have been reported worldwide. It is often a multisystemic disease with skeletal, cardiovascular, urologic, renal, retroperitoneal, pulmonary, endocrine, cutaneous, and neurologic involvement. MAPK pathway mutations, such as *BRAF* activating and *MAP2K1* mutations, play a key role in its pathogenesis. In addition to the characteristic clinical, radiological, and histopathological findings, identifying underlying mutations helps diagnose and treat patients with highly effective targeted therapies such as BRAF and MEK inhibitors. We report a case of a man, aged 55 years, with an extensive and prolonged course of an unexplained multisystemic disease, later diagnosed with *BRAF* V600E–negative and *MAP2K1*-positive ECD on cell-free DNA testing. Additionally, we review common clinical manifestations, mutations, diagnoses, and targeted therapies for ECD.

Introduction

Erdheim-Chester disease (ECD) is a rare type of non-Langerhans cell histiocytosis (LCH).[1] It was first described as "lipoid granulomatosis" by Jakob Erdheim and William Chester in 1930 and was later named after its discoverers.[2] It is a rare disease, but its prevalence has increased substantially in the past few years due to increased awareness about the disorder, and 1500 cases have been reported worldwide.[1]

Infiltration of tissues with foamy CD68+, CD1a– histiocytes is one of the characteristic features of ECD.[3] It is most commonly a multisystemic disease with skeletal, cardiovascular, urologic, renal, retroperitoneal, pulmonary, endocrine, cutaneous, and neurologic involvement, and clinical manifestations vary depending upon the system(s) involved.[2] Pathogenesis of ECD involves mutations in the MAPK pathway, such as *BRAF* V600E and *MAP2K1* mutations.[2] ECD's diagnostic criteria are based on clinical, radiological, histopathological, and molecular findings.[2] The ability to find the underlying mutations has significantly helped treat patients with highly efficacious and robust targeted therapies, including BRAF and MEK inhibitors.[1]

We report a case of a man, aged 55 years, with an extensive and prolonged course of an unexplained multisystemic disease, later diagnosed with *BRAF* V600E–negative and *MAP2K1*-positive ECD on cell-free DNA testing. Additionally, we review common clinical manifestations, mutations, diagnoses, and targeted therapies for ECD.

Case Presentation

A man, aged 55 years, presented with the chief complaint of bilateral leg swelling. On the physical exam, he was found to have bilateral lower extremity edema, ascites, and hepatomegaly. CT of the abdomen revealed retroperitoneal fibrosis. An exploratory laparotomy with a biopsy of the retroperitoneal area confirmed fibrosis. Multiple studies

to determine the cause of fibrosis were unsuccessful, and he was started on steroids for idiopathic retroperitoneal fibrosis. Subsequent CT scans showed pleural thickening and mediastinal fibrosis in addition to the unchanged retroperitoneal fibrosis encasing both kidneys and the aorta. Because of the diffuse multifocal involvement, he was thought to have systemic fibrosclerosis. It was further complicated by testicular insufficiency secondary to bilateral testicular fibrosis, and he eventually required bilateral orchiectomies. Further, he developed right and left heart failure symptoms, and the thoracic CT scan showed thickening of the pericardium with no significant fluid in the pericardial cavity. Subsequently, he needed a pericardiectomy for constrictive pericarditis.

Progression of the disease continued with the development of paranasal sinus symptoms. A CT scan revealed opacification of bilateral maxillary sinuses, and sinus biopsy was remarkable for fibrosis. Concurrently, he also had resistant hypertension secondary to stenoses of renal arteries; renal artery stent placement was necessary to control hypertension. Furthermore, he had other vascular occlusions, including of the internal carotids, superior mesenteric artery, celiac artery, and bilateral iliac arteries. Even the coronary arteries were not spared; he presented with acute coronary syndrome, for which he underwent percutaneous coronary intervention of multiple coronary arteries. Later, he developed dyspnea on exertion, and pulmonary function tests were consistent with restrictive lung disease. A CT of the chest revealed centrilobular nodules, pleural thickening, and interlobular septal thickening (**Figure 1D**). This constellation of clinical and radiological findings raised suspicion of ECD.

Further work-up included bone scintigraphy to assess skeletal involvement; repeat imaging to confirm pulmonary, abdominal, and vascular findings of ECD; and then tissue and liquid biopsy to detect histopathological and molecular findings of ECD. Bone scintigraphy showed abnormal uptake in the bilateral tibia, bilateral maxillary bones, and shoulder regions consistent with ECD (**Figure 1A**). In addition, a CT scan showed diffuse circumferential wall thickening and calcification throughout the thoracic and abdominal aorta and its

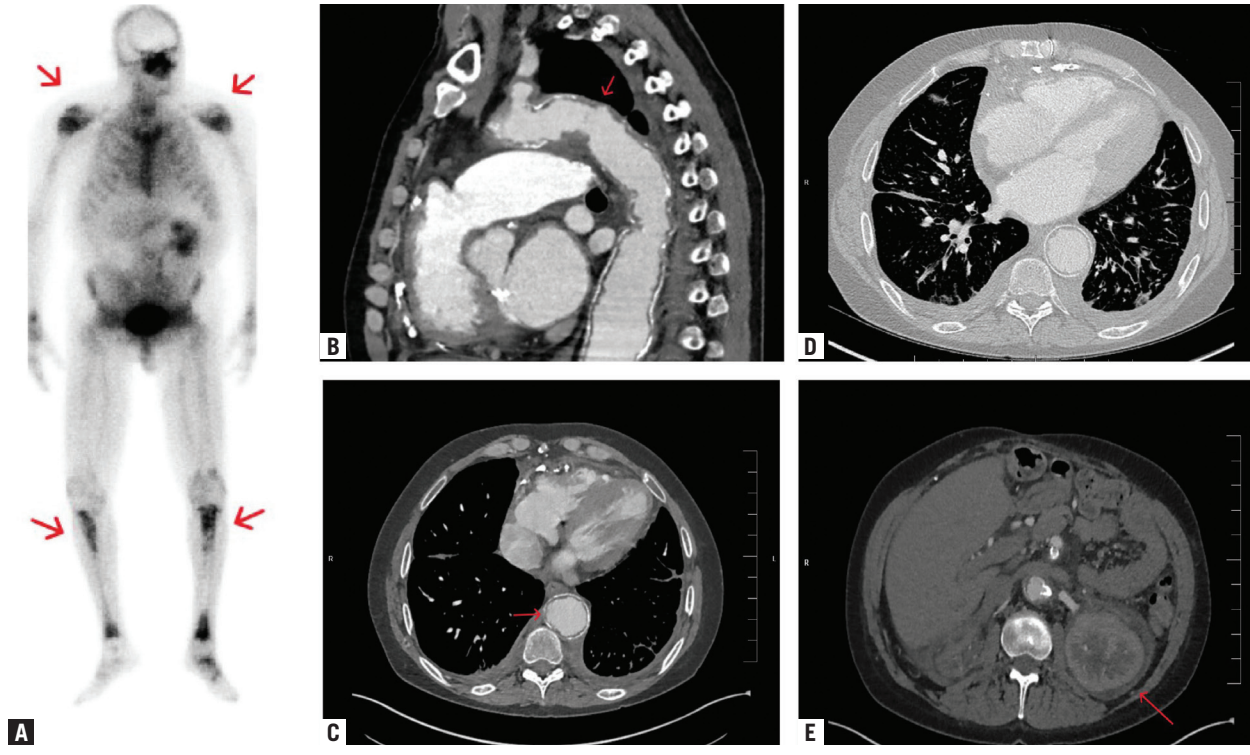

FIGURE 1. **CT Scan of Patient With ECD**

(A) Bone scintigraphy showed increased uptake in bilateral tibia, bilateral maxillary bones, and shoulder regions.

(B, C) CT showed diffuse circumferential wall thickening and calcification of the aorta.

(D) CT of the chest revealed centrilobular nodules, pleural thickening, and interlobular septal thickening.

(E) CT of the abdomen showed the "hairy kidney" sign.

major branches (**Figure 1B**), conditions associated with ascending thoracic aortic ectasia and type V thoracoabdominal aortic aneurysm. It is important to note that the aorta was coated circumferentially (**Figure 1C**), pointing toward ECD as the diagnosis. The posterior wall of the aorta is rarely affected in idiopathic retroperitoneal fibrosis.[4]

A CT scan of the abdomen showed the "hairy kidney" sign with irregular, symmetric infiltration of the bilateral perirenal and posterior pararenal spaces (**Figure 1E**). Right-sided tibial biopsy showed extensive fibrosis and calcification, but foamy histiocytes were not present; this was not inconsistent with ECD but was also not diagnostic due to the scant cellularity of the specimen (**Figure 2A**). Immunohistochemical staining of the spindle and ovoid cell population was negative for CD1a and S100 (**Figure 2B and 2C**). However, the oval cells that were morphologically suggestive of histiocytes and a component of the spindle cells were CD68 +, which confirmed the histiocytic nature of the cells (**Figure 2D**). Based on the immunohistochemistry, molecular testing was not ordered because of insufficient representative cellularity.

Subsequently, the patient underwent bronchoscopy with endobronchial ultrasound and fine-needle aspiration of a 5-cm subcarinal lymph node that showed blood, respiratory cells, and benign cartilage. However, the tissue sample was inadequate, with no lymphoid tissue. Later, an incisional pleural biopsy was performed that revealed dense fibrous tissue with rare chronic inflammatory cells; unfortunately, the tissue sample was insufficient for further testing. Finally, a liquid biopsy was obtained to look for mutations for targeted therapy; it came back negative for *BRAF* V600E mutation but positive for *MAP2K1* (*MEK1*) K57N mutation with a variant allele frequency of 1.2%, confirming the diagnosis of ECD. The time between symptom onset and the diagnosis was around 22 years.

There are 3 different functional classes of *MEK1* mutations, and *MEK1* K57N is a class II mutant that is sensitive to currently available MEK inhibitors like trametinib.[5] Therefore, the patient was started on targeted therapy with trametinib, an inhibitor of MEK1 and MEK2. However, within 2 weeks of starting the medication, the patient started experiencing intolerable adverse effects (AEs) including nausea, vomiting, diarrhea, fever with chills, body aches, mouth sores, fatigue, and headache. Trametinib was held for a few days and the plan was to resume it later at a lower dose. However, the patient refused further treatment due to intolerable AEs. Posttreatment imaging studies could not be obtained as the patient was on treatment only for about 2 weeks. Unfortunately, the patient died 3 months later from complications of the disease.

Discussion

ECD is a rare histiocytic disorder with variable clinical presentation ranging from mild localized disease to life-threatening multisystemic illness.[3] It is 70% to 75% more common in men than women and in the United States, it is most frequently diagnosed in middle-aged adults (mean age at diagnosis, 46 years).[3] *BRAF* V600E mutation is seen in 57% to 70% of cases, followed by *MAP2K1* mutation in about 20% of cases.[2] The discovery of underlying mutations in ECD, such as activating kinase mutations and fusions involving MAPK and P13K/AKT pathways, helped establish ECD as a clonal neoplastic disorder; it is classified among the "L" (Langerhans) group of the 2016 revised histiocytosis classification of the Histiocyte Society.[6] In addition, these mutation discoveries transformed the diagnostic and management approaches for ECD.[3]

Clinical Manifestations

ECD is most commonly a multisystemic disease and can affect almost any organ.[3] In this review, we will discuss the most common manifestations of ECD.

Skeletal manifestations

The most frequent manifestation of ECD is long-bone osteosclerosis, which is observed in 80% to 95% of cases.[7,8] It is usually asymptomatic but may present with mild leg bone pain.[7] Although radiological imaging such as x-rays, CT scans, and MRIs can detect osteosclerosis, bone scintigraphy and PET scans are more sensitive modalities. Bone scans show increased radiotracer uptake, and PET scans show ^{18}F-fluorodeoxyglucose uptake most commonly in bilateral femurs and tibia.[7]

Cardiovascular manifestations

Cardiovascular involvement is seen on CT angiography in the form of aortic sheathing ("coated aorta"), secondary to periaortic infiltration. Extension into the main branches of the aorta may or may not be present, and periaortic infiltration is usually asymptomatic.[1] In addition, fibrosis in ECD tends to encircle the aorta without sparing any wall; in contrast, idiopathic retroperitoneal fibrosis rarely affects the posterior wall of the aorta.[4] Other cardiac manifestations include right atrium pseudotumor, coronary artery stenosis, and myocardial infarction due to infiltration of coronary arteries; pericardial involvement may be in the form of pericarditis, pericardial effusion, or cardiac tamponade. Dedicated cardiac MRI is the preferred type of imaging to detect cardiac involvement in ECD.[1]

Pulmonary manifestations

Pulmonary involvement is seen in 30% to 50% of cases.[1] It is generally asymptomatic, but some patients may present with dyspnea on exertion. Thoracic CT scans may reveal pleural involvement as pleural thickening due to infiltration of the pleura or pleural effusions.[9] In addition, interstitial lung disease–like

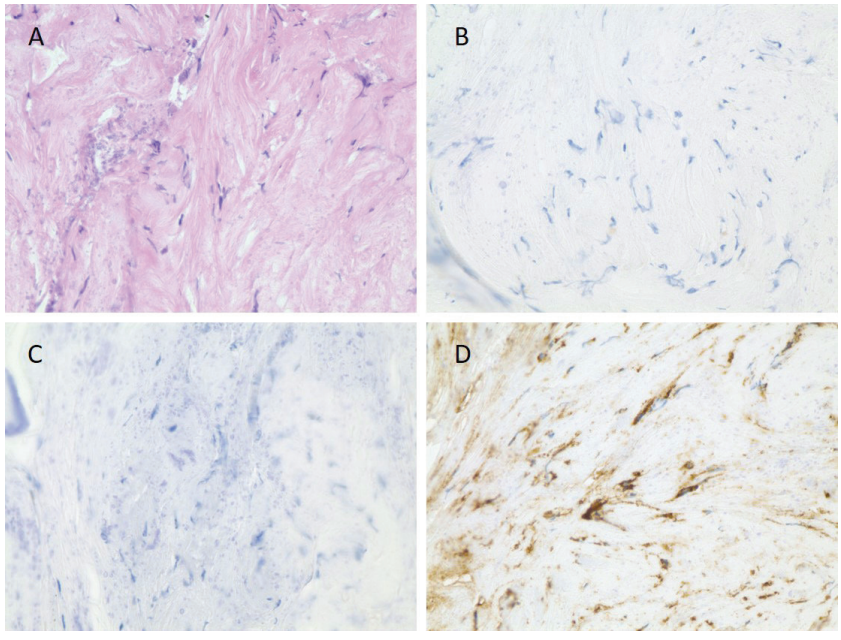

FIGURE 2. **Tibial Biopsy**

(A) Hematoxylin-eosin stain showing hypocellular bone marrow with extensive fibrosis and calcification but an essential lack of xanthomatous histiocytes

(B) Negative CD1a stain

(C) Negative S-100 stain

(D) Positive CD68 stain

patterns—including interlobular septal thickening or, rarely, small centrilobular nodular opacities, ground-glass opacities, and interlobar fissure thickening—can be seen due to infiltration of the lung parenchyma.[2,7,9] Pulmonary function tests show a restrictive pattern in 30% of cases.[7]

Retroperitoneal manifestations

Retroperitoneal involvement is not uncommon.[1] Perirenal fat infiltration and encasement of the kidneys ("hairy kidneys") can be seen on an abdominal CT scan.[1] Retroperitoneal fibrosis can cause renal artery stenoses, which require renal artery stents to control hypertension. It can also cause hydronephrosis due to ureteral obstruction, which may require ureteral stent placement.[7,8]

Endocrine manifestations

ECD can affect any endocrine organ.[1] Diabetes insipidus is usually the first and most common endocrine manifestation in ECD, observed in 33% of cases.[10] Anterior pituitary involvement is not uncommon and can manifest as growth hormone deficiency (53.1%), hyperprolactinemia (44.1%), gonadotrophic hormone (luteinizing hormone and follicle-stimulating hormone) deficiencies (22.2%), thyrotropin deficiency (9.5%), or adrenocorticotropic hormone deficiency (3.1%).[10] Testicular deficiency is seen in 53.1% of men with ECD and is associated with sonographic evidence of bilateral testicular infiltration in 29% of the cases.[10] MRI pituitary reveals infiltration of the pituitary and its stalk in some cases.[10] Although adrenal insufficiency is rare, adrenal infiltration is a common finding on an abdominal CT, present in 39.1% of patients.[10]

Neurological, orbital, and facial manifestations

ECD is known for numerous and diverse neurological manifestations. Cerebellar and pyramidal syndromes are the most frequent signs (41% and 45% of cases, respectively).[11] Also reported are such other manifestations as seizures (12%), cognitive symptoms like dementia and amnesia (21%), neuropsychiatric symptoms (5%), headaches (5%), cranial nerve paralysis, sensory disturbances, and asymptomatic lesions.[11] A cerebral MRI reveals either infiltrative lesions or meningeal lesions.[11] Infiltrative lesions are seen in the form of nodules or intracerebral masses.[11] Meningeal lesions can be either solitary or multiple meningioma-like tumors or diffuse thickening of pachymeninges.[11] Infiltration of retro-orbital soft tissues that leads to exophthalmos, often bilateral, is seen in one-fourth of patients.[2] Infiltration of sinuses is also common in ECD and more frequently involves maxillary and sphenoid sinuses (47%) than ethmoid and frontal sinuses (17%).[1,12]

Cutaneous manifestations

Skin involvement in ECD is most frequently seen as xanthelasma-like lesions in 25% to 30% of patients; upper eyelids are the most common location.[13] Other cutaneous manifestations of ECD include nonspecific patches or papulonodular lesions affecting the legs, trunk, and/or back.[13,14]

Diagnosis

Diagnosing ECD can be challenging because it requires the interpretation of characteristic histopathologic findings in conjunction with clinical, radiological, and molecular disease findings.[3,15] A biopsy is needed to make the diagnosis of ECD. Histopathology of the affected tissues shows infiltration by foamy or lipid-laden histiocytes surrounded by fibrosis with or without the presence of Touton giant cells.[3,15] On immunohistochemical staining, histiocytes in ECD are positive for CD68, CD163, and factor XIIIa and negative for CD1a and

CD207.[3,15] All patients must be tested for *BRAF* V600E mutation.[3] In *BRAF* V600E mutation–negative cases, alterations in other genes of the MAPK/ERK pathway and P13K/AKT pathways should be tested using targeted-capture next-generation sequencing with a commercially available assay.[3] Cell-free DNA testing can be used as a reasonable alternative in cases where the tissue specimen is insufficient for molecular analysis.[3]

Treatment

Due to the rarity of this disease and the relative lack of sample size, no clinical treatment trials have been designed solely for ECD.[1] However, approximately 60% of patients with ECD have BRAF-activating mutations, making BRAF inhibitors an appealing therapeutic choice.[1] In 2012, 3 patients with ECD and a *BRAF* V600E mutation were treated with and responded to vemurafenib, a BRAF inhibitor.[2] Responses were similar in the phase 2 VE-BASKET trial (NCT01524978) at Memorial Sloan Kettering Cancer Center.[16,17] As for long-term outcomes, the LOVE study (NCT02089724) showed that relapses after 6 months occurred in 75% of patients who stopped vemurafenib.[18] Treatment was restarted in 10 patients, leading to eventual remission.[18] AEs reported with BRAF inhibitors include arthralgia, skin complications (such as keratosis pilaris, spinocellular carcinoma, photosensitivity, and melanoma), DRESS syndrome, pancreatitis, and QT prolongation.[1,18] Tolerance to the treatment varies, as demonstrated by the VE-BASKET trial.[19]

Before the discovery of BRAF inhibitors, interferon alfa was the best initial choice of treatment for ECD, and it still is a possibility for those with *BRAF* V600E mutation–negative disease.[20] In one report of a series of 8 patients who were treated with interferon alfa for a median duration of 23 months, the treatment was said to be well tolerated. However, response to treatment varied from partial regression to complete failure.[21] Reported AEs include severe depression and fatigue.[1,2]

Other possible treatment options include MEK inhibitors like cobimetinib and trametinib. As more evidence emerged that other MAPK/ERK pathway mutations, like *MAP2K1* mutations, exist among *BRAF* V600E mutation–negative patients with ECD, downstream blockade of this pathway was successfully explored in patients with refractory ECD, resulting in robust responses to either cobimetinib or trametinib.[3] The efficacy of cobimetinib as monotherapy has been reported in 3 patients with *BRAF* V600E mutation–negative ECD who were refractory to conventional therapy. All 3 patients showed a sustained metabolic response; they experienced minimal AEs, including vomiting and acneiform rash, but no cardiac or ocular complications.[22]

In a case study of a patient with a *MAP2K1* gene mutation who lacked a complete response to the original treatment of interferon alfa, the regimen was changed to cobimetinib. After 8 months of treatment with cobimetinib, the patient had a normal PET/CT indicative of remission.[23] Another case report revealed a novel "dropped head syndrome," in which a patient with ECD was treated with cobimetinib but developed neck pain and reduced mobility, with no discernible etiology. Symptoms improved upon cessation of the drug, and the patient was then eventually able to tolerate a decreased dosage, which led to the eventual resolution of the disease as evidenced by no new lesions and reduction of old lesions on PET/CT.[24] Another patient with ECD with *MAP2K1* Q56P–mutant disease who was refractory to 4 lines of prior therapy, responded to cobimetinib within a month of treatment; there was resolution of PET-avid disease in renal, aortic, and maxillary sinus infiltrations.[25]

The literature review revealed that trametinib is effective in treating LCH, and we also found a few case reports demonstrating trametinib's efficacy in treating patients with ECD. A case report of a patient with multisystem, multifocal LCH showed that low doses and even intermittent use of trametinib were associated with rapid improvement in most of the disease manifestations.[26] In another case report, a patient with multisystem LCH harboring *MEK1* mutation responded to targeted therapy with trametinib, with complete remission of skin lesions and significant improvement in the symptoms of LCH-induced diabetes insipidus.[27] Moreover, the efficacy of trametinib has also been reported in a patient with ECD who had progressive disease after treatment with both interferon alfa and anakinra and was symptomatic due to inflammatory ascites and renal failure. The patient was then treated with trametinib after *MAP2K1* K57N mutation was detected in perirenal lesions, which resulted in complete resolution of ascites and renal failure.[25] Another patient with ECD was treated with trametinib after dabrafenib failure and had alleviation of symptomatology from the syndrome as well as decreasing C-reactive protein levels, indicating reduction of the disease.[28] A case report of a patient with ECD who received combination therapy of trametinib with dabrafenib reported an AE of a rash, which required dose adjustments and eventually resolved. With this treatment regimen, the patient had a reduction in lesions in the liver, bone, and brain.[29] ■

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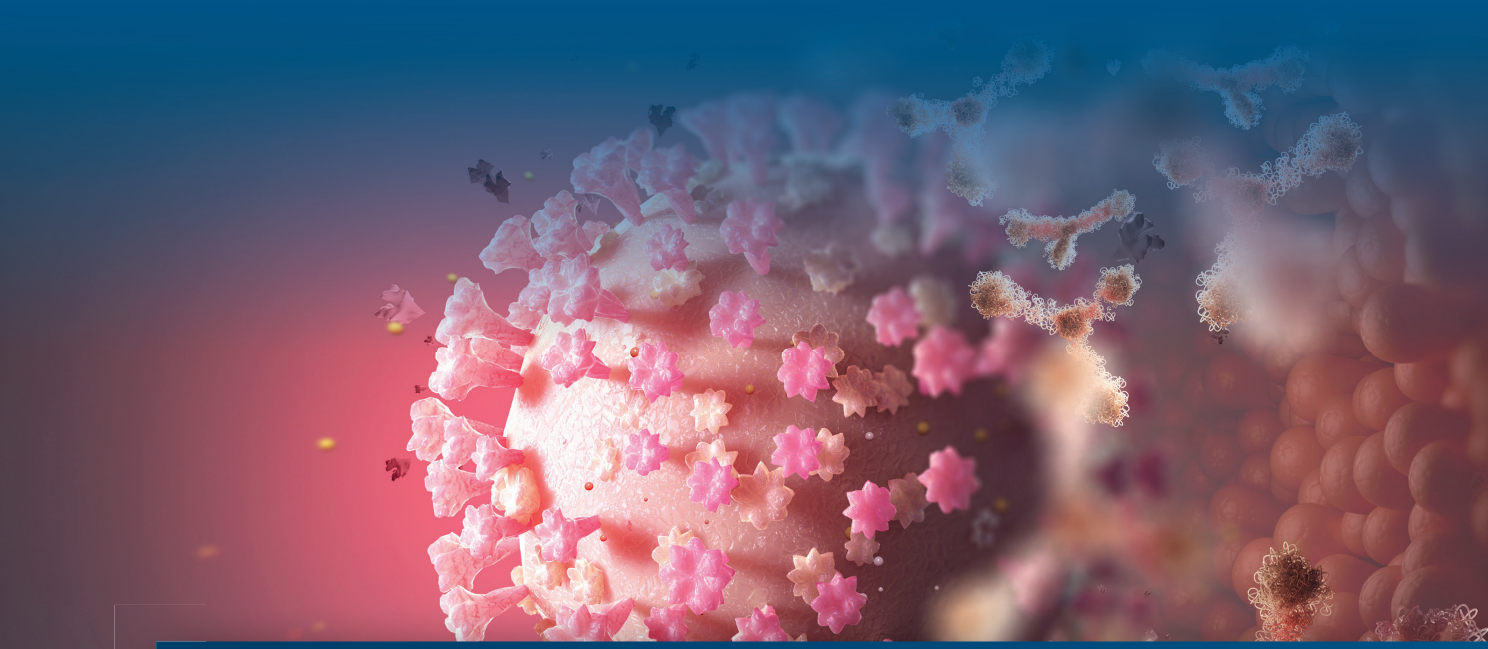

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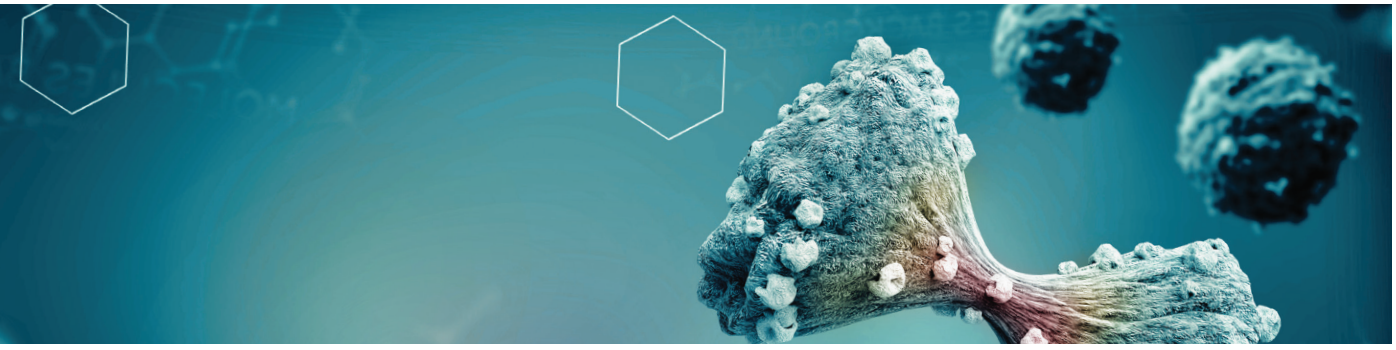
Available Treatment Options in Transplant-Eligible Multiple Myeloma



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At the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, experts in the multiple myeloma space gathered to discuss recent updates and how to implement these new practices in real-world settings. The panel touched on current treatment options for patients who are transplant eligible and have been newly diagnosed with the disease.

The panel was led by **Luciano Costa, MD**, professor of medicine at the University of Alabama at Birmingham. Other panelists included **Susan Bal, MD**, assistant professor of medicine at the University of Alabama at Birmingham; **Matthew James Pianko, MD**, clinical assistant professor at University of Michigan Health; **Joselle Cook, MBBS**, assistant professor of medicine at the Mayo Clinic; **Timothy Schmidt, MD**, assistant professor at the University of Wisconsin; and **Binod Dhakal, MD**, associate professor at the Medical College of Wisconsin.

Options for Determining Transplant Eligibility

The conversation began by discussing how transplant eligibility is determined, and which therapy might be best for this population. Cook noted that to identify patients who are eligible for transplant, she considers chronological and physiologic age, frailty, and comorbidities. She will also consider any patient values that may be expressed when treatment options are discussed.

Pianko approaches transplant eligibility the same way, and typically, when meeting with patients, he presents recent data about how transplant can prolong the duration of time until relapse. Patients who may be eligible for transplant can also be defined as high risk or standard risk, which may determine the type of treatment they'll receive. For those who are high risk, Pianko will recommend a transplant, as better treatment outcomes may be more likely.

Cytogenetics risk may also play a role in determining transplant eligibility for patients who are newly diagnosed. If they have t(4;14), del(17p), t(14;16), and/or gain 1q amplification, each abnormality will factor into making the decision for transplant and a patient's specific treatment path.

A recent study evaluated the combination of daratumumab (Darzalex), carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone as an aggressive treatment to help manage response, and those patients who received a transplant still experienced benefit after transplant, noted Bal. If a patient has 2 or more cytogenetic risk factors, a transplant helps deepen and prolong response and increases the likelihood of remission.

Costa asked Dhakal how he decides on which treatment regimens to give patients, specifically for induction therapy. Dhakal said that the longer follow-up results from the phase 2 GRIFFIN trial (NCT02874742) have shown a benefit from quadruplet therapy as an induction regimen.[1]

"If you look at the standard-risk patients with the DVRd [daratumumab, bortezomib (Velcade), lenalidomide, and dexamethasone] induction followed by transplant and even single-agent maintenance after that, the PFS [progression-free survival] benefit is pretty significant," said Dhakal about the GRIFFIN trial results.

At Mayo Clinic, the Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy is used when treating patients. Often, those with standard-risk disease will receive a triplet regimen and those with high-risk myeloma will receive quadruplet therapy.

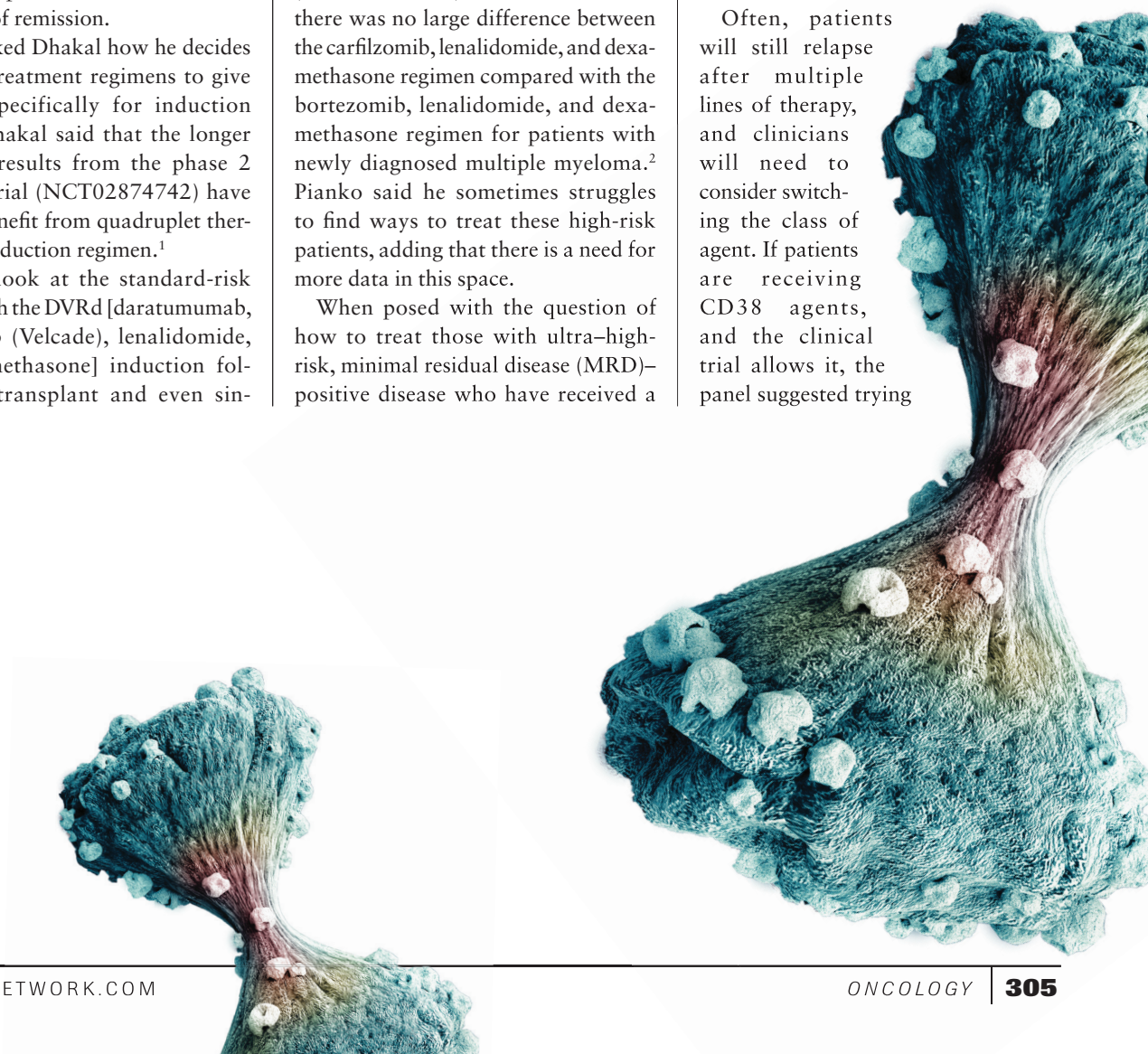
At the University of Michigan, Pianko noted that almost all patients receive quadruplet therapy based on the results of the GRIFFIN trial. However, Pianko mentioned that the results from the phase 3 ENDURANCE trial (NCT01863550) demonstrated that there was no large difference between the carfilzomib, lenalidomide, and dexamethasone regimen compared with the bortezomib, lenalidomide, and dexamethasone regimen for patients with newly diagnosed multiple myeloma.[2] Pianko said he sometimes struggles to find ways to treat these high-risk patients, adding that there is a need for more data in this space.

When posed with the question of how to treat those with ultra–high-risk, minimal residual disease (MRD)–positive disease who have received a transplant, the panelists discussed the treatment options.

"It's important, early on, to define that static feature of their disease, or at least the baseline cytogenetic risk that's present. That's something we know at the time that they present," said Bal.

In high-risk patients who are MRD positive after induction therapy and MRD positive post transplant, the best course of treatment would be to enroll them in a clinical trial. If a trial is not available, begin a doublet therapy, noted Bal. Patients should also be evaluated for risk and comorbidities, the use of immunomodulatory (IMiD) agents, proteasome inhibitors, as well CD36 antibodies plus an IMiD.

Often, patients will still relapse after multiple lines of therapy, and clinicians will need to consider switching the class of agent. If patients are receiving CD38 agents, and the clinical trial allows it, the panel suggested trying



a bispecific B-cell maturation antigen.

Schmidt admitted he was a bit of a latecomer in adapting his practice to include quadruplet regimens for this population. However, patient-reported outcomes, including improvements in symptoms, pain, and quality of life, helped him to determine what regimens he should be using.

Costa asked Dhakal how to define a response that means transplant should be considered and whether treatment options are ever switched halfway through treatment. "I always struggle in the clinic because now we have good drugs, and if you give DVRd to somebody, and after 2 cycles they don't achieve a [partial response], I always get anxious. Having said that, right now my practice is to proceed to transplant as early as possible, again, based on the retrospective data that we have," said Dhakal.

Maintenance Therapy

As the conversation transitioned, Costa asked his colleagues what they believe the ideal amount of time is to keep patients on maintenance therapy after transplant. Cook said that she keeps patients on maintenance therapy indefinitely, or until it's no longer tolerated or progression is observed. Many of her patients tolerate this regimen, even those who are older and at high risk.

Pianko agrees with this practice, especially in helping to dose-manage lenalidomide to mitigate the adverse effects (AEs) experienced. With this management, patients can have ongoing good quality of life and continue therapy.

The panel discussed results from the phase 3 Myeloma XI trial (NCT01554852) presented at the 2022 American Society of Hematology Annual Meeting.[3] This trial aimed to determine the appropriate amount of time for maintenance therapy after transplant. Patients with transplant-eligible disease were randomly assigned 3 months after receiving allogeneic stem cell transplant to be treated with either lenalidomide at 10 mg for days 1 to 21 on each 28-day cycle or undergo observation.

At a median follow-up of 44.7 months, patients demonstrated an improved PFS of 64 months in the lenalidomide arm vs 34 months in the observation arm (HR, 0.52; 95% CI, 0.45-0.61; $P < .001$).

In discussing results from the phase 3 SWOG S0777 (NCT00644228) and MAIA (NCT02252172) trials, Costa wanted to know how to determine the use of DVRd vs daratumumab, lenalidomide, and dexamethasone (DRd). Schmidt tends to prefer the DRd option, as bortezomib may cause peripheral neuropathy and other problems for this population.

Pianko agreed, as he wants his patients to be able to live

full lives without worrying about AEs. "What we've seen, particularly from the MAIA data, is that this [quality of life] is achievable in an older, frail population…we can use a triplet [regimen] and still get patients to have good disease control."

For Dhakal, if there is trouble physically seeing a patient in the clinic, and they might be transplant eligible, he will prescribe the DVRd regimen. He will prescribe a stress test, and if the results are positive, he will send the patient to transplant.

Closing Thoughts

Bal noted that she hoped to see the use of novel immunotherapies in the earlier-line settings to improve responses in this population, specifically for those who are high risk and those who have already received a quadruplet therapy.

As for Schmidt, he said he is hopeful for the future. "I am most excited to see these novel T-cell engagers and [chimeric antigen receptor] T cells move into the early-line settings," he said. "We're all very impressed by the efficacy. The big question, particularly as we move these [treatments] earlier in lines of therapy, is going to be: What is the right way to use these? Particularly with the bispecifics, [the question is]: Do we need to give them indefinitely?" He said he also hopes to find a way to move on from indefinite therapy for patients across the board. ■

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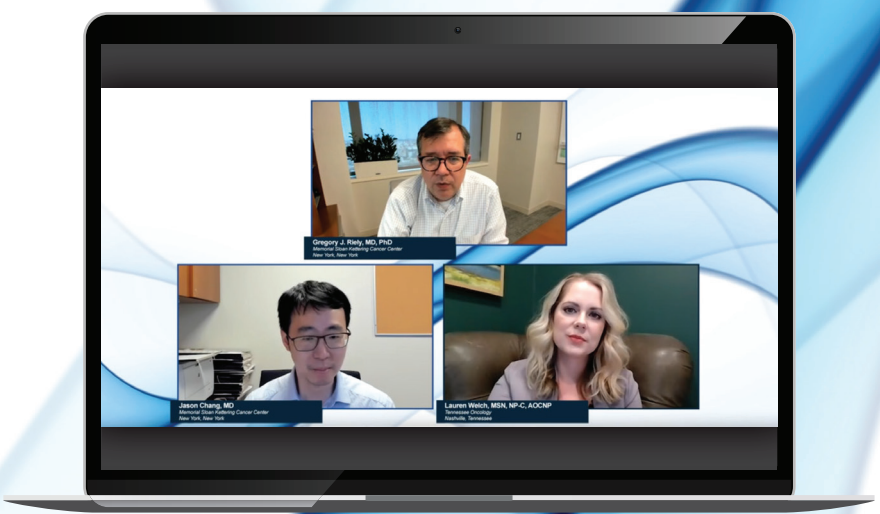

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Since the first randomized clinical trials showed their superiority to chemotherapy nearly 30 years ago, high-dose melphalan followed by autologous stem cell transplantation (ASCT) after the completion of induction therapy has remained the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM).[1] However, accumulating data show that impressive efficacy and deep responses can be achieved with newer triplet and quadruplet induction regimens that contain combinations of immunomodulatory drugs and proteasome inhibitors. This has raised the question of whether ASCT is needed for the initial treatment of eligible patients with NDMM. Krina Patel, MD, MSc, is a leading multiple myeloma expert at the University of Texas MD Anderson Cancer Center. In this article, Patel shares her views on the current role of ASCT in multiple myeloma and how it may change in the future.

Q: Can you start by summarizing some of the most recent clinical data on up-front ASCT in the era of novel therapies?

PATEL: Transplant has been available for a long time now as a sort of consolidation after induction therapy for patients with multiple myeloma.[1] There have been several randomized trials comparing outcomes between transplant vs no transplant in newly diagnosed myeloma. IFM 2009 [NCT01191060] was one of the initial randomized studies involving a novel triplet induction regimen.[2]

The study included 700 patients with newly diagnosed multiple myeloma who were assigned to get 8 cycles of lenalidomide, bortezomib, and dexamethasone (RVd) vs 3 cycles of RVd plus high-dose melphalan consolidation with ASCT, and then 2 cycles of RVd consolidation, with both arms receiving lenalidomide maintenance for 1 year. What we saw was that patients in both arms did really well compared with historical controls from before we had any available triplet regimens. The median progression-free survival (PFS) was 50 months in the transplant arm and 36 months with RVd alone. More than 60% of patients in both arms were alive at 8 years, but the study wasn't designed to answer the question of whether transplant improves overall survival (OS).[3] The other major finding from this study was that the rate of patients with undetectable minimal residual disease (MRD) at 10^{-5} was 29.8% in the transplant arm compared with 20% with RVd alone.

More recently, the DETERMINATION trial [NCT01208662] evaluated 722 patients who received 3 cycles of RVd and were randomly assigned to receive high-dose melphalan plus ASCT and 2 additional RVd cycles or 5 additional RVd cycles alone.[4] Patients in both arms received lenalidomide until disease progression. And again, this study found that patients in the transplant arm had a much longer median PFS of 67.5 months vs 46.2 months in the nontransplant arm.

The key piece of information this study added was regarding quality of life. We know that it decreases in the initial months after transplant, especially if patients are in the hospital with nausea, vomiting, hair loss, weight loss, and low appetite. The DETERMINATION trial showed that the drop in quality of life usually resolves after the first couple of months following transplant and was actually higher in the long term for these patients compared with those who received RVd alone, possibly because continued therapy with bortezomib led to more neuropathy or higher risk of clots with lenalidomide or fatigue from longer doses of both treatments.

Finally, in February 2023, results from the CARDAMON trial [NCT02315716] were published by Yong et al in *The Lancet Haematology*.[5] This study was conducted in the United Kingdom and included treatments that are a little bit different from what we usually use in the United States. They looked at 281 patients who received carfilzomib, cyclophosphamide, and dexamethasone (KCd) and were randomized to either high-dose melphalan plus ASCT or 4 additional cycles of KCd, followed by 18 cycles of carfilzomib, in both arms.

The study found that the 2-year PFS rate was 75% for the patients who got transplant vs 68% for the patients who were treated with KCd alone, which exceeded the prespecified noninferiority margin. The biggest safety findings were grade 3 or 4 lymphocytopenia events with lymphocytopenia and infection resulting from the combination of cyclophosphamide and carfilzomib, as well as hypertension from the maintenance carfilzomib. In the end, this was another study showing that more patients are getting deeper responses with ASCT, but it matters what induction and maintenance treatment you use in terms of both efficacy and quality of life.

Q: How do you reconcile the absence of data showing an OS benefit for transplant?

PATEL: The lack of data showing an OS benefit is a big issue. You'll see some of our colleagues in both academia and the community ask, if there's no OS benefit, then how can we say transplant is better? These trials weren't built to look at OS. The challenge is that it's hard to determine the effect of transplant in newly diagnosed patients because we now have so many other options for them. For example, what if a patient who didn't undergo ASCT got access to early chimeric antigen receptor (CAR) T-cell therapy on a clinical trial, but a patient who got a transplant wasn't eligible? Survival includes all the other therapies these patients got down the road. It's so hard to differentiate the effect of transplant from the different therapy

that they got in the end, so it ends up looking like everybody fared about the same.

But from a practical view, if 2 patients come in today and 1 relapsed at 56 months vs the other at 32 months, I'll be treating those 2 patients very differently in their second line. And every 6 months to a year, we tend to get brand-new treatments that are pulled up earlier, and that's likely to make a big difference for OS over time. So, in the academic world, I think many more of us think that transplant is still something we should be doing for a lot of our patients because it is the most effective way of clearing the bone marrow and getting to MRD undetectability, which then prolongs PFS and theoretically OS, since these patients are then able to enroll in trials of newer agents in earlier settings.

"In the academic world, I think many more of us think that transplant is still something we should be doing for a lot of our patients."

Q: So, putting this all together, what is your approach to counseling patients on ASCT in your practice?

PATEL: It really comes down to the fact that not all patients with myeloma are the same. At first, it's all about finding the high-risk patients. We talk about MRD undetectability and depth of response, and again, if the data show that you have roughly 30% of patients in the transplant arm getting to MRD undetectability, vs 20% of patients in the nontransplant arm, you're increasing the chances by 10%.[3] We know those patients with high-risk cytogenetics can reach MRD undetectability and then 2 months later relapse with horrible disease. Those are the patients that, no matter what, I'm saying, "Hey, let's do a transplant and get you the best depth of response that we can."

For my older patients, those who are 75 or older, I'll be the first one to say that age is just a number when it comes to transplant and it's really about their functional status. However, at most centers, older patients automatically get a decreased dose of 140 mg/m^2 because they have less reserve.[6] And if they end up with an infection or have significant weight loss, it's a lot harder for them to get back to normal. There's also a higher risk of developing a secondary cancer for these patients.[7] Now that we have data from the MAIA study [NCT02252172] in older, transplant-ineligible patients showing that daratumumab with lenalidomide and dexamethasone has a median PFS of over 5 years, you start thinking even more about the risks vs benefits of transplant.[8]

Then we have our patients who are somewhere between standard and high risk, where there are less data on the potential benefits of transplant. A lot of oncologists and myeloma specialists will use MRD undetectability as a marker in these patients.[9] For those who get a stringent complete response after 4 or 5 cycles of induction and are MRD negative at 10^{-6}, do they really need transplant? I'll say we probably don't have enough data yet, but a lot of us use MRD detectability as a biomarker.

"For those who get a stringent complete response after 4 or 5 cycles of induction and are MRD negative at 10^{-6}, do they really need transplant?"

Q: Let's talk a little bit about the definition of transplant eligibility. How do the criteria used in clinical trials compare with what you use in your practice?

PATEL: Transplant eligibility for clinical trials usually requires better cardiac function, so patients must have ejection fractions of 50% to 60%. In terms of kidney function, creatinine clearance has to be at least 30 mL/min, and sometimes even 45 to 60 mL/min. In terms of blood counts, trials typically require absolute neutrophil count above 1, platelets above 50 or even 100, and hemoglobin above 8, with or without transfusions allowed. Most patients have an ECOG performance status of 0 or 1, and any other comorbidities need to be well controlled.[2,4,5]

In the real world, our criteria for transplant look at 2 things: lung function and cardiac function. Patients can have a slight decrease in their lung diffusion test (DLCO) from mild chronic obstructive pulmonary disease, for example, but moderate to severe decreases in DLCO put them at high risk for pneumonia and infection, so we do not take those patients to transplant.[10] For patients with severe cardiac impairments, with ejection fractions of 30% or less, we have to be very careful because melphalan puts them at risk for atrial fibrillation and arrythmias, especially if they are older.[11]

With regard to kidney function, even if someone is on dialysis, we can still take them to transplant. For patients who are not quite on dialysis but have stage 4 or 5 kidney disease, we discuss the possibility that inflammation during the transplant period could put them onto dialysis. However, the goal is that, if we can get their light chains down and kill the myeloma, we will hopefully help their kidney function in the long term.[12]

Q: Another important consideration about ASCT is access. Can you share some of the recent data about racial disparities in utilization of ASCT?

PATEL: I think the access question is such an important one. There was a study by Fiala et al from 2017 published in *Cancer* that looked at disparities in treatment use for multiple myeloma.[13] They found that 54% of the approximately 21,000 patients in the SEER database were eligible for transplant, but overall, the use of transplant was very low. Only 7% of patients underwent the procedure. Their initial regression model, which controlled for comorbidities and overall health, found that ASCT was used in 8% of White patients vs 4% of Black patients, with Black patients being 49% less likely to use ASCT. When they controlled for other potential access barriers, such as Medicaid and urban vs rural geography, Black patients were still found to be 37% less likely to undergo stem cell transplant.

This highlights that we need to learn more about how to get access for all our patients. It's more complicated than just socioeconomics or comorbidities. And, unfortunately, we've seen a similar trend in clinical trials that have been done for CAR T-cell therapies, where our minority patients aren't represented as much as they should be.[14]

"Black patients [were] 49% less likely to use ASCT.... This highlights that we need to learn more about how to get access for all our patients."

Q: What steps is your institution taking to try to improve equitable access to stem cell transplant and other novel therapies?

PATEL: At MD Anderson, we are conducting several studies looking at the socioeconomic aspects of care, including social determinants of health, zip codes of where our patients are coming from, and how we might improve access from our county hospitals. We also look at our enrollment in clinical trials every week to see how many patients were Black, Hispanic, Asian, or White to make sure we are at least offering these trials to all our patients.

The other big thing is that everyone on our team—from the faculty to the nursing staff, research teams, data coordinators, and people drawing blood—comes from different backgrounds. We all try to tell our patients the same story of why we do research and why clinical trials are important. A lot of our patients are scared of participating in clinical trials because of the history of medicine in minorities, so we take that extra time to say that they're not a guinea pig, that these trials might be a way for them to have access to a great therapy before it's even available as a standard of care, and to answer any questions. It takes a lot of infrastructure, time, and effort, but I think it's really worth it.

Q: Looking now to the future, CAR T cells and bispecific antibodies are the latest breakthroughs in multiple myeloma. Can you share some of the recent data on moving CAR T-cell therapy into earlier lines of treatment?

PATEL: Among myeloma doctors, I think that the results from CARTITUDE-4 [NCT04181827], which were revealed at ASCO and then repeated at EHA, were the most anticipated data from the summer meetings.[15,16] This was a randomized, phase 3 study in the second- to fourth-line setting looking at ciltacabtagene autoleucel (cilta-cel) vs standard-of-care pomalidomide, bortezomib, and dexamethasone or daratumumab, pomalidomide, and dexamethasone in patients who were refractory to lenalidomide. The study found a huge PFS benefit, with a HR of 0.26, and a 12-month PFS rate of 76% in the cilta-cel arm when looking at the entire study population. The 12-month PFS rate was even higher at 90% in the patients who actually received the cilta-cel infusion. But, when you're comparing CAR T-cell therapy to something like off-the-shelf bispecific antibodies or daratumumab, then you have to include everybody in the analysis, and there were several people in the study who did not receive cilta-cel because of disease progression during the bridging phase.

I was also able to present another abstract on a subgroup analysis of the KarMMa-3 study in high-risk patients.[17] KarMMa-3 [NCT03651128] looked at idecabtagene vicleucel (ide-cel) in the third to fifth line vs 5 different standard-of-care therapies. Roughly 85% to 90% of patients in the study would be considered in some kind of high-risk category because of high-risk cytogenetics, Revised International Staging System III disease at study enrollment, extramedullary disease, more than 50% myeloma in their bone marrow, or triple-class refractory disease. And in all those different subgroups, we were able to show that the HRs were still in favor of the ide-cel arm.

Right now, having approval for CAR T in the fifth line often doesn't help our high-risk patients because we can't get them that therapy soon enough. Our hope is that if it is approved in the second- or third-line, my high-risk patients who can't get into trials because their disease explodes too fast will finally have something that can change their outcomes.

Q: Do you think CAR T-cell therapy could one day replace ASCT?

PATEL: I hope so! Having [performed] a transplant I was all for

melphalan. It works great, it's cheap, and it's available around the world. But this is a hammer of a drug, and we need to be smarter against myeloma. I think treatments like CAR T-cell therapy are finally getting us there, and there are several exciting ongoing clinical trials. CARTITUDE-5 [NCT04923893] is looking at first-line cilta-cel in transplant-ineligible patients and CARTITUDE-6 [NCT05257083] is randomly assigned transplant-eligible patients to cilta-cel or transplant.[18,19] I'm really excited. I think we're going to see better MRD undetectable rates with cilta-cel compared to transplant. Long term, the questions are going to be around PFS and treatment-related mortality, but I do think there's a chance that cilta-cel could beat transplant. And down the road, I think a combination of BCMA and GPC5D targeting agents, or an anti-BCMA/CD19 CAR T, or even CAR T plus a bispecific antibody for consolidation, may get us to a 100% MRD undetectable rate.[20,21]

Another approach that was looked at in the KarMMA-2 [NCT03601078] cohort 2c was to use ide-cel as a sort of consolidation after transplant in patients who got less than a very good partial response after ASCT, with lenalidomide maintenance at the discretion of the investigator.[22] All 8 of the patients who received lenalidomide maintenance are still in complete remission over 2 years out. The planned phase 3 KarMMa-9 trial will look at this approach more closely.[23] Maybe our high-risk patients are going to need transplant plus consolidation with CAR T-cell therapy.

Q: Are there any final points you'd like to make about the evolving role of stem cell transplant in multiple myeloma?

PATEL: I think melphalan and ASCT in general have revolutionized myeloma treatment for the past 30 years and improved outcomes for patients around the world. In terms of cost benefits, melphalan probably gives us the best bang for the buck out of everything that we can give our myeloma patients right now and has improved PFS and OS when compared with what we had before stem cell transplant. So, transplant isn't completely gone yet.

I do think it's slowly potentially being pushed out, partly because patients do not want to go to transplant and also because of side effects and potential for secondary transplants. We really want to find something that is more efficacious and durable with fewer [adverse] effects. I'm hoping that CAR T, with or without another treatment targeting a different antigen, is going to be the answer. And I'm very hopeful that one day soon during my career, we can officially say that most myeloma patients don't need transplant anymore. ■

For references visit
gotoper.com/dpmm23asc-transplantation