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PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

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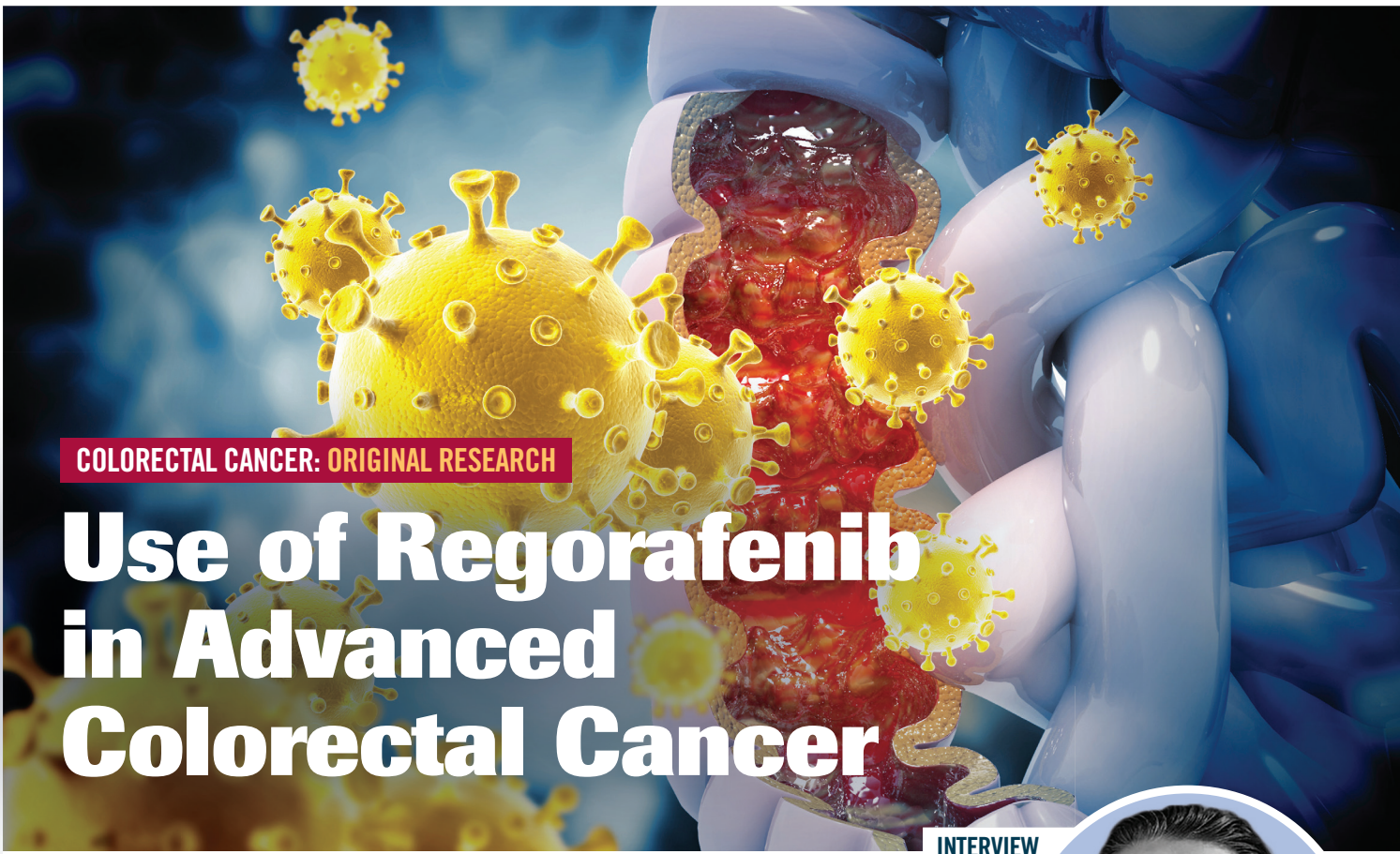


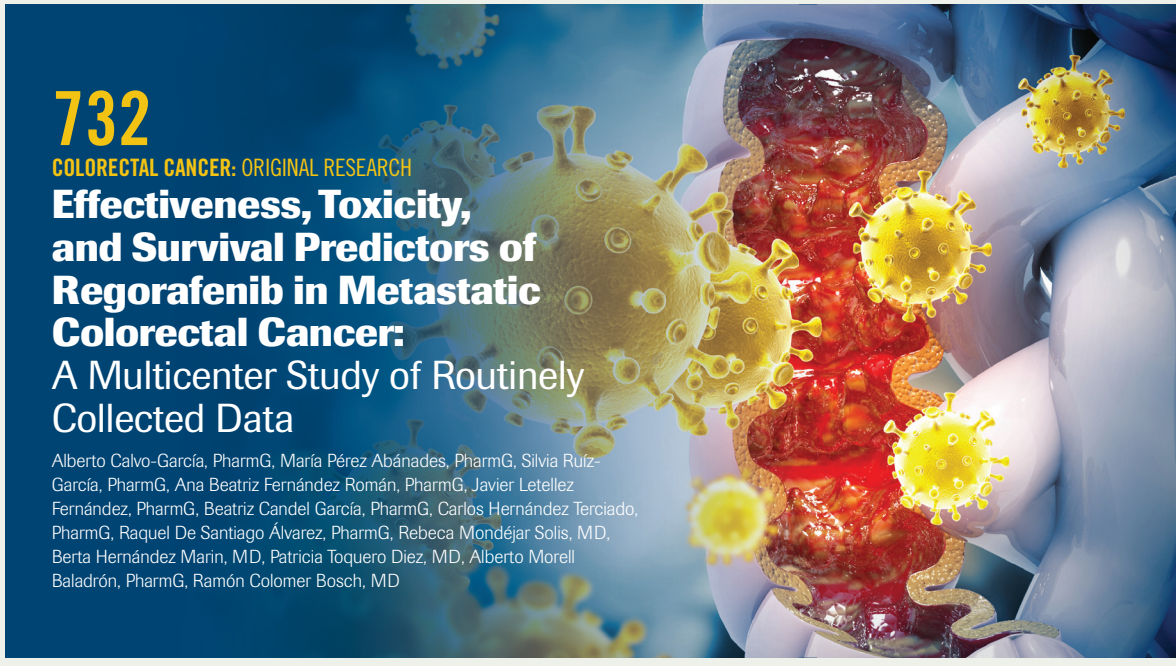
COLORECTAL CANCER: ORIGINAL RESEARCH

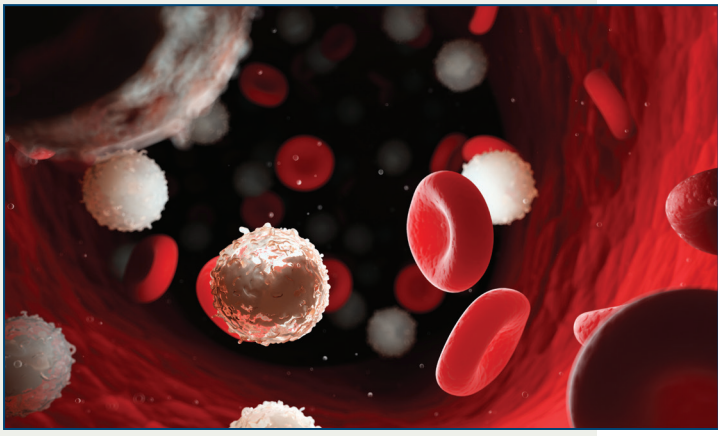
Use of Regorafenib in Advanced Colorectal Cancer

INTERVIEW

Omid Hamid, MD, on Trailblazing Research in Melanoma

OMID HAMID, MD





PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

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PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

DECEMBER 2022 ▪ VOL. 36▪ NO. 12

INDICATION

XPOVIO® (selinexor) is a prescription medicine approved:

- in combination with bortezomib and dexamethasone (XVd) to treat adult patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION

Thrombocytopenia: XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma.

Thrombocytopenia is the leading cause of dosage modifications. Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Monitor patients for signs and symptoms of bleeding. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia: XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection.

Monitor more frequently during the first 3 months of treatment. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity: XPOVIO can cause severe gastrointestinal toxicities in patients.

Nausea/Vomiting/Diarrhea: Provide prophylactic antiemetics or treatment as needed.

Anorexia/Weight Loss: Monitor weight, nutritional status, and volume status at baseline and throughout treatment and provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia: XPOVIO can cause severe or life-threatening hyponatremia.

Monitor sodium level at baseline and throughout treatment.

Serious Infection: XPOVIO can cause serious and fatal infections. Atypical infections reported after taking XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Neurological Toxicity: XPOVIO can cause life-threatening neurological toxicities.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities until the neurological toxicity fully resolves. Institute fall precautions as appropriate.

XPOVIO®
(selinexor)

In multiple myeloma

RESTORE YOUR PATIENTS' OWN CANCER DEFENSES

XPOVIO® is the first and only FDA-approved XPO1 inhibitor that helps restore the body's own tumor suppressor pathways to fight multiple myeloma (MM) as early as first relapse.[1]

FACTOR

XPOVIO combined with bortezomib and dexamethasone (XVd) is approved for adult patients who have received ≥1 prior MM therapy.[1]

See the clinical results at xpoviopro.com.

Embryo-Fetal Toxicity: XPOVIO can cause fetal harm when administered to a pregnant woman.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Cataracts: New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataract requiring clinical intervention was reported.

ADVERSE REACTIONS

The most common adverse reactions (ARs) (≥20%) in patients with multiple myeloma who received XVd were fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract, and vomiting.

Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

Fatal ARs occurred in 6% of patients within 30 days of last treatment. Serious ARs occurred in 52% of patients. Treatment discontinuation rate due to ARs was 19%. The most frequent ARs requiring permanent discontinuation in >2% of patients included fatigue, nausea, thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting. Adverse reactions led to XPOVIO dose interruption in 83% of patients and dose reduction in 64% of patients.

USE IN SPECIFIC POPULATIONS

No overall difference in effectiveness of XPOVIO was observed in patients >65 years old when compared with younger patients. Patients ≥65 years old had a higher incidence of discontinuation due to an adverse reaction (AR) and a higher incidence of serious ARs than younger patients. The effect of end-stage renal disease (CL_{CR} <15 mL/min) or hemodialysis on XPOVIO pharmacokinetics is unknown.

Please see full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact Karyopharm Therapeutics Inc. at 1-888-209-9326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: 1. XPOVIO (selinexor) [prescribing information]. Newton, MA: Karyopharm Therapeutics Inc.; April 2021.

Karyopharm® Therapeutics

XPOVIO Brief Summary

XPOVIO® (selinexor)

BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary is not intended to provide all the information needed to use XPOVIO safely and effectively. Please see XPOVIO Full Prescribing Information at XPOVIOpro.com.

INDICATIONS AND USAGE
XPOVIO is a nuclear export inhibitor indicated:
- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

WARNINGS AND PRECAUTIONS
Thrombocytopenia
XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia is the leading cause of dosage modifications.

Thrombocytopenia was reported in 92% of patients and severe (Grade 3-4) thrombocytopenia was reported in 43%. The median time to first onset was 22 days for any grade thrombocytopenia and 43 days for Grade 3 or 4 thrombocytopenia. Bleeding occurred in 16% of patients with thrombocytopenia, clinically significant bleeding (Grade ≥3 bleeding) occurred in 4% of patients with thrombocytopenia, and fatal hemorrhage occurred in 2% of patients with thrombocytopenia. Permanent discontinuations of XPOVIO due to thrombocytopenia occurred in 2% of patients.

Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia
XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection.

Neutropenia was reported in 48% of patients and severe neutropenia (Grade 3-4) was reported in 12% of patients. The median time to onset of the first event was 23 days for any grade neutropenia and 40 days for Grade 3-4 neutropenia. Febrile neutropenia was reported in <1% of patients.

Obtain white blood cell counts with differential at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity
XPOVIO can cause severe gastrointestinal toxicities.

Nausea/Vomiting
With use of antiemetic prophylaxis (88% of patients), nausea was reported in 50% of patients and Grade 3 nausea was reported in 8% of patients. The median time to onset of the first event was 6 days. Vomiting was reported in 21% of patients and Grade 3 vomiting was reported in 4.1%. The median time to onset of the first event was 8 days. Permanent discontinuation due to nausea occurred in 3.1% of patients and due to vomiting occurred in 2.1% of patients.

Provide prophylactic antiemetics. Administer 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with XPOVIO. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Diarrhea
Diarrhea was reported in 32% of patients and Grade 3 diarrhea was reported in 6% of patients. The median time to onset of the first event was 50 days. Permanent discontinuation due to diarrhea occurred in 1% of patients.

Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Anorexia/Weight Loss
Anorexia was reported in 35% of patients and Grade 3 anorexia was reported in 3.6% of patients. The median time to onset of the first event was 35 days. Permanent discontinuations due to anorexia occurred in 2.1% of patients. Weight loss was reported in 26% of patients and Grade 3 weight loss was reported in 2.1% of patients. The median time to onset of the first event was 58 days. Permanent discontinuation due to weight loss occurred in 1% of patients.

Monitor weight, nutritional status, and volume status at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia
XPOVIO can cause severe or life-threatening hyponatremia. Hyponatremia was reported in 58% of patients and Grade 3-4 hyponatremia was reported in 14% of patients. The median time to first onset was 21 days for any grade hyponatremia and the median time to first onset for Grade 3 or 4 hyponatremia was 22 days.

Monitor sodium level at baseline and throughout treatment. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Assess hydration status and manage hyponatremia per clinical guidelines, including intravenous saline and/or salt tablets as appropriate and dietary review. Interrupt, reduce dose or permanently discontinue based on severity of the adverse reaction.

Serious Infection
XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia. 69% of patients experienced any grade of infection. Grade ≥3 infections were reported in 32% of patients, and deaths from infections occurred in 3.1% of patients. The most frequently reported Grade ≥3 infection was pneumonia in 14% of patients, followed by sepsis in 4.1% and upper respiratory tract infection in 3.6%.

Atypical infections reported after XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Monitor for signs and symptoms of infection, evaluate and treat promptly.

Neurological Toxicity
XPOVIO can cause life-threatening neurological toxicities. Neurological adverse reactions (excluding peripheral neuropathy) including dizziness, syncope, depressed level of consciousness, vertigo, amnesia and mental status changes (including delirium and confusional state) occurred in 26% of patients and severe events (Grade 3-4) occurred in 3.6% of patients. The median time to the first event was 29 days. Permanent discontinuation due to neurological adverse reactions occurred in 2.1% of patients.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurological toxicity fully resolves. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

Embryo-Fetal Toxicity
XPOVIO can cause fetal harm when administered to a pregnant woman.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Cataract
New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataracts requiring clinical intervention was reported in 22% of patients. The median time to new onset of cataract was 228 days and was 237 days for worsening of cataract in patients presenting with cataract at start of XPOVIO therapy. Treatment of cataracts usually requires surgical removal of the cataract.

ADVERSE REACTIONS
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.

Multiple Myeloma
XPOVIO in Combination with Bortezomib and Dexamethasone (SVd)

The safety of XPOVIO in combination with bortezomib and dexamethasone was evaluated in BOSTON. Patients were randomized to receive XPOVIO 100 mg orally once weekly in combination with bortezomib and dexamethasone (SVd) (n=195) or bortezomib and dexamethasone (Vd) (n=204). Among patients who received XPOVIO, the median duration of XPOVIO treatment was 29 weeks (range: 1 to 120 weeks) and the median dose was 80 mg (range: 30 to 137 mg) per week.

Serious adverse reactions occurred in 52% of patients who received XPOVIO in combination with bortezomib and dexamethasone. Serious adverse reactions in >3% of patients included pneumonia (14%), sepsis, diarrhea and vomiting (4% each). Fatal adverse reactions occurred in 6% of patients within 30 days of last treatment, including pneumonia (n=3) and sepsis (n=3).

Grade ≥2 peripheral neuropathy, a pre-specified key secondary endpoint, was lower in the SVd arm (21%) compared to the Vd arm (34%); odds ratio 0.50 [95% CI: 0.32, 0.79]). The median treatment duration was 30 weeks (range: 1-120 weeks) in patients who received once weekly SVd as compared to 32 weeks (range: 1-122 weeks) in patients who received twice weekly Vd.

Permanent discontinuation of XPOVIO due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation of XPOVIO in >2% of patients included fatigue (3.6%), nausea (3.1%), thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting (2.1% each).

Table 5: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received XPOVIO in Combination with Bortezomib and Dexamethasone (SVd) with a Difference Between Arms of >5% Compared to Vd in BOSTON

	Weekly SVd (n=195)		Twice Weekly Vd (n=204)	
Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal				
Nausea	**50**	**8**	**10**	**0**
Diarrhea	**32**	**6**	**25**	**<1**
Vomiting	**21**	**4.1**	**4.4**	**0**
General Conditions				
Fatigue[a]	**59**	**28**	**21**	**5**
Pyrexia	**15**	**1.5**	**11**	**1**
Metabolism and Nutrition				
Appetite decrease	**35**	**3.6**	**5**	**0**
Weight decrease	**26**	**2.1**	**12**	**1**
Nervous System				
Peripheral neuropathy[b]	**32**	**4.6**	**47**	**9**
Dizziness	**12**	**<1**	**3.9**	**0**
Infections				
Upper respiratory tract infection[c]	**29**	**3.6**	**22**	**1.5**
Eye Disorders				
Cataract	**22**	**9**	**6**	**1.5**
Vision blurred[d]	**13**	**<1**	**6**	**0**

Key: S=selinexor, Vd=bortezomib-dexamethasone

a. **Fatigue** includes fatigue and asthenia.

b. **Peripheral neuropathy** includes neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, peripheral sensorimotor neuropathy, toxic neuropathy and peripheral motor neuropathy.

c. **Upper respiratory tract infection** includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, and viral upper respiratory tract infection.

d. **Vision blurred** includes blurred vision, visual acuity reduced and visual impairment.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose (see *Data*). Advise pregnant women of the risks to a fetus.

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.

Data

Animal data

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor at 0, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve [AUC] at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

Lactation

Risk Summary

There is no information regarding the presence of selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with XPOVIO and for 1 week after the last dose.

Females and Males of Reproductive Potential

XPOVIO can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating XPOVIO.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Males

Advise males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Infertility

Females and Males

Based on findings in animals, XPOVIO may impair fertility in females and males of reproductive potential.

Pediatric Use

The safety and effectiveness of XPOVIO have not been established in pediatric patients.

Geriatric Use

Of the 195 patients with multiple myeloma who received XPOVIO in combination with bortezomib and dexamethasone, 56% were 65 years of age and older, while 17% were 75 years of age and older. No overall differences in effectiveness were observed between these patients and younger patients. When comparing patients 65 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (28% vs 13%) and a higher incidence of serious adverse reactions (56% vs 47%).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Dosing Instructions:

- Instruct patients to take XPOVIO exactly as prescribed.
- Advise patients to swallow the tablet whole with water. The tablet should not be broken, chewed, crushed, or divided.
- If a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of XPOVIO, advise them to take the next dose on the next regularly scheduled day.
- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to take their prescribed dexamethasone (if applicable) and prophylactic anti-nausea medications exactly as directed.
- Advise patients that blood tests and body weight will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first three months of treatment.
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment.

Hematologic Adverse Reactions

Thrombocytopenia

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment. Advise patients to report signs of bleeding right away.

Anemia

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia.

Neutropenia

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

Gastrointestinal Adverse Reactions

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist.

Advise patients that they may experience weight loss or decreased appetite. Advise patients to report decreased appetite and weight loss.

Hyponatremia

Advise patients that they may develop low sodium levels (hyponatremia). Most cases of hyponatremia were not associated with specific symptoms. Advise patients that levels of sodium will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first two months of treatment.

Serious Infection

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever).

Neurotoxicity

Advise patients that they may experience confusion and dizziness. Advise patients to report symptoms of neurological toxicity right away. Advise patients not to drive or operate hazardous machinery until the neurological toxicity fully resolves. Advise patients to use fall prevention measures as warranted.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to contact their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the final dose.

Cataract

Advise patients of the potential risk of worsening or new onset of cataract, that may require surgery. Advise patients to readily inform their healthcare professionals of changes in vision (i.e. blurred vision) and that ophthalmologic evaluation may be performed as clinically indicated.

Fatigue

Advise patients that they may experience fatigue.

Lactation

Advise women not to breastfeed during treatment with XPOVIO and for 1 week after the final dose.

Concomitant Medications

Advise patients to take 5-HT3 antagonist prophylactic treatment and other anti-nausea agents prior to and during treatment with XPOVIO.

Advise patients to speak with their physician about other medications they are currently taking and before starting any new medication.

Karyopharm® Therapeutics

For more information, call 1-888-209-9326 or go to www.XPOVIOpro.com.

US-XPOV-01/21-00020 (05/21)

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2022 The Oncology Year in Review

The year 2022 has been a promising one in terms of advancements in the oncology space. Multiple FDA approvals came through, providing additional treatment options across various cancer types. The past year's growth will certainly help further propel treatment improvement in 2023. Here, we discuss some events of the past 12 months that will also impact our patients with cancer, moving forward.

1 Inflation Reduction Act of 2022. This law will provide the most sweeping insurance reform since the Affordable Care Act, and it may actually help even more patients. The cost of oral oncolytics is now a staggering $20,000 to $30,000 per month, and insurance plans with 20% co-pays were never designed for this. Lifetime caps for insurance payments now viciously affect our survivors and these will be eliminated so patients will maintain coverage as they live longer.

Several additional provisions will definitely help our patients financially. Beginning in 2023, insulin and durable supplies will be capped at $35 per month for Medicare patients. In 2024, the "catastrophic phase" of drug costs will no longer require patient co-payments, and in 2025, the full cap on all drug payments will be $2500. Medicare "expansion" and affordable drug plans will continue to be offered through the marketplace and subsidies will continue through the end of 2025, saving approximately $800 per year for each patient enrolled in these Medicare plans.

2 Drug price controls. As a result of the Inflation Reduction Act, Medicare will be able to negotiate drug prices for the first time ever, beginning in 2024. Rather than paying the price for a new drug, CMS will announce 10 drugs (selected from the most costly brand name drugs without competitors) for negotiation, with the negotiated prices starting in 2026. Fifteen more drugs will be negotiated in 2027, and from 2028 on, 20 drugs will be negotiated annually. For the first time, Americans will benefit from the same process used by many government health authorities around the globe, so that we will no longer carry more than our fair share of the costs of new drugs.

3 New drug approvals. The FDA approved 7 new oncology drugs this year, most recently a novel antifolate receptor antibody-drug conjugate (ADC) for ovarian cancer, mirvetuximab soravtansine-gynx (Elahere). The others approved were tebentafusp-tebn (Kimmtrak), a bispecific gp100xCD3 antibody for uveal melanoma; relatlimab-rmbw (Opdualag), a fixed-dose combination of relatlimab, an LAG-3–blocking antibody, plus nivolumab (Opdivo) for melanoma; futibatinib (Lytgobi), an FGFR inhibitor for cholangiocarcinoma; tremelimumab (Imjudo) plus durvalumab (Imfinzi) for unresectable hepatocellular carcinoma; teclistamab-cqyv (Tecvayli), a bispecific B-cell maturation antigen (BCMA) CD3 antibody for use in fifth line or later relapsed/refractory multiple myeloma; and a second peptide radionuclide receptor therapy (PRRT) agent, lutetium Lu 177 vipivotide tetraxetan (Pluvicto), for prostate cancer.

4 Immunotherapy. There was continued progress in the use of immune checkpoint inhibitors (ICIs), with new agents directed against LAG-3 and new indications for combined anti–CTLA-4 and anti–PD-1. In addition, the benefits of earlier use of anti–PD-1 for microsatellite instability–high tumors were shown for the first time in cases of colon and rectal cancer, perhaps eventually to supplant chemotherapy, radiation therapy, and surgery.

5 Cellular therapy. Chimeric antigen receptor (CAR) T-cell therapies continued to expand their utility, with approvals for their use in extended relapsed and refractory

follicular lymphoma. Lisocabtagene maraleucel (Breyanzi) was approved for second-line therapy in large cell lymphoma, and idecabtagene vicleucel (Abecma), directed against BCMA, was approved for refractory myeloma.

6 CRISPR entered the clinic. This novel technology incorporates DNA guides based on bacterial "clustered regularly interspersed palindromic repeats," and it can now be used for actual gene engineering in human patients. With the FDA approval of betibeglogene autotemcel (Zynteglo) in August, under the 21st Century Cures Act (specifically, the provisions for Regenerative Medicine Advanced Therapy), patients with transfusion-dependent double-mutated β-thalassemia, who cannot be treated with stem cell transplantation, can undergo CRISPR editing of their own stem cells to reinsert copies of normal β-hemoglobin genes. This one-time treatment will cost an estimated $1.8 million, but it is felt to be cost-effective, given the costs of frequent transfusions and treatments of iron overload syndromes.

7 Biosimilar approvals. With 4 more biosimilars approved in 2022—pegfilgrastim, bevacizumab, an additional filgrastim, and ranibizumab, a VEGF product for ocular injection—the number of approved biosimilars has now reached 34. These continue to be identified by 4-letter suffixes to create "branded biosimilars." These are not interchangeable or substitutable, causing chaos in our pharmacies and approval processes. We again call on the FDA to make these more like "generics" when prescribing, as there is no clinical basis for preferring one biosimilar over another at this time.

Looking ahead to 2023, what can we expect? To start, more immuno-oncology trials reading out, and further defining the use of current and new ICIs. We will also see novel ADCs, new PRRT agents, and continued advances in cellular therapies including CAR T, T-cell receptor-based therapy, and tumor-infiltrating lymphocytes. We can expect further gene engineering using CRISPR now that the barrier has been broken, with costs of up to $3 million per treatment. It promises to be an exciting year ahead. Happy New Year to all. ■

MEET OUR EXPERT

Omid Hamid, MD is the director of the Melanoma Center and Phase I Immuno-Oncology Program and chief of Translational Research and Immunotherapy at Cedars-Sinai The Angeles Clinic and Research Institute in Los Angeles, California. He also is co-chair of the 18th Annual International Symposium on Melanoma and Other Cutaneous Malignancies®, hosted by Physicians' Education Resource®, LLC.

Omid Hamid, MD, on Trailblazing Research in Melanoma

"You have to be on your game continually, you have to continually self-evaluate, and the field moves quickly."

Novel immune checkpoint inhibitors and adoptive T-cell therapies have dramatically changed the treatment landscape in melanoma over the past several years. Moreover, many treatments originating in the melanoma field also have been successful in other solid tumors. Future advancements, such as T cell–manipulative therapies, promise to expand the armamentarium available to clinicians.

In an interview with *ONCOLOGY*®, **Omid Hamid, MD**, discussed the trailblazing research at the Angeles Clinic and Research Institute in Los Angeles, California, and promising advances in melanoma more generally. He explored the profuse diversity of available treatments and the challenging rigor of clinical research. Additionally, Hamid provided an overview of the prospects for future developments in this treatment landscape.

Q: Which approved treatments for melanoma have you or your colleagues worked with as part of a clinical trial?

HAMID: [I've worked with] ipilimumab [Yervoy], nivolumab [Opdivo], tebentafusp-tebn [Kimmtrak], lifileucel, and the Instil Bio drug ITIL-168. [I was also involved with the] first trial to publish data on MK-3475, which became lambrolizumab and then pembrolizumab [Keytruda]. We [at the Angeles Clinic] have examined all the PD-1 targeting antibodies, including nivolumab, avelumab [Bavencio], durvalumab [Imfinzi], atezolizumab [Tecentriq], and pembrolizumab, in phase 1/2 clinical trials focused on melanoma, lung, and similar solid tumors. We've also been building out our oncolytics program.

Notably, developments in melanoma will now trickle out into other solid tumors. The successes of mass-produced adoptive T-cell therapies [in melanoma] mean they will play a larger and larger role in multiple solid tumors, including head and neck tumors, cervical cancer, lung cancer, and others. [They will follow] the same path as immune checkpoint inhibitors in solid tumors.

Q: Why has melanoma research been a trailblazer for so many years?

HAMID: It's necessary to get buy-in from the community at large [when conducting research]. Additionally, because of the significant immunogenicity of melanoma, the magnitude of response [seen with some of these agents] allows us to venture into other solid tumors where the response may not be as great but where we can nonetheless move our understanding forward. Response rates with single agents in melanoma are lower [than those with combinations], and so we're developing combination regimens for this disease [that may also] improve outcomes in other solid tumors.

On the other side of the coin, [there can be] intense toxicities [with these agents] because the dosing regimens are intense. Those of us working in melanoma have learned from this, and so we've also been trailblazers in dealing with immune toxicities.

Q: What do you enjoy about working in clinical trials?

HAMID: It's hard to maintain the appropriate scientific rigor [in clinical trials] when you have a large staff. Everything has to be precise, and you have to be willing to submit your clinic to review. [For instance], we've been audited multiple times by the FDA to allow us to move drugs into approval. Trials we've performed have led to the approval of many drugs, and [consequently] the FDA has reviewed our clinic and found that we do phenomenal work, but this represents a huge amount of excess labor at a time when there's a physician crunch. That's what makes clinical research so difficult. You have to be on your game continually, you have to continually self-evaluate, and the field moves quickly.

The field of oncology is somewhat like the field of hematology—it's so dynamic that you can't just read up to a point and stop because you'll go to sleep and tomorrow there will be more to know. It's a constant enterprise [requiring] a mastery of these solid tumors.

I'm very happy to be part of my clinic because we've moved away from relying on a single person to know everything. [Instead, we've moved] toward a clinical system [relying on] many experts, not just in solid tumors but also in specific types of treatment processes. For example, in the field of lung cancer there are experts in chemotherapeutics, experts in targeted therapies and targeted therapy resistance, and experts in the new field of immunotherapeutic positions. All of these subfields necessitate significant expertise.

Q: What do you think about optimal treatment planning in melanoma?

HAMID: The major phase 3 clinical trials help us understand how to line up these therapies and the optimal order in which patients should receive them. Moreover, we'll hopefully expand our understanding of predictive and prognostic markers, whatever they might be—PD-1 or PD-L1 staining, mutational burden, microbiome analysis, [or even] the time of day when treatment is given. This can make you want to hit your head against a brick wall because these answers can only come from the rigor of clinical trials and from collaboration.

[Speaking of which], that's the most rewarding non–patient care aspect of my job: being part of a like-minded community of people from around the world whom you enjoy as friends and collaborators. It's a very special community. I started out as a student and then eventually became an apprentice to Jeffrey Weber, MD, PhD. Now I come once a year and sit at the [*18th Annual* International Symposium on Melanoma and Other Cutaneous Malignancies®] as a colleague and learn at the feet of masters. We all recognize the limited amount of time we have, and so a meeting like this symposium serves as a massive download of advancements, standards, thought processes, and collaboration.

Q: What are we learning about adjuvant vs neoadjuvant care? Have any recent data changed your thinking?

HAMID: [Recent data] haven't changed our thinking as a community, but [the data have] lent credence to the fact that relapse-free survival is the wrong signal [to rely on]. We still need to know about combinations as they relate to other combinations through upcoming trials like the phase 3 NADINA [NCT04949113] trial. Neoadjuvant therapy is only [appropriate] for bulky stage III disease. Adjuvant therapy is still the standard of care for all patients, especially those with high-risk stage II and early stage III disease who aren't candidates for neoadjuvant therapy.

Q: Looking over the past year, which trials have been most interesting, and are there any results you're excited about?

HAMID: The data coming from Iovance-sponsored trials and others examining adoptive T-cell therapy, taken together with some of the data on tebentafusp or the new PRAME [preferentially expressed antigen in melanoma]–targeted agents, confirm what we knew [about these agents].

After checkpoint inhibitor therapy, we're looking to use T-cell manipulative therapies, some of which are coming down the pike and already available through clinical trials. This enables us to help patients who become resistant to checkpoint inhibitors by allowing us other treatment pathways to explore.

We're only at the beginning. There are many therapies being developed and refined. [For example], clinicians are refining the administration of adoptive T-cell therapy, adjusting either the conditioning, the interleukin stimulus, or the T cells themselves. There are also other agents [being developed] that manipulate the microbiome, or the tumor microenvironment. We still need more intelligence on this modality.

Q: Given the near-infinite number of variables and treatment combinations, how do you design trials to maximize their usefulness?

HAMID: I build programs offering multiple options for patients [to eliminate the need for] repeated, similar trials. I also try to target multiple arms of the immune system. It's also important to continually expand your knowledge base to act as a resource for your patients, rather than just enrolling them on trials without insight into their disease process. ■

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]:

ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial[1-3]

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

Powerful efficacy to start the treatment journey[1,4]

After a median ~30 months* of follow-up, **mPFS was not reached** with DARZALEX® + Rd vs 31.9 months with Rd alone.[1,4]

- **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)

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

- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia
- 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%)

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 PFS.[1]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRR=injection-related reaction; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

*Range: 0.0-41.4 months.[4]

†Kaplan-Meier estimate.

‡Range: 0.03-69.52 months.[3]

§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.

‖3 to 5 minutes refers to the time it takes to administer DARZALEX *FASPRO*® and does not account for all aspects of treatment. For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.[1,5]

Efficacy results in long-term follow-up[2,3]

At median ~5 years (56 months)‡ of follow-up, **mPFS was not reached** with DRd vs 34.4 months with Rd alone.[2]

- **53% of patients had not progressed** after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35)†

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.

Safety results in long-term follow-up (median treatment duration of 47.5 months)[2]

At median ~5 years of follow-up[2,3]:

- Most frequent TEAEs§ ≥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 (19% vs 11%), 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 included in the current Prescribing Information.

With an **~3 to 5 minute subcutaneous injection**, DARZALEX *FASPRO*® can be administered **substantially faster** than intravenous daratumumab[1,5‖]

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appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. 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*®: Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Overall survival results with daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: phase 3 MAIA study. Poster presented at: Virtual 26th European Hematology Association (EHA) Annual Congress; June 9-17, 2021. **3.** Data on file. Janssen Biotech, Inc. **4.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115. **5.** DARZALEX *FASPRO*® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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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.

<u>Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant</u>

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, none of the 111 evaluable monotherapy patients, and 2 of the 1,383 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

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-271933v2

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

cp-267681v2

The Evolving Role of Radiation Therapy in DLBCL: From Early-Stage to Refractory Disease

Gavin Jones, MD[1]; John P. Plastaras, MD, PhD[2]; Andrea K. Ng, MD, MPH[3]; and Chris R. Kelsey, MD[4]

ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Historically, radiation therapy (RT) served as the primary treatment modality for patients with localized disease. While still an option for select patients who are not candidates for systemic therapy, RT is currently used most frequently as a consolidation treatment after chemoimmunotherapy. Consolidation RT is most commonly recommended after an abbreviated course of systemic therapy in patients who have bulky disease or multiple risk factors, or in the setting of a partial response. Consolidation RT is also appropriate in some patients with advanced DLBCL, including those presenting with bulky disease (≥7.5 cm). While many patients achieve sustained remissions after first-line therapy, up to 50% of patients with DLBCL will eventually relapse. The most common salvage options include second-line chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) and chimeric antigen receptor (CAR) T-cell therapy. RT can be used in both settings to optimize clinical outcomes. This includes consolidation RT in patients with localized presentations or bulky disease in the setting of ASCT and bridging RT in select patients undergoing CAR T-cell therapy. RT is also a valuable modality in any patient with symptomatic disease requiring palliation.

PERSPECTIVE

Bradford S. Hoppe, MD, MPH; and Omran Saifi, MD, shares perspective on radiation therapy in DLBCL on page 722

Introduction

Several major advances have been incorporated into the management of diffuse large B-cell lymphoma (DLBCL) over the past 2 decades. PET-CT not only improves the accuracy of initial staging but also provides a means to more precisely assess response to therapy and provide risk-adapted treatment. The incorporation of rituximab into multiagent chemotherapy regimens has significantly improved survival in all stages of disease. Finally, chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed and refractory (R/R) disease.

One of the first modalities used to treat DLBCL was radiation therapy (RT).[1,2] Historically, early-stage DLBCL was managed with RT alone, which successfully controlled about 40% to 45% of cases.[3-5] RT subsequently transitioned to a consolidation modality after chemotherapy[6,7] or chemoimmunotherapy.[8] RT has always been a valuable palliative intervention to alleviate symptoms such as pain. The role of RT continues to evolve in the setting of improved systemic therapies and disease response assessment tools. This article will review the evolving role of RT in

DLBCL, from a consolidation modality in early-stage disease to a bridging modality prior to CAR T-cell therapy in refractory disease.

Consolidation RT: Early-Stage Disease

Pre–Rituximab/PET-CT Era: Prospective Trials

Several randomized studies conducted before the use of rituximab or PET-CT evaluated whether RT provides benefit as a consolidation treatment after a full course of chemotherapy or whether RT might allow for fewer cycles of chemotherapy (**Table 1**).[6,7,9] While now of historical significance, these influential studies shaped the management of DLBCL for many years and provide valuable insights that are still relevant today.

The primary objective of ECOG 1484 was to assess the role of consolidation RT if a complete response (CR) was achieved after a full course of chemotherapy.[6] Patients were initially treated with 8 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). If a CR was achieved by CT imaging, then patients either received consolidation RT (30 Gy) or were observed, depending upon prior randomization. All patients achieving only a partial response (PR) received a higher dose of RT (40 Gy). Notably, the ECOG study enrolled higher-risk patients (31% had disease bulk ≥10 cm; 68% had stage II disease). Among the patients achieving a CR, disease-free survival was significantly greater with consolidation RT (73% vs 56%; P = .05). Overall survival (OS), a secondary end point, also favored consolidation RT but was not statistically significant (82% vs 71%; P = .24). Local failure occurred in only 3 of 79 patients (4%) receiving RT.

The SWOG 8736 study explored a different question: Could RT replace (many) cycles of chemotherapy?[7] Patients were randomized to 8 cycles of CHOP or 3 cycles of CHOP with consolidation RT (40-55 Gy). The SWOG study enrolled more favorable patients than the ECOG trial (68% had stage I; 29% had all gross disease resected at the time of diagnostic biopsy; patients with stage II bulky disease were not eligible). Perhaps unexpectedly, the SWOG study showed that abbreviated chemotherapy with consolidation RT improved both progression-free survival (PFS; 77% vs 64%; P = .03) and OS (82% vs 72%; P = .02) at 5 years compared with a full course of chemotherapy alone, and with less cardiac toxicity. However, there were more late systemic relapses with only 3 cycles of CHOP, such that PFS and OS curves merged by year 10.[10]

Finally, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) 93-4 study was designed to evaluate whether consolidation RT provides value in older patients without risk factors after 4 cycles of chemotherapy.[9] Patients older than 60 years with no adverse prognostic factors per the International Prognostic Index (IPI) were randomly assigned to 4 cycles of CHOP or 4 cycles of CHOP with consolidation RT (40 Gy). This study showed no difference in event-free survival (EFS; 61% vs 64%; P = .6) or OS (72% vs 68%; P = .5) between the 2 arms.

Several lessons can be drawn from these heterogeneous studies conducted in the pre–rituximab/PET-CT era:

- Consolidation RT can still provide value even after a full course of chemotherapy (ECOG 1484);
- A combined modality approach is better than maximizing chemotherapy alone in terms of both efficacy and toxicity (SWOG 8736);
- 3 cycles of chemotherapy (and possibly even chemoimmunotherapy) provides inadequate systemic coverage for some early-stage patients (SWOG 8736);
- Older patients without risk factors derive less benefit from consolidation RT (GELA 93-4).

Rituximab/PET-CT Era: Prospective Trials

More recent studies have evaluated treatment programs in which rituximab is incorporated into the treatment regimen and/or PET-CT imaging is used (**Table 1**). These trials are also heterogeneous regarding eligibility criteria and trial design. RT was often not a randomized variable or even included in the treatment programs investigated. Nevertheless, a careful study of these trials can provide helpful guidance on the optimal management of DLBCL in the current era.

The Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang trial (LYSA/GOELAMS [NCT00841945]) enrolled 319 patients with nonbulky (<7 cm), stage I/II DLBCL.[11] Patients were randomly assigned to 4 to 6 cycles of R-CHOP-14 with or without consolidation RT (40 Gy). Only patients in CR by PET-CT after 4 cycles (n = 281) proceeded with treatment according to their random assignment. A negative scan was defined as having "no abnormally increased ^{18}fluorodeoxyglucose (^{18}F-FDG) at any site." The study was designed as a noninferiority study with an original noninferiority margin of 10%, later decreased to 8%.

By intention-to-treat analysis, the LYSA/GOELAMS study demonstrated that R-CHOP was noninferior to R-CHOP plus RT (5-year EFS rate, 89% vs 92%; HR, 0.61; 95% CI, 0.3-1.2; P = .18). Crude rates of local failure were 4% (5/137) vs 0% (0/144). Several nuances of this study deserve attention. First, 62 patients (~20%) had a negative staging PET-CT after diagnostic excisional biopsy. This would significantly dilute the effect of

consolidation RT. Further, 8 patients randomized to receive consolidation RT declined treatment. Since nonadherence to an allocated treatment in noninferiority studies will bias results in favor of the investigational arm, a per-protocol analysis is typically standard with such trial designs. Yet, no per-protocol analysis was reported for this trial. Finally, 94% of patients had a very favorable modified IPI score (0-1).

The FLYER study (NCT00278421) did not examine the role of RT in early-stage DLBCL but has influenced RT recommendations.[12] Patients 60 years and younger with nonbulky (<7.5 cm) DLBCL and high-grade B-cell lymphoma (HGBCL), without risk factors such as elevated lactate dehydrogenase (LDH) or poor performance status, were randomly assigned to 4 cycles of R-CHOP with 2 additional cycles of rituximab or to 6 cycles of R-CHOP. PET-CT imaging was not standardized within the protocol. This study had 588 evaluable patients and used a noninferiority design with a margin of 5.5%. The PFS rate at 3 years did not differ between arms (96% vs 94%) in the intention-to-treat analysis. A per-protocol analysis (n = 482) showed similar findings (98% vs 94%). The investigators concluded that young patients without risk factors can be successfully treated with 4 cycles of R-CHOP with 2 additional cycles of rituximab.

The Intergroup National Clinical Trials Network Study S1001 (NCT01359592), like the FLYER trial, did not specifically investigate the role of consolidation RT in early-stage DLBCL.[13] In this phase 2 trial, patients with nonbulky (<10 cm) stage I to II DLBCL or HGBCL with or without gene rearrangements and with an ECOG performance status of 0 to 2 were eligible. Patients received 3 cycles of R-CHOP and then underwent an interim PET-CT. Those with a negative PET-CT (Deauville 1-3) received an additional cycle of R-CHOP without consolidation RT. Patients with a positive PET-CT (Deauville 4-5) received consolidation RT (36-45 Gy) followed by ibritumomab tiuxetan.

In general, patients in the S1001 study had more risk factors than those on the LYSA/GOELAMS or FLYER studies but were still relatively low risk (70% stage-modified IPI 0-1). All gross disease was resected in 10% of patients before initiating systemic therapy. More than half (54%) were older than 60 years, an elevated LDH was noted in 15%, and 3% had a performance status of 2. A negative PET-CT was achieved in 110 of 128 patients (86%) after 3 cycles of R-CHOP. Among patients with a negative interim PET-CT who received 4 cycles of R-CHOP, 5-year PFS and OS rates were 89% and 91%, respectively. Among the 14 patients with a positive interim PET-CT, all but 1 received consolidation RT. With the addition of RT, the 5-year PFS rate was 86%, similar to that among patients who had a negative interim PET-CT. Only 2 of these patients relapsed: 1 refused RT and 1 received just a single cycle of chemotherapy

TABLE 1. **Select Randomized Trials in Early-Stage DLBCL**

Study	N	Disease characteristics, stage	Randomization	Progression-free survival rate[a]	Comments
Pre-rituximab/PET-CT era					
SWOG[4,7]	401	I II (nonbulky)	CHOP × 8 CHOP × 3 + RT	64% 77% (*P* = .03)	No difference with long follow-up
ECOG[3]	172	I (high risk) II	CHOP × 8 CHOP × 8 + RT	56% 73%b (*P* = .05)	Only patients in CR by CT were randomized
GELA 93-4[6]	576	I-II without risk factors	CHOP × 4 CHOP × 4 + RT	61% 64% (*P* = .6)	Only patients 60 years or older
Rituximab/PET-CT era					
LYSA/GOELAMS[8]	301	I-II nonbulky	R-CHOP × 4-6 R-CHOP × 4-6 + RT	89% 92% (*P* = .18)	In PET-CT CR
FLYER[9]	592	I-II nonbulky	R-CHOP × 4 + 2R R-CHOP × 6	96% 94%c (*P* = NS)	No risk factors

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GELA, Groupe d'Étude des Lymphomas de l'Adulte; LYSA/GOELAMS, Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang; NS, not significant; R, rituximab; RT, radiation therapy.

[a]5-year, unless otherwise noted; [b]6-year; [c]3-year.

before going off treatment.

The following conclusions can be drawn from modern studies conducted in the rituximab/PET-CT era:

- Chemoimmunotherapy alone, typically with 4 cycles of R-CHOP, provides excellent outcomes in patients with favorable-risk disease who achieve a CR by PET-CT (LYSA/GOELAMS, FLYER);
- Recent studies have excluded patients with bulky disease (variably defined) and almost exclusively enrolled patients with more favorable characteristics compared with the older ECOG and SWOG studies (LYSA/GOELAMS, FLYER, S1001);
- Consolidation RT should be considered for patients who achieve only a PR on interim or postchemotherapy PET-CT (S1001);
- Patients with bulky disease (≥7.5 cm) appear to benefit from consolidation RT (see subsequent discussion on RICOVER-60/RICOVER-noRTh and UNFOLDER studies below, which included early-stage disease).

Consolidation RT: Advanced-Stage DLBCL

Patients with stage III to IV DLBCL are at higher risk of recurrence than those with localized disease. A number of different strategies have been explored to improve outcomes, including incorporation of rituximab,[14] more chemotherapy cycles,[15] more intense chemotherapy[16] or chemoimmunotherapy regimens,[17] dose-dense chemotherapy,[18,19] maintenance rituximab,[20] and high-dose chemotherapy and autologous stem cell transplantation (ASCT).[21] Of these, only the incorporation of rituximab has consistently proved beneficial, and 6 cycles of R-CHOP remains the cornerstone of treatment.

One strategy that has not been studied in depth is consolidation RT. Most recurrences after R-CHOP, even when a CR is achieved by PET-CT, occur at originally involved sites.[22] Several retrospective studies have suggested a benefit for consolidation RT,[22-24] but well-designed randomized studies are lacking.

The RICOVER-60 (NCT00052936), and the subsequent RICOVER-noRTh trial amendment, primarily enrolled patients with advanced disease (50% and 60%, respectively).[25] The original RICOVER-60 trial was a randomized study that investigated different chemoimmunotherapy regimens in older adults (aged 61-80 years) with both early and advanced DLBCL. Those with bulky (≥7.5 cm) or extranodal disease were to receive RT to those areas if a CR or PR was achieved by CT imaging. The original study found that 6 cycles of R-CHOP-14 with 2 additional cycles of rituximab and RT as outlined above achieved the best outcomes. The RICOVER-noRTh trial was an amendment to the original trial in which the optimal chemoimmunotherapy regimen was administered but without RT to bulky or extranodal disease. Comparing outcomes from the 2 studies, the risk of relapse in patients with bulky disease achieving a CR was higher when RT was not administered (22% vs 4%; P = .007). A per-protocol analysis of all patients with bulky disease revealed improved PFS in patients receiving RT (88% vs 62%; P <.001). Of course, these were not randomized comparisons but they suggest that RT improves outcomes in the setting of bulky disease. A limitation of this study was the lack of PET-CT imaging.

The UNFOLDER trial (NCT00278408) enrolled patients 60 years or younger with high-grade non-Hodgkin lymphomas (NHLs), including DLBCL, presenting with an age-adjusted IPI (aaIPI) of 1 or aaIPI of 0 with bulky disease (≥7.5 cm).[26] Patients were randomized to R-CHOP-14 or R-CHOP-21 with a secondary randomization to consolidation RT or observation. PET-CT imaging was not used. A planned interim analysis demonstrated a significantly better 3-year EFS rate for patients randomized to RT (84% vs 68%; P =.001), in part because patients randomized to observation who achieved only a PR (by CT imaging) to chemotherapy proceeded to RT and were scored as an event. This study is published in abstract form only.

A recent retrospective study from British Columbia is notable.[27] Per institutional policy, patients with advanced DLBCL were initially treated with at least 6 cycles of R-CHOP. Only patients who were PET positive at the completion of chemoimmunotherapy received consolidation RT. Patients who achieved a complete response by PET-CT with R-CHOP experienced a 3-year time-to-progression rate of 83% without consolidation RT. However, survival curves demonstrated a continued risk of progression over time. Notably, patients who were PET positive at the completion of chemoimmunotherapy and received consolidation RT had outcomes similar to the PET-negative cohort and far better outcomes than those who were PET positive but did not receive RT. Neither bulky disease nor skeletal involvement were prognostic in the cohort of patients who achieved a CR by PET-CT. Given the favorable outcomes in the PET-positive cohort after consolidation RT (a population at very high risk of progression) and the relatively high risk of recurrence (~25%) in the PET-negative cohort, it seems logical to hypothesize that consolidation RT may be fruitful even after a CR is achieved.

A retrospective analysis of 9 prospective trials of the German High-Grade Non-Hodgkin Lymphoma Study Group evaluated 292 patients with skeletal involvement, 60% of whom had stage III to IV disease.[28] Consolidation RT

PERSPECTIVE BY

Bradford S. Hoppe, MD, MPH[1]; and Omran Saifi, MD[1]

Radiation Therapy in Diffuse Large B-Cell Lymphoma: A Little Boost Gets You Over the Finish Line

Recent advancements in systemic therapies for diffuse large B-cell lymphoma (DLBCL) have revolutionized outcomes and prognosis. Chemotherapy, conjugate antibody systemic therapy, transplant therapy, and chimeric antigen receptor (CAR) T-cell therapy are currently the dominant therapeutic options for DLBCL. Radiation therapy (RT), historically the key treatment for DLBCL, has been swept aside in favor of systemic therapies that are presumed less toxic and more efficacious.

Despite the excellent outcomes with the current upfront PET/CT response-based treatment in early-stage DLBCL without RT,[1,2] one must not overlook certain situations in which RT can have an important positive impact on outcomes. The predominant pattern of relapse of DLBCL following chemotherapy involves the original sites of disease, even in patients who achieve complete remission (CR).[3] Conversely, the predominant pattern of relapse in patients who receive consolidative RT is outside the field of RT.[4] Such predictable patterns of relapse emphasize the important utility of RT to improve local control in patients with high risk of relapse. This may translate into an event-free survival benefit and eventual overall survival (OS) benefit.

Unfavorable factors associated with increased risk of relapse include bulky disease and skeletal involvement, which have been shown to benefit from consolidative RT.[5-9] Further, certain biological factors are associated with increased risk of relapse, such as activated B-cell, double-hit, and triple-hit histologies.[10] While the additional benefit of RT has not been well studied in these patients, their higher risk of relapse, even among those with early-stage favorable disease,[10] calls for consideration of consolidative RT. Similarly, patients whose PET/CT scan results indicate a slow early response (SER) and/or partial response (PR) to initial systemic therapy are at higher risk of relapse. RT can improve these patients' outcomes to the point where they are comparable with those of patients who achieved CR.[7,8,10]

The outcomes of DLBCL in the relapsed/refractory (R/R) setting are poor. This calls for treatment escalation to help improve outcomes. RT plays an important role in the peritransplant[11] and peri–CAR T-cell settings.[12] As the authors mentioned, RT improves outcomes when offered as part of the peri–autologous stem cell transplant (ASCT) regimen. The benefit may be most evident in patients who have bulky or limited sites of disease, or those with a pre-ASCT PR. Similarly, RT is promising as a bridge to CAR T-cell, with a favorable impact beyond palliating symptomatic sites and improving rates of CAR T-cell infusion. Recent work has shown the predominant pattern of relapse following CAR-T in unirradiated patients to involve preexisting sites of disease.[13] This highlights the possibility of using RT to augment local control and durable response rates in patients who present with limited disease prior to CAR T-cell infusion. Patients with limited disease who received comprehensive bridging RT had a trend to better progression-free survival compared with those who did not receive RT.[13] The 1-year local control rate of disease sites bridged with RT is greater than 80%.[12-14] This is impressive when compared with the CAR T-cell therapy historical 1-year durable response rate of about 50%.[15-17] We agree with the authors that patients who present with limited disease prior to CAR T-cell therapy should be treated comprehensively to definitive RT doses. There are no clear data or guidelines on the recommended dose of bridging RT. One might consider escalating the dose in the presence of high-risk features that can predict in-field local failure, which include, but are not limited to, bulky tumor size, Myc/BCL rearrangements,[14] and high tumor metabolic volume.[18]

The combination of a narrow bridging time window and late referrals to radiation oncology constitutes a major challenge for definitive bridging RT attempts. At our institution, we have addressed this challenge with accelerated treatment using twice-daily radiation treatment and early referrals to radiation oncology whenever possible. For patients who present with diffuse disease prior to CAR T-cell therapy, palliative low-dose RT may be sufficient to control both symptoms and disease. R/R DLBCL is radiosensitive, and low-dose RT is sufficient to reprime the immune system and sensitize

the lymphoma cells to CAR T-cell therapy.[19,20]

Despite all the first- and second-line treatment efforts, a significant number of DLBCL patients relapse. At that point, multiple other systemic treatment options can be offered, and RT can provide palliative treatment. However, a subset of patients might still benefit from curative RT. For instance, patients with 1 site of relapse following ASCT had improved OS when treated with salvage RT compared with salvage chemotherapy.[21] This might also apply to patients with limited relapsed disease, post CAR T-cell therapy; recent data show a survival benefit with comprehensive salvage RT.[22]

RT toxicity was a major concern when it was delivered as a systemic therapy—eg, total body irradiation, total lymphatic irradiation, or subtotal lymphatic irradiation. Doses prescribed to these large fields were sometimes up to 40 to 50 Gy. However, modern RT utilizes lower doses.[23] It is more targeted and utilizes contemporary fields[24] and techniques, which leads to reduced doses to the organs at risk, minimizing the acute and late-RT toxicity. The International Lymphoma Radiation Oncology Group has developed expert consensus for treating extranodal and nodal NHL using involved-site radiotherapy (ISRT). These fields are much smaller and more personalized to the patient's initial sites of involvement compared with the previously used involved-field radiotherapy. Toxicity can be further lowered by using newer techniques available, including intensity-modulated radiotherapy and proton therapy for disease located in critical locations such as the mediastinum.[25,26] While data on late effects with contemporary techniques are immature, early data have demonstrated that they are safe and effective.[27-29]

In summary, selected patients with DLBCL have excellent outcomes without RT. However, ISRT in the upfront or R/R setting may prolong remission and avoid subsequent toxic therapeutic approaches when offered to the right subset of patients, who include those with unfavorable characteristics and/or predictable site of relapse (ie, limited disease, bulky disease, SER/PR). ■

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to osseous sites was associated with improved EFS. As in RICOVER-noRTh, PET-CT imaging was not used. Finally, the RICOVER-noRTh study demonstrated a benefit for RT in bulky disease, and it consisted largely of patients with advanced disease (60% of all patients and 77% of those with bulky disease).[25]

Consolidation RT: Treatment Recommendations

Given the data heretofore discussed, we recommend the following for patients who have achieved a CR with chemoimmunotherapy. For patients with stage I to II nonbulky DLBCL with 0 to 1 IPI risk factors, 4 cycles of R-CHOP or 3 cycles of R-CHOP plus RT (30 Gy) are reasonable options. For stage I to II nonbulky DLBCL with ≥2 IPI risk factors, consolidation RT (30 Gy) can be considered after completing chemoimmunotherapy depending upon distribution of disease, response to therapy, risks of RT, etc. We recommend consolidation RT in patients with early or advanced disease in the presence of bulky disease (variably defined in randomized studies; most commonly, >7.5 cm). Select patients with advanced DLBCL without bulky disease can also be considered for consolidation RT, including those with limited skeletal involvement (1-2 sites) or disease located in sensitive areas. A prospective study by the International Lymphoma Radiation Oncology Group is assessing whether 20 Gy is sufficient in the setting of a complete response by PET-CT (Deauville 1-3). In the setting of a partial metabolic response (Deauville 4), a higher dose of RT would be appropriate (40-44 Gy).

Relapsed/Refractory DLBCL

CAR T-Cell Therapy

The majority of patients diagnosed with DLBCL will achieve long-term remission with chemoimmunotherapy. Nevertheless, 20% to 50% of patients will have either primary refractory disease or

TABLE 2. **Select Retrospective Studies Comparing Outcomes of Patients Treated With Peritransplant RT**

Institution/group	Timing	Fields	Dose	Result
PARMA Study Group[43]	Pre-ASCT	Bulky disease >5 cm; extranodal disease	1.3 Gy BID; 26 Gy total	RT: 8/22 (36%) relapsed No RT: 18/33 (54%) relapsed
University of Chicago[52]	Pre-ASCT: n = 1 Post ASCT: n = 6	Bulky or persistent disease	24-58 Gy	RT: 0/7 (0%) failed at prior sites No RT: 16/39 (41%) failed at prior sites
University of Utah[53]	Pre-ASCT: n = 19 Post ASCT: n = 31 Both: n = 3	Variable	NS	RT associated with inferior DFS and no difference in OS; many patients in "no RT" group received TBI
Memorial Sloan-Kettering[54]	Pre-ASCT	Limited disease, bulky disease (≥5 cm), residual masses	1.5 Gy BID to 30 Gy (18 Gy if TBI utilized)	RT: 94% local control No RT: 60% RT associated with improved PFS on MVA
University of Rochester[55]	Post ASCT	Variable	CR: 20-26 Gy PR: 30 Gy Refractory: 30-36 Gy	RT: 37/78 (47%) relapsed No RT: 47/83 (57%) relapsed RT associated with improved DFS and OS on MVA
Autologous Blood and Marrow Transplant Registry[56]	Post ASCT	Variable	NS	RT was associated with improved survival on MVA

ASCT, autologous stem cell transplant; BID, twice daily; CR, complete response; DFS, disease-free survival; MVA, multivariable analysis; NS, not stated; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, radiation therapy; TBI, total body irradiation.

will experience relapse after achieving a CR to systemic therapy. Second-line chemotherapy, typically followed by high-dose chemotherapy and ASCT, has until recently been the most common approach for these patients. Unfortunately, approximately half of patients with R/R DLBCL are not transplant candidates due to age and/or comorbidities; more than 60% of patients with R/R DLBCL will fail to respond to second-line chemotherapy; and about 50% of patients undergoing ASCT will relapse again despite this procedure.[29]

In 2017, the US FDA approved a novel therapy for R/R DLBCL: CAR T-cell therapy. CAR T cells are a type of adoptive cellular transfer immunotherapy, consisting of autologous T cells that are harvested from a patient and then genetically engineered to express chimeric antigen receptor molecules that can target a specific antigen of interest on malignant cells. CD19, a transmembrane protein expressed on all B cells, has proved to be an ideal target for DLBCL. In a typical course, patients undergo leukapheresis, wait a minimum of 2 weeks for the CAR T-cell production process, and are then treated with lymphodepleting chemotherapy several days prior to infusion of the autologous CAR T-cell product. This allows for optimal CAR T-cell survival, expansion, and tumor cell killing upon reinfusion. The genetic engineering breakthrough of CAR T cells, which combine the exquisitely specific antigen-recognition capabilities of antibodies with the downstream cytotoxic effector functions of T cells, has generated considerable interest as one of the most enterprising and technically advanced forms of immunotherapy available.

Three seminal phase 2 clinical trials—JULIET (NCT02445248), ZUMA-1 (NCT02348216), and TRANSCEND-NHL-001 (NCT02631044)—demonstrated overall response rates (ORRs) between 52% and 82% and CR rates between 40% and 54%, with sustained PFS rates around 40% following a single infusion of the engineered cellular product.[30-32] Four autologous CD19-directed CAR T-cell therapies are currently FDA approved for R/R DLBCL: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), brexucabtagene autoleucel (brexu-cel), and lisocabtagene maraleucel (liso-cel).

While CAR T-cell therapy continues to evolve, several major challenges persist affecting utilization (eg, cost), tolerance (eg, cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]), inherent treatment delays, and efficacy. For example, it may take up to 2 months to obtain insurance approval and then manufacture the CAR T-cell product, which necessitates some form of bridging therapy in many patients (discussed in more detail below). Further, about 60% of patients relapse despite CAR T-cell therapy. A European cohort study of 116 patients treated with axi-cel and

tisa-cel for R/R DLBCL revealed that high baseline total metabolic tumor volume (the volume of tumor on PET-CT) at the time of infusion, increased C-reactive protein, and multiple involved extranodal sites were all predictive of early disease relapse.[33] High tumor burden was also associated with a higher risk of recurrence and greater toxicity in ZUMA-1 and in a series from Moffitt Cancer Center.[34,35]

CAR T-Cell Therapy and Bridging Therapy

CAR T-cell production is a multistep process that requires several weeks between T-cell harvesting and reinfusion. In some clinical trials, bridging therapy was allowed during this time frame for patients with symptomatic disease. The intention of bridging therapy is both to provide immediate palliation of symptoms and to prevent disease progression that may jeopardize success of the upcoming CAR T-cell intervention. Bridging therapy may consist of steroids, chemotherapy, immunotherapy, targeted agents, and/or RT.[36] Hematologic malignancies, including DLBCL, are inherently sensitive to RT. As many patients with R/R DLBCL are refractory to chemoimmunotherapy, RT may be an ideal bridging modality.

There are currently few published studies evaluating bridging RT in DLBCL. One of the first case series was from the Moffitt Cancer Center.[37] Patients with high-risk DLBCL (n = 6) or HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements (n = 6) who were treated with bridging RT prior to axi-cel were evaluated. Bulky disease was present in 6 of the 12 patients. Median dose of RT was 20 Gy (range, 6-30 Gy). Patients tolerated RT well, with improvement in symptoms in most patients, no unanticipated adverse effects after CAR T-cell administration, and early outcomes consistent with published studies.

A study from The University of Texas MD Anderson Cancer Center (MDACC) illustrates the difficulty in evaluating outcomes after bridging therapy.[38] Two cohorts of patients with R/R DLBCL were compared: 81 patients received bridging therapy prior to planned axi-cel, and 67 patients did not. Bridging therapy consisted of either systemic therapy alone, RT alone, or RT combined with systemic therapy. As expected, patients requiring bridging therapy had higher-risk disease and inferior PFS rates (20% vs 40% at 1 year; P =.01) and OS rates (48% vs 65% at 1 year; P =.05), in part because many patients who received bridging therapy never ultimately received axi-cel. Among the 3 bridging strategies, those patients who received RT alone had an improved median PFS of 8.9 months, compared with a median PFS of 4.7 months for the cohort that received systemic therapy alone (P =.05). Additionally, bridging RT was associated with increased CR compared with systemic therapy (82% vs 38%; P =.01). Comprehensive RT (treating all sites of active disease), compared with focal RT (treating only select sites), seemed to be associated with improved outcomes (1-year PFS rate, 57% vs 17%; P =.12). Given that the proportions of patients with IPI of at least 3 (P =.48), bulky disease (P =.73), and elevated LDH (P =.09) at the time of leukapheresis were not significantly different between RT and systemic therapy groups, this result suggests that RT may be an effective bridging modality in patients with R/R DLBCL. Larger studies are needed to evaluate this further.

Arscott et al evaluated 41 patients enrolled on a phase 2a study of tisa-cel for various hematologic malignancies, including DLBCL.[39] Patients were divided into 2 groups: those who received RT prior to CAR T-cell infusion and those who had never received RT. The RT cohort was further divided into 3 subgroups: induction RT (<30 days prior to infusion), prior RT (>30 days but <12 months prior to infusion), and remote RT (>12 months prior to infusion). One-year PFS and OS rates in the "no RT" vs "induction RT" groups were 44% vs 78% and 65% vs 100%, respectively. Moreover, grade 3 or higher CRS occurred in 10 of 41 patients overall but in no patients within the induction RT group. The use of radiation therapy did not affect CAR T cell expansion or timing of peak CAR T cell counts.

Finally, a series from the University of Pennsylvania evaluated 31 patients receiving either tisa-cel or axi-cel for R/R DLBCL, 5 of whom received bridging RT.[40] None of the patients receiving bridging RT developed grade 3 or greater CRS or ICANS, whereas the risks of grade 3 or greater CRS and ICANS were 23% and 15%, respectively, among patients who did not receive bridging RT. Clinical outcomes were similar among the 2 groups. Findings from these studies suggest that RT does not impact the efficacy of anti-CD19 CAR T-cell therapy, may improve outcomes in select patients, and may reduce the risk of CRS and ICANS.

Three cohorts of patients may be ideal candidates for bridging RT prior to CAR T-cell therapy. First, RT should be considered for patients with symptomatic disease that is refractory to systemic therapy. Maintaining performance status and controlling pain and other symptoms will help the patient better tolerate the CAR T-cell procedure. Second, patients with bulky disease, or with disease that threatens such organs as the spinal cord or airway at the time of leukapheresis, may also benefit from bridging RT. Bulky disease is known to decrease the efficacy of CAR T-cell therapy, presumably by overwhelming the ability of the immune system to eradicate the entire extent of disease.[34,41] Third, it may be appropriate to consider bridging RT in patients with localized

refractory disease. Treating all gross disease with RT, followed by CAR T-cell therapy, may optimally leverage both modalities and increase the likelihood of success.

The optimal RT schedule, timing, and other such issues remain to be clarified; they are likely dependent on a number of patient-specific factors, including the anatomical location and extent of disease. Nevertheless, certain suggestions and inferences can be drawn from the available data while major consensus awaits the results of clinical trials.

Regarding timing, it seems advisable to delay RT until after apheresis has taken place. Even with low RT doses and minimal bone marrow exposure, circulating lymphocytes within the bloodstream remain susceptible to RT. Prior studies primarily treated patients after apheresis (84% for Moffit, 65% for MDACC, 100% for University of Pennsylvania).[37,38,40] Such concerns must be counterbalanced against the need to treat patients with symptomatic disease awaiting insurance approval, etc.

The optimal dose for bridging RT is also uncertain. In some circumstances, the dose is limited by logistical timing of the CAR T-cell schedule. While many patients have been treated with palliative doses (20-30 Gy), at least 1 study suggests that "definitive" doses may be ideal. Sim et al demonstrated that local control was 100% in patients who received at least an equivalent total dose in 2 Gy fractions (EQD2) of 39 Gy.[34] Of the 12 patients (40%) in this series who progressed despite receiving bridging RT, 8 (67%) experienced progression within the prior RT fields as part of their relapse, while only 4 (33%) progressed systemically, illustrating the importance of local control. Moreover, 7 of the 9 in-field lesion failures that were seen in this series had a baseline lesion of metabolic tumor volume (MTV) greater than 50 cm^3. Very low doses of bridging RT (2-4 Gy × 2) are being considered with the goal of immune "priming." However, there have not been any clinical reports using this strategy to date. The utility of higher doses and prolonged fractionation schemes must be weighed against the putative benefits of shorter RT courses allowing more prompt CAR T-cell infusion.[42]

Bridging RT: Treatment Recommendations

For patients with localized presentations that can be safely encompassed in RT fields, we recommend comprehensive treatment, ideally to definitive doses (eg, ~40 Gy). This can often be accomplished in a hypofractionated manner (eg, 3 Gy per fraction) to expedite treatment and minimize reinfusion delays. If definitive doses are not feasible or practical given the circumstances, a total dose of 20 Gy to 30 Gy in 2 Gy to 4 Gy fractions could be pursued.

Patients with more extensive disease who present with bulky tumors, symptomatic disease, or lymphoma in sensitive locations (eg, spinal cord, airway), we suggest localized irradiation of select sites to a dose of 20 Gy to 30 Gy. Hypofractionation is often feasible (see below).

ASCT and RT

In the PARMA trial, 215 patients with relapsed high-grade NHL were initially treated with second-line chemotherapy.[43] Those who had chemotherapy-sensitive disease (n = 109) were randomized to additional conventional chemotherapy or high-dose chemotherapy and ASCT. Consolidation RT (1.3 Gy twice daily to 26 Gy) was given in the ASCT arm for those with extranodal disease and sites of disease bulk at relapse (≥5 cm). The chemotherapy-alone arm also used RT to a slightly higher dose (1.75 Gy daily; 35 Gy total) but limited RT to sites of disease bulk (≥5 cm).

ASCT was associated with statistically significant improvements in rates at 5 years for both EFS (46% vs 12%) and OS (53% vs 32%), and PARMA established ASCT as a standard for younger patients with R/R DLBCL with chemotherapy-sensitive disease. An analysis of the patterns of failure within the PARMA trial showed that those patients who received RT had fewer relapses (36% vs 55%) compared with patients who did not receive RT, even though the overall irradiated group consisted exclusively of patients with bulky or extranodal disease.[44] Of the 34 irradiated patients who relapsed, 7 experienced recurrences at initial sites of disease. This contrasts with 38 local failures among 75 patients who did not receive RT. Combined with results of multiple smaller institutional series, these results suggest that RT can play an important role in the setting of ASCT (**Table 2**).

The International Lymphoma Radiation Oncology Group has published detailed guidelines regarding RT in the setting of ASCT.[44] We generally recommend post-ASCT RT for patients with bulky and/or localized disease at the time of relapse. A dose of 30 Gy is recommended in the setting of a CR, with higher doses reserved for PRs. With the recent FDA approval of axi-cel as second-line therapy for patients with refractory or early-relapsed DLBCL (discussed below), the role of ASCT in R/R DLBCL will likely diminish and will mostly be limited to those with late relapses (>1 year) after primary therapy.

CAR T-Cell vs ASCT

Three trials have compared CAR T-cell therapy with ASCT in R/R DLBCL. The ZUMA-7 trial (NCT03391466) compared axi-cel with ASCT for patients with refractory or early-relapsed (<12 months) disease and found statistically significant improvements in CR rates (65% vs 32%; P <.001) and EFS (8.3 vs 2 months; P <.001) in those treated with axi-cel.[31] Similarly, the TRANSFORM trial compared liso-cel with ASCT for the same population and also observed higher CR rates (66% vs

39%; P <.001) and median EFS (10.1 vs 2.3 months; P <.001) with the use of CAR T-cell therapy.[45] Finally, the BELINDA trial (NCT03570892) randomized 300 patients with R/R aggressive lymphoma to tisa-cel or salvage chemotherapy and ASCT, with no significant differences seen in the EFS rate at 3 months, ORR (46% vs 43%), or CR rate (28% each) between arms.[46] While these 3 trials differ from one another in certain key respects (eg, crossover allowances, stratification factors, cell manufacturing time, and bridging therapy options), the FDA has approved axi-cel therapy as an acceptable second-line therapy for refractory DLBCL or in patients relapsing within 12 months of completing first-line therapy.

RT as a Palliative Modality

RT has an important role in the management of patients with R/R DLBCL with symptomatic disease. Short courses of RT can alleviate a number of different symptoms, including pain, bleeding, airway or bowel obstruction, and neurologic compromise.[44] Disease that is asymptomatic but threatening critical organs, such as the spinal cord or airway, can also be addressed with RT to prevent impending complications. Finally, RT can also be used as an effective treatment modality for localized progression to delay the need for systemic therapy, which may be associated with a greater adverse effect profile.[47]

In one of the largest and most comprehensive studies of this topic, Tseng et al evaluated 110 patients with R/R DLBCL at Brigham and Women's Hospital/Dana-Farber Cancer Institute who received salvage RT to 121 sites. The median dose was 37.8 Gy (range, 16.5-55.7 Gy).[48] Despite the poor prognosis of such patients, 84% achieved a response (clinical or imaging) and 80% who presented with symptoms experienced improvement during or immediately after RT. Outcomes were not improved with higher doses. A study from the University of British Columbia also found that higher doses were not associated with improved outcomes in the palliative setting.[49] A more recent series from the University of Pennsylvania evaluated outcomes in 92 patients with hypofractionated RT (median dose, 20 Gy) for R/R DLBCL. The ORR was 72% with a CR rate of 53%. Local control at 1 year was 54%.[50]

The optimal doses for palliation of R/R DLBCL remain undefined, and the most suitable regimen may ultimately depend on the clinical scenario. Doses of 20 to 30 Gy administered in a hypofractionated manner are used most frequently. Some studies support the use of very low-dose RT (2 Gy × 2), which is more commonly used in low-grade NHLs. A phase 2 single-institution study of 25 patients with R/R DLBCL reported an ORR of 70%; 13% to 60% functional improvement on day 21 post treatment; a median response duration of 6 months; and a 1-year local control of 34%.[51] Patients with bulky disease or activated B-cell (ABC) subtype may not respond well to this regimen. Given the small number of patients studied and the short response duration, very low-dose RT for DLBCL may be suitable only for patients with an anticipated life expectancy of less than 6 months.

Palliative RT: Treatment Recommendations

A number of different approaches may be appropriate depending upon the clinical circumstances. For patients with a limited life expectancy, very brief regimens would be preferred, such as 4 Gy × 5, 8 Gy × 1, or even 2 Gy × 2 or 4 Gy × 1. For patients with a more favorable outlook, especially with a limited burden of disease, more protracted regimens may be more appropriate (eg, 3 Gy × 10 or 2.5 Gy × 15). The treatment volumes should normally be restricted to gross disease with a small margin. ■

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

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INDICATION AND USAGE

Indication: NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Limitations of Use: NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.
- **Gastrointestinal Toxicities,** including diarrhea, constipation, nausea and vomiting were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

- **Peripheral Neuropathy** was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.
- **Peripheral Edema** was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.
- **Cutaneous Reactions,** including a fatal case of Stevens-Johnson syndrome, were reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated. Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.
- **Thrombotic Microangiopathy** has been reported with NINLARO. Fatal cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.
- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.
- **Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting:** In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) in the NINLARO regimen compared to placebo in combination with lenalidomide plus dexamethasone, respectively were thrombocytopenia (85%, 67%; pooled from adverse event and laboratory data), neutropenia (74%, 70%; pooled from adverse event and laboratory data), diarrhea (52%, 43%), constipation (35%, 28%), peripheral neuropathy (32%, 24%), nausea (32%, 23%), edema peripheral (27%, 21%), rash (27%, 16%), vomiting (26%, 13%), and bronchitis (22%, 17%). Serious adverse reactions reported in ≥ 2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%).

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.
- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

Please see additional Important Safety Information on the previous page and accompanying Brief Summary.

REFERENCES: 1. Moreau P, Masszi T, Grzasko N, et al; for TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-1634. **2.** Minarik J, Pika T, Radocha J, et al. Survival benefit of ixazomib, lenalidomide and dexamethasone (IRD) over lenalidomide and dexamethasone (Rd) in relapsed and refractory multiple myeloma patients in routine clinical practice. *BMC Cancer.* 2021;21(1):7. **3.** Terpos E, Ramasamy K, Maouche N, et al. Real-world effectiveness and safety of ixazomib-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma. *Ann Hematol.* 2020;99(5):1049-1061. **4.** NINLARO. Prescribing Information. Takeda Pharmaceuticals America, Inc.; 04/2022. **5.** Hájek R, Minařík J, Straub J, et al. Ixazomib-lenalidomide-dexamethasone in routine clinical practice: effectiveness in relapsed/refractory multiple myeloma. *Future Oncol*. Published online March 26, 2021. doi:10.2217/fon-2020-1225. **6.** Gandolfi S, Laubach JP, Hideshima T, Chauhan D, Anderson KC, Richardson PG. The proteasome and proteasome inhibitors in multiple myeloma. *Cancer Metastasis Rev.* 2017;36(4):561-584.

NINLARO® (ixazomib) capsules

4mg | 3mg | 2.3mg

NINLARO® (ixazomib) capsules 4mg | 3mg | 2.3mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION
NINLARO (ixazomib) capsules, for oral use

1 INDICATIONS AND USAGE

NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Limitations of Use: NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. The rate of platelet transfusions was 10% in the NINLARO regimen and 7% in the placebo regimen. Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 52% of patients in the NINLARO regimen and 43% in the placebo regimen, constipation in 35% and 28%, respectively, nausea in 32% and 23%, respectively, and vomiting in 26% and 13%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 16% in the placebo regimen) and Grade 2 (11% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 27% and 21% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (17% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. Peripheral edema resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 27% of patients in the NINLARO regimen and 16% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (15% in the NINLARO regimen and 9% in the placebo regimen) or Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Serious adverse reactions of rash were reported in <1% of patients in the NINLARO regimen. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher. Stevens-Johnson syndrome, including a fatal case, has been reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated.

5.6 Thrombotic Microangiopathy: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

5.7 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animal studies. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

5.9 Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting: In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

6 ADVERSE REACTIONS

6.1 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 from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=361) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=359).

The most frequently reported adverse reactions (≥20% with a difference of ≥5% compared to placebo) in the NINLARO regimen were thrombocytopenia, neutropenia, diarrhea, constipation, peripheral neuropathy, nausea, peripheral edema, rash, vomiting, and bronchitis. Serious adverse reactions reported in ≥2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%) and bronchitis (2%). One or more of the three drugs was permanently discontinued in 4% of patients reporting peripheral neuropathy, 3% of patients reporting diarrhea and 2% of patients reporting thrombocytopenia. Permanent discontinuation of NINLARO due to an adverse reaction occurred in 10% of patients.

Table 4 summarizes the non-hematologic adverse reactions occurring in at least 5% of patients with at least a 5% difference between the NINLARO regimen and the placebo regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥5% of Patients with a ≥5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

	NINLARO + Lenalidomide and Dexamethasone N=361			Placebo + Lenalidomide and Dexamethasone N=359		
System Organ Class / Preferred Term	(%)			(%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Gastrointestinal disorders						
Diarrhea	52	10	0	43	3	0
Constipation	35	<1	0	28	<1	0
Nausea	32	2	0	23	0	0
Vomiting	26	1	0	13	<1	0
Nervous system disorders						
Peripheral neuropathies†	32	2	0	24	2	0
Musculoskeletal and connective tissue disorders						
Back pain*	27	<1	0	24	3	0
Infections and infestations						
Upper respiratory tract infection*	27	1	0	23	1	0
Bronchitis	22	2	0	17	2	<1
Skin and subcutaneous tissue disorders						
Rash†	27	3	0	16	2	0
General disorders and administration site conditions						
Edema peripheral	27	2	0	21	1	0

Note: Adverse reactions included as preferred terms are based on MedDRA version 23.0.

*At the time of the final analysis, these adverse reactions no longer met the criterion for a ≥5% difference between the NINLARO regimen and the placebo regimen.

†Represents a pooling of preferred terms

(Continued on next page)

Table 5 represents pooled information from adverse event and laboratory data.

Table 5: Thrombocytopenia and Neutropenia

	NINLARO + Lenalidomide and Dexamethasone N=361		Placebo + Lenalidomide and Dexamethasone N=359	
	(%)		(%)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Thrombocytopenia	85	30	67	14
Neutropenia	74	34	70	37

Herpes Zoster

Herpes zoster was reported in 6% of patients in the NINLARO regimen and 3% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider's discretion. Patients treated in the NINLARO regimen who received antiviral prophylaxis had a lower incidence (1%) of herpes zoster infection compared to patients who did not receive prophylaxis (10%).

Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 38% in patients in the NINLARO regimen. The most common adverse reactions of the eyes were cataract (15%), conjunctivitis (9%), blurred vision (7%), and dry eye (6%).

Other Clinical Trials Experience

The following serious adverse reactions have each been reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inducers: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. 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 2-4% and 15-20%, respectively.

8.2 Lactation: Risk Summary: There are no data on the presence of ixazomib or its metabolites in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions from NINLARO in a breastfed infant, advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential: NINLARO can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO. Contraception: *Females:* Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the last dose. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. *Males:* Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days after the last dose.

8.4 Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment: In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: Overdosage, including fatal overdosage, has been reported in patients taking NINLARO. Manifestations of overdosage include adverse reactions reported at the recommended dosage. Serious adverse reactions reported with overdosage include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death. In the event of an overdosage, monitor for adverse reactions and provide appropriate supportive care. NINLARO is not dialyzable.

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdosage has led to deaths *[see Overdosage (10)]*.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

[see Dosage and Administration (2.1)]

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising. *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their healthcare providers if these adverse reactions persist. *[see Warnings and Precautions (5.2)]*.

Peripheral Neuropathy: Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs. *[see Warnings and Precautions (5.3)]*.

Peripheral Edema: Advise patients to contact their healthcare providers if they experience unusual swelling of their extremities or weight gain due to swelling *[see Warnings and Precautions (5.4)]*.

Cutaneous Reactions: Advise patients to contact their healthcare providers immediately if they experience new or worsening rash *[see Warnings and Precautions (5.5)]*.

Thrombotic Microangiopathy: Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur *[see Warnings and Precautions (5.6)]*.

Hepatotoxicity: Advise patients to contact their healthcare providers if they experience jaundice or right upper quadrant abdominal pain *[see Warnings and Precautions (5.7)]*.

Other Adverse Reactions: Advise patients to contact their healthcare providers if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, herpes zoster, cataracts, dry eyes, blurred vision, conjunctivitis and thrombotic thrombocytopenic purpura *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose. Advise women using hormonal contraceptives to also use a barrier method of contraception *[see Use in Specific Populations (8.1)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose *[see Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose *[see Use in Specific Populations (8.2)]*.

Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLAROhcp.com.

05/22 USO-IXA-0420

Effectiveness, Toxicity, and Survival Predictors of Regorafenib in Metastatic Colorectal Cancer:

A Multicenter Study of Routinely Collected Data

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ABSTRACT

OBJECTIVES: To assess the effectiveness and toxicity of regorafenib in patients with metastatic colorectal cancer (mCRC) in routine clinical practice, as well as predictive factors of effectiveness.

METHODS: This was a retrospective multicenter study in patients with mCRC who received regorafenib from November 2013 to May 2020. Effectiveness was evaluated by overall survival (OS) and progression-free survival (PFS) using the Kaplan-Meier method. Cox regression was performed to determine survival predictors.

RESULTS: Ninety patients were enrolled (median age, 64.3 years). Fifty-two patients (57.8%) were male, and 57 (63.3%) had an ECOG performance status (PS) of 0 to 1. Median follow-up was 2.80 months. Median OS was 8.03 months (95% CI, 5.90-10.17), and median PFS was 2.90 months (95% CI, 2.59-3.21). Eighty-eight patients (97.8%) experienced drug-related adverse events. The most frequent were fatigue in 66 patients (73.3%), followed by palmar-plantar erythrodysesthesia in 40 (44.4%). Low liver tumor burden score (LTBS) and good ECOG PS were independent OS predictive factors.

CONCLUSIONS: Patients taking regorafenib had OS and PFS rates similar to those reported in previous randomized trials; the agent had a poor toxicity profile. We identified low LTBS and good ECOG PS as possible predictive factors of better OS, useful in selecting patients with mCRC who might benefit from regorafenib.

Introduction

Colorectal cancer (CRC) is a heterogeneous disease that involves a wide variety of driving mutations.[1] According to GLOBOCAN, CRC was the third most common cancer and the second most common cause of cancer death worldwide in 2020.[2] In United States (US) and Spain, approximately 155,098 and 37,172 new cases of CRC were diagnosed in 2018, respectively.[3,4]

The current treatment of choice for metastatic CRC (mCRC) is chemotherapy combined with antibodies against either VEGF or EGFR.[5] Despite the treatment options, CRC mortality represented the 8.6% and 9.2% of all deaths caused by cancer in 2018 in US and Spain, respectively.[3,4]

Regorafenib is an oral multikinase drug currently approved for use in third-line therapy of mCRC. It inhibits tyrosine kinase receptors involved in tumor angiogenesis (*VEGFR1/3* and *TIE-2*), oncogenesis (*c-KIT, RET, RAF-1, BRAF,* and *BRAF* V600E), metastasis (*PDGFR-b, FGFR-1,* and *VEGFR3*) and immunity *(CSF1R*).[6] The dose approved by the Food and Drug

Administration is 160 mg per day for 21 days in 28-day cycles.[7]

Regorafenib has demonstrated an increase in overall survival (OS) compared with placebo in two phase 3 clinical trials in patients with mCRC who had previously become refractory to fluoropyrimidine-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy. The median OS with regorafenib was 6.4 months (vs 5.0 with placebo) in the CORRECT trial (NCT01103323) and 8.8 months (vs 6.3 with placebo) in the CONCUR trial (NCT01584830). The median progression-free survival (PFS) was 1.9 months (vs 1.7 months) and 3.2 months (vs 1.7 months), respectively.[8,9] In both trials, drug-related adverse events (AEs) of grade 3 or higher occurred in 54.0% of patients. Palmar-plantar erythrodysesthesia was the most frequent AE, occurring in 17.0% and 16.0%, respectively.[8,9]

On the European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS), which measures the clinically significant benefit that can be expected from cancer treatments, regorafenib as third-line treatment of mCRC received a score of 1, indicating low clinical benefit.[10]

The primary outcome of the present study was to evaluate the routine clinical practice use of regorafenib, evaluating its effectiveness and safety. As a secondary objective, we aimed to establish predictive factors for survival.

Methods

Study Design

A multicenter retrospective study was conducted in 3 Spanish hospitals (La Princesa University Hospital, Fuenlabrada University Hospital, and Puerta de Hierro University Hospital). The inclusion criteria were being 18 years or older, diagnosed with mCRC, and beginning treatment with regorafenib between November 2013 and May 2020. Patients participating in any clinical trial were excluded. Data were collected in September 2020 to have a minimum treatment period per patient of 4 months.

Variables

Sociodemographic, clinical, hematological, and biochemical variables from patients were collected from the electronic medical records. The main efficacy variables were OS (defined as the length of time from the initial administration of regorafenib until the last control performed before the study ended or patient death) and PFS (defined as the time between the beginning of treatment and clinical or radiological disease progression). Progression was evaluated by CT scan every 3 months. To evaluate the safety of the drug, AEs were recorded, including those reflected in the clinical history and test results as well as those reported by the patients in pharmaceutical care and oncology consultations. The blood parameter alterations were defined according to the normal limit values and the specifications of the drug.[7] Drug-related AEs were graded

TABLE 1. **Sociodemographic Characteristics**

Baseline characteristic (N = 90)	n (%)
Sex, male	52 (57.8)
ECOG PS	
0–1	57 (63.4)
2–3	8 (8.8)
Unknown	25 (27.8)
Previous metastatic treatments, n	
1	2 (2.2)
2	42 (46.7)
3	27 (30.0)
4 or more	19 (21.1)
LTBS	
Low-medium (<9)	29 (32.2)
High (≥9)	25 (27.8)
Unknown	36 (40.0)
Metastasis	
Liver	72 (80.0)
Lung	65 (72.2)
Adenopathy	39 (43.3)
Bone	8 (8.9)
Kidney	4 (4.4)
Ovary	2 (2.2)
Other	11 (12.2)

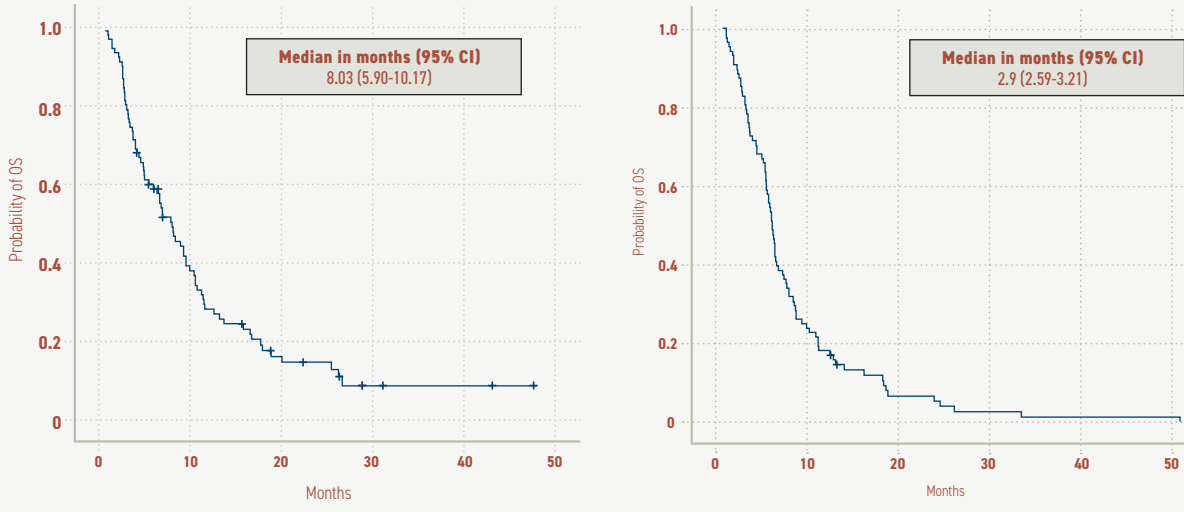
LTBS, liver tumor burden score; PS, performance status.

TABLE 2. **Clinical Baseline Characteristics**

Clinical baseline characteristics (N = 90)	n (%)
Number of metastases: mean (SD)	1.86 (0.92)
Hemoglobin (gr/dl): mean (SD)	12.9 (1.7)
Platelet count (cells/mm3): mean (SD)	233.6 (102.8)
Basal leukocyte count (cells/mm3): mean (SD)	7.7 (4.6)
Basal neutrophil count (cells/mm3): mean (SD)	6.9 (4.1)
Basal lymphocyte count (cells/mm3): median (IQR)	1.7 (1.2-2.4)
AST (UI/L): median (IQR)	28.5 (20.8-40.0)
ALT (UI/L): median (IQR)	21.5 (15.0-40.5)
GGT (UI/L): median (IQR)	86.0 (33.0-273.0)
Basal bilirubin (mg/dl): median (IQR)	0.54 (0.40-0.81)
CEA (ng/ml): median (IQR)	21.9 (5.4-152.0)
CA 19.9 (U/ml): median (IQR)	68.3 (13.6-549.6)
Basal creatinine (mg/dl): mean (SD)	0.79 (1.19)

ALT, alanine transaminase; AST, aspartate aminotransferase; CA 19.9, carbohydrate antigen 19.9; CEA, carcinoembryonic antigen; GGT, gamma-glutamyltransferase.

FIGURE 1. **Progression-Free Survival (PFS) and Overall Survival (OS) Kaplan-Meier Curves of Regorafenib**



PFS, progression free survival: OS, overall survival.

using the Common Terminology Criteria for Adverse Events, version 5.0.[11]

To identify potential predictive response factors to regorafenib in relation to OS, we evaluated clinical parameters, the patient's functional status measured by ECOG performance status (PS),[12] and the liver tumor burden score (LTBS), which is calculated by the number of liver metastases and the diameter of the largest lesion obtained from radiologists' report data.[13] Patients were divided into 3 groups: those with LTBS lower than 3 (LTBS-low; low liver tumor burden), LTBS 3 to 9 (LTBS-med; medium liver tumor burden), and LTBS higher than 9 (LTBS-high; high liver tumor burden).[13] Patients in whom LTBS was not available were classified as unknown.

Statistical Analysis

Normal distribution variables were calculated as proportions, means, and SD; nonnormal distribution variables were calculated as medians and IQRs. A Kaplan-Meier survival analysis was carried out to evaluate OS and PFS. To establish how clinical and pathological variables influenced OS and PFS, univariate and multivariate Cox regressions, keeping OS and PFS as independent variables, were performed. Only variables with *P* less than or equal to.05 for the OS were included in multivariate analysis, with the exception of the liver metastasis variable, which was not included because it was a dependent variable of the LTBS variable. The results were considered statistically significant if *P* less than or equal to .05. The software used was SPSS version 22.0.

Results

Sociodemographic and Clinical Characteristics

The study included 90 patients treated with regorafenib; 52 (57.8%) were male, with a mean age of 64.3 (SD, 9.3) years. **Table 1** shows sociodemographic characteristics and **Table 2** shows clinical baseline characteristics.

The median number of pretreatment lines was 2.9 (SD, 1.2). The median time of treatment was 2.8 (range, 1.0-2.8) months. Fifty-five patients (61.1%) started with the full initial dose of 160 mg, 18 (20.0%) with 120 mg, 16 (17.8%) with 80 mg, and 1 patient (1.1%) with 40 mg of regorafenib. Thirty-one patients (34.4%) did not receive full doses of regorafenib at any time during treatment.

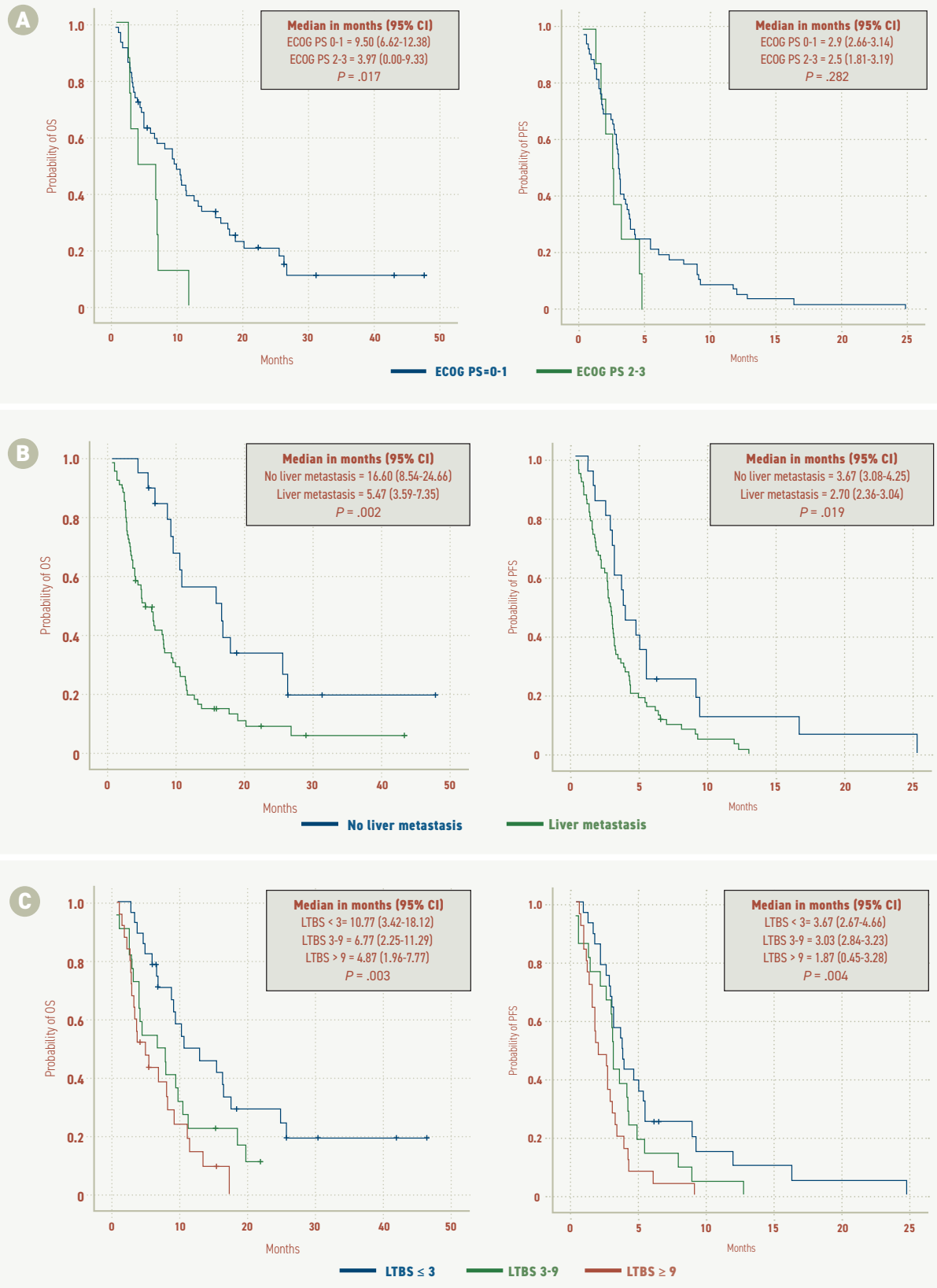
Effectiveness: OS and PFS

Survival analysis showed a median OS of 8.03 months (95% CI, 5.90-10.17) and a median PFS of 2.90 months (95% CI, 2.59-3.21). The OS and PFS curves are shown in **Figure 1**.

Median OS in patients with ECOG PS 0 or 1 was 9.50 months (95% CI, 6.62-12.38) vs 3.97 months (95% CI, 0.01-9.33) in patients with ECOG PS 2 or 3 (*P* = .017). PFS in those with ECOG PS 0 or 1 was 2.9 months (95% CI, 2.66-3.14) vs 2.5 months (95% CI, 1.81-3.19) in those with ECOG PS 2 or 3 (*P* = .282; **Figure 2A**).

The Kaplan-Meier curves showed that median OS was higher in the LTBS-low group than in the LTBS-med and LTBS-high groups, at 10.77 months (95% CI, 3.42-18.12) vs 6.77 months (95% CI, 2.25-11.29) vs 4.87 months (95% CI, 1.96-7.77; *P* = .003) respectively. Median PFS was also higher in LTBS-low patients at 3.67 months (95% CI, 2.67-4.66) vs 3.03 months

FIGURE 2. **Progression-Free Survival (PFS) and Overall Survival (OS) Kaplan-Meier Curves of Regorafenib in Stratified Group Analysis**



Kaplan-Meier curves (A) OS and PFS stratified by ECOG PS; (B) OS and PFS stratified by LTBS subgroups; (C) OS and PFS stratified by baseline liver metastases. LTBS, liver tumor burden score; OS, overall survival; PFS, progression-free survival; PS, performance status.

(95% CI, 2.84-3.23) and 1.87 months (95% CI, 0.45-3.28) in the LTBS-med and LTBS-high groups, respectively (P = .004; **Figure 2B**).

Patients without liver metastasis had a median OS of 16.60 months (95% CI, 8.54-24.66) vs 5.47 months (95% CI, 3.59-7.35) in patients with liver metastasis (P = .002). A similar difference between patients with and without liver metastasis was also observed in median PFS, at 3.67 months (95% CI, 3.08-4.25) vs 2.70 months (95% CI, 2.36-3.04), respectively (P = .019; **Figure 2C**).

Safety

Eighty-eight patients (97.8%) experienced drug-related AEs during treatment. The most frequent were fatigue in 66 patients (73.3%), followed by palmar-plantar erythrodysesthesia in 40 (44.4%). Grade 3/4 drug-related AEs occurred in 52 patients (57.8%). Toxicity data are shown in **Table 3**. The dose of regorafenib had to be decreased due to toxicity in 37 patients (41.1%), of whom only 4 (11.8%) reached the maximum dose prior to the AE. Regorafenib treatment was discontinued in 30 patients (33.3%) and was interrupted in 29 (32.2%) due to drug-related AEs.

Prognostic Factors for OS

Univariate survival Cox regression analyses were performed (**Supplement Table S1**). Three variables were chosen for multivariate analysis based on their clinical relevance and our cohort size: ECOG PS, LTBS, and the number of metastases. The variable of liver metastasis was not included in the multivariate analysis because it interfered with LTBS (all patients without liver metastases had an LTBS value of 0). The results are shown in **Table 4**. The correlations of ECOG PS (HR, 2.901; 95% CI, 1.195-7.040; P =.019) and LTBS (HR, 1.582; 95% CI, 1.050-2-382; P = .028) to OS were statistically significant.

TABLE 3. **Drug-Related AEs**

Events	All grade: n (%)	Grade 3/4: n (%)
Overall	88 (97.8)	52 (57.8)
Fatigue	40 (44.4)	6 (6.6)
Palmar-plantar erythrodysesthesia	34 (37.8)	17 (18.9)
GGT increase	34 (37.8)	5 (5.5)
AST increase	33 (36.7)	3 (3.3)
ALT increase	25 (27.8)	5 (5.5)
Bilirubin increase	19 (21.1)	3 (3.3)
Lymphopenia	19 (21.1)	1 (1.1)
Anemia	15 (16.7)	1 (1.1)
Thrombocytopenia Hypertension	14 (15.6)	8 (8.8)
Skin toxicity	14 (15.6)	1 (1.1)
Diarrhea	13 (14.4)	3 (3.3)
Hyperoxia	12 (13.3)	1 (1.1)
Aphonia/hoarseness	11 (12.2)	–
Nausea/vomiting	9 (10.0)	1 (1.1)
Mucositis	6 (6.7)	–
Neutropenia	3 (3.3)	–
Creatine increase	3 (3.3)	–
Others	12 (13.3)	–

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transferase.

Discussion

Regorafenib, an oral multikinase inhibitor of the tyrosine kinase receptor, is used to treat refractory mCRC. According to the ESMO-MCBS scale, regorafenib is considered a drug with low clinical benefit in metastatic disease.[10] In clinical practice, regorafenib is often administered in patients with advanced, aggressive disease and impaired functional status, which might further limit its effectiveness. Therefore, we evaluated the routine clinical practice use of regorafenib and identified predictive factors of OS.

Our multicenter study included 90 patients. This study population had as many or more patients than many other retrospective studies[14-17] but fewer than the studies led by Yamaguchi and Adenis.[18,19] Almost half the patients in our study received regorafenib after 2 previous lines of treatment for metastatic disease, whereas the other half received it after 3 or more previous lines of therapy for metastatic disease. This fact might indicate that our study population was dominated by patients with refractory and aggressive disease. Most of the patients in our study had an ECOG PS of 0 or 1, as did most in the aforementioned pivotal trials[8,9,20] and observational studies.[19,21]

The effectiveness of regorafenib was not affected by the number of previous lines of treatment in our cohort: OS was similar to what was reported in the CONCUR trial[9] and higher than that reported in the CORRECT trial[8] and in the REBECCA cohort evaluating regorafenib in earlier treatment lines.[22,23]

Regarding OS, the Kaplan-Meier analysis showed that patients with an ECOG PS of 0 or 1 achieved a

TABLE S1. **Univariate Cox Regression Analysis**

Variables	OS		PFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age[a]	1.093 (0.694-1.723)	.701	0.860 (0.559-1.323)	.492
Sex	1.086 (0.684-1.723)	.727	0.991 (0.641-1.533)	.968
Previous treatments for metastatic disease	0.635 (0.432-0934)	.062	0.770 (0528-1.124)	.176
Line of treatment for metastatic disease[b]	2.696 (0.370-19.62)	.327	1.918 (0.464-7.921)	.368
Initial dose of regorafenib[c]	0.631 (0.393-1.013)	.057	0.745 (0.477-1.163)	.195
ECOG PS[d]	2.500 (1.144-5.464)	.022	1.510 (0.707-3.223)	.287
LTBS group[e]	1.063 (0.998-1.133)	.050	1.066 (1.009-1.127)	.045
Number of metastases[f]	1.341 (1.054-1.707)	.017	1.172 (0.942-1.458)	.154
Liver metastasis[g]	1.878 (1.907-3.212)	.003	2.417 (1.313-4.353)	.022
Bilirubin[h]	1.000 (0.989-1.010)	.954	1.021 (1.008-1.034)	.002
Hemoglobin[i]	0.850 (0.733-1.009)	.059	0.886 (0.777-1.010)	.070

The results were considered statistically significant if $P \leq .05$.
LTBS: liver tumor burden score; OS, overall survival; PFS, progression-free survival; PS, performance status.
[a]Patients were divided into 2 groups: aged ≥64 or <64 years.
[b]Patients were divided into 2 groups: those who received 1 or 2 lines of treatment for metastatic disease, or 3 lines.
[c]Patients were divided into 2 groups: those who received the full initial dose of regorafenib (160 mg) or a lower initial dose.
[d]Patients were grouped according to their ECOG PS into 2 groups: PS 0 or 1, or PS 2 or 3.
[e]Patients were grouped according to their LTBS into 3 groups: LTBS <3, LTBS of 3-9, and LTBS >9.
[f]Number of metastases was defined as a continuous variable.
[g]Patients were grouped according to the presence or absence of liver metastases.
[h]Bilirubin was defined as a continuous variable.
iHemoglobin was defined as a continuous variable.

TABLE 4. **Predictive Factors of Regorafenib Effectiveness (multivariate Cox regression)**

Variables	OS		PFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
ECOG PS groups[a]	2.901 (1.195-7.040)	.019	1.684 (0.723-3.924)	.227
LTBS groups[b]	1.582 (1.050-2.382)	.028	1.424 (1.001 -2.027)	.049
Number of metastasis[c]	1.352 (0.958-1.907)	.087	1.285 (0.951-1.735)	.102

The results were considered statistically significant if $P \leq .05$.
LTBS, liver tumor burden score; OS, overall survival; PFS, progression-free survival; PS, performance status.
[a]Patients were divided into 2 groups according to ECOG PS: PS 0-1 and PS 2-3
[b]Patients were divided into 3 groups according to their LTBS: LTBS < 3, LTBS = 3-9 y LTBS >9
[c]Number of metastasis was defined as a continuous variable.

median OS twice as long as that of patients with an ECOG PS of 2 or 3.[18,21] Further, patients in the LTBS-low group had superior clinical benefit compared with patients in the LTBS-med group and especially compared with the LTBS-high group; there are currently no studies that analyze regorafenib survival based on LTBS with which we could compare these results. Finally, patients without liver metastases achieved a median OS 3 times higher than that of patients with liver metastases.

We found 2 predictive factors of OS benefit: the ECOG PS[8,9,20,24] and LTBS. The number of metastases did not reach statistical significance in the multivariate analysis, but a positive trend was observed. A prior study which examined more patients than this one confirmed this variable as a predictor of higher OS.[24] Therefore, we conclude that patients with an ECOG PS of 0 or 1, or who are LTBS-low and have no liver metastases, will benefit most from regorafenib treatment.

Like other tyrosine kinase inhibitors, regorafenib is associated with significant drug-related AEs, which can appear from the earliest cycles and impact the patient's quality of life. AEs also affect treatment adherence, continuation of treatment, and dose reduction.[25] In our study, nearly all patients reported some drug-related AEs—most frequently asthenia, followed by palmar-plantar erythrodysesthesia and liver enzyme alterations. These results show a higher incidence of drug-related AEs in routine clinical practice than in several prior clinical trials.[8,9,20] In almost half the patients, dosage was reduced, and in one-third, treatment was discontinued or suspended due to drug-related AEs, similar to results reported by Rizzo and colleagues.[26]

In our cohort, almost half of all patients experienced grade 3/4 drug-related AEs, which could have a

significant impact on quality of life and impaired functional status regardless. In addition, almost one-third of patients did not reach the full dose of 160 mg, which can alter efficacy. However, the ReDOS trial (NCT02368886) has shown that weekly dose escalation during the first cycle, from 80 mg to 160 mg daily, maintains the effectiveness (clinical outcomes) of the drug and reduces interruptions caused by drug-related AEs.[27] All of these findings demonstrate that the toxicity profile of regorafenib is more complex in routine clinical practice28 than in phase 3 clinical trials.[8,9]

Limitations

This study had some limitations. As a retrospective analysis, it did not include a comparison cohort, and comparisons with other trials and studies were indirect. Furthermore, other studies have included larger sample sizes. Dose density duration was also not considered in the efficacy analysis.

Conclusions

In conclusion, in our study of routinely collected data of 90 patients with mCRC, treatment with regorafenib was associated with OS outcomes similar to those in randomized clinical trials and higher than those in some observational studies. Patients with ECOG PS of 0 or 1, LTBS lower than 3, and no liver metastases achieved higher OS. Regorafenib has low clinical benefit, but our data might be useful in identifying patients with mCRC who would be among the most likely to benefit from regorafenib treatment. ■

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board (IRB) of La Princesa University Hospital. Approval number 4199.The study was granted an exemption from requiring written informed consent by the Institutional Review Board (IRB) of La Princesa University Hospital because of the retrospective character of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Rebeca Mondéjar Solis, Berta Hernández Marin, Alberto Morell Baladrón, and Ramón Colomer Bosch contributed to the study conception and design. Material preparation and data collection were performed by Alberto Calvo-Garcia, Silvia Ruíz-García, Ana Beatriz Fernández Román, Javier Letellez Fernández, Beatriz Candel García, Carlos Hernández Terciado, Raquel De Santiago Álvarez, and Patricia Toquero Diez. Analysis was performed by Maria Pérez Abánades. The first draft of the manuscript was written by Alberto Calvo-Garcia and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data sets generated during and/or analyzed during the current study are available from the corresponding author on request.

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CONTINUING MEDICAL EDUCATION (CME)

Leukemia Therapy– A Look Into the Future

FACULTY

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Research advances over the past 2 decades have greatly improved the outlook for many leukemias. Targeted therapies, immunotherapies, antibody-drug conjugates (ADCs), bispecific T-cell engagers (BiTEs), chimeric antigen receptor T-cell (CAR T) therapy, and synergistic combinations of approved therapies are providing fresh hope for patients and suggesting to many that, one day, normal survival will be the routine prognosis. **Hagop M. Kantarjian, MD**, is one such optimist. In this article, Kantarjian reviews recent developments in leukemia and looks ahead to the bright future of the field.

Q: The fast pace of new research has led to many new therapies for leukemia in recent years. What have been the most important breakthroughs?

KANTARJIAN: I would like to give a general view of the state of the art of leukemia. It's important to note that, over the past decades, there have been major changes in treatment and outcomes across all leukemias. In 1981, when I started my training in hematologic oncology, there was no cure for either chronic myeloid leukemia (CML) or chronic lymphocytic leukemia (CLL). With intensive chemotherapy, the cure rate for acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) was about 20% to 30%. Fast forward to today, both CML and CLL are functionally and potentially molecularly curable with oral medications. In the acute leukemias, by adding newer treatments to intensive chemotherapy, we have increased cure rates to a range of 60% to even 90% in some subsets. I'm going to go over the leukemias one at a time, but the way I like to divide them is into what I call the "easily curable leukemias" or the "easy leukemias," the "intermediate curable leukemias," and the "bit more difficult to cure leukemias."

Easily Curable Leukemias

Q: What have we learned from clinical trials of cladribine plus rituximab in patients with hairy cell leukemia?

KANTARJIAN: If we start with hairy cell leukemia, it is a disease where, historically, the average survival was about 5 to 7 years and there were not many therapies that were available or curative. Fast forward to today, we have developed a regimen that combines cladribine, which is an adenosine nucleoside analog, followed by rituximab for 8 doses. Now the 10-year event-free survival is close to 95%.[1]

Q: What has been the impact of all-*trans*-retinoic acid (ATRA), chemotherapy, and arsenic trioxide combinations?

KANTARJIAN: The second easily curable leukemia is acute promyelocytic leukemia (APL). This is a subset of about 5% to 10% of AML, where the cure rate with intensive chemotherapy was about 40%. Today, with nonchemotherapy-targeted regimens with ATRA (a vitamin A analog) and arsenic trioxide (a poison used in tiny amounts), the combination of ATRA–arsenic trioxide with or without gemtuzumab ozogamicin for the high-risk patient is producing cure rates over 90%.[2]

Q: How has the regimen known as FLAG-GO changed survival rates in patients with core binding factor (CBF) AML?

KANTARJIAN: The third entity is the CBF AML, and this comprises 15% of adult AML and 30% of childhood AML. These are patients with either a translocation (t[8;21]) or inversion of chromosome 16. For FLAG-GO, what we did was to combine fludarabine with high-dose cytarabine and granulocyte colony–stimulating factor (G-CSF), and we added gemtuzumab ozogamicin, which is the CD33 ADC. By adding the gemtuzumab to the chemotherapy, we have increased the cure rates from 50% to about 80%.[3-5]

Q: Now that survival rates for these leukemias are 80% to 90%, can we expect more improvements in therapy?

KANTARJIAN: I think with hairy cell leukemia, we cannot improve much. With APL, we're trying to develop an oral formulation of arsenicals.[6] This way, they don't have to take the medication intravenously for 120 doses, and so APL treatment will be taken orally. In the CBF leukemias, I think we may improve the outcomes further with the addition of the targeted therapies.

Q: How has the introduction of tyrosine kinase inhibitor (TKI) therapy changed outcomes in patients with CML?

KANTARJIAN: CML is an entity in which, before the year 2000, the average survival was about 5 to 6 years, and the 10-year survival rate was about less than 20%. In 2000, we started developing what is called the BCR::ABL1 TKI. These therapies target the Philadelphia chromosome (Ph) abnormality that causes CML. We developed 6 BCR::ABL1 kinase inhibitors. Imatinib was the first-generation TKI.[7] Then we had dasatinib, bosutinib, and nilotinib, which are second-generation TKIs.[8-10] And more recently, we developed ponatinib and asciminib, which are the third-generation TKIs.[11,12] These also work in patients who develop the T315I mutation within BCR::ABL1.[13] That mutation makes the leukemia resistant to both imatinib and the second-generation TKI.

By using any of the first 4 TKIs (imatinib, dasatinib, bosutinib, nilotinib) in frontline CML therapy, we can normalize the survival of the patients. So now, the estimated 20-year survival is

about 75%.[14] And if you look at causes of deaths from CML, the estimated 15-year survival is close to 90% to 95%. Essentially, this disease is functionally curable, meaning that the patients will live a normal life similar to that of an age-matched normal population.

> Essentially, [CML] is functionally curable.

The second end point of therapy is a treatment-free remission, meaning that we can stop the treatment and the disease doesn't come back. And what we found was that if we have patients on those TKI therapies, and they achieve what is called deep, durable molecular response, meaning the *BCR::ABL1* transcripts go to below 1:10,000 for 5 years, we can stop the treatment. The disease is curable in 80% of patients.[15] There are some patients who relapse on the first- and second-generation TKI, and this is where ponatinib and asciminib could be extremely helpful. Ponatinib is probably the most powerful of the TKIs, and it is probably the more toxic one, so we have designed regimens that do not use ponatinib at 45 mg, which is the FDA-approved dose. We can get by with ponatinib at 30 mg or 15 mg and most patients do very well.[16,17]

There are additional TKIs that we're investigating. There's one from China called HQP1351 that is approved in China, and we're doing the studies in the United States. It looks like this drug is also very effective and much less toxic.[18] So, in the next 5 years, we'll have several more of the TKIs to work with in the patients who become resistant to multiple TKIs.

Q: CLL was once considered incurable. Is that still true?

KANTARJIAN: In CLL, a new breakthrough has happened in the past, maybe, 5 to 8 years. In 2010, the pathophysiology of CLL was deciphered. We understood that Bruton tyrosine kinase (BTK) plays an important role in the evolution of CLL and also that the CLL cells can live longer than the normal lymphocytes. First, there was the development of the BTK inhibitors. The first one was ibrutinib, and the next ones were acalabrutinib and zanubrutinib.[19-22] There's also what is called the noncovalent BTK inhibitors (eg, pirtobrutinib), which are highly effective, even in the patients who develop BTK mutations and become resistant to ibrutinib and acalabrutinib.[23]

The second drug that was very important is venetoclax, which is a BCL2 inhibitor. It shortens the life span of the CLL cells and causes them to die. Very recently, around 2017, we developed a combined regimen of ibrutinib with venetoclax at The University of Texas MD Anderson Cancer Center. We found, in 120 patients, that almost all of them achieved a complete molecular response. The treatment duration was 2 years. When we stopped the treatment, very few of these patients relapsed molecularly after a follow-up from discontinuation of about 2 years.[24-26]

So CLL in the textbooks is still called an incurable disease. I think, in the past 5 years, we have developed a potentially highly curable regimen with those 2 oral medications, BTK inhibitor with venetoclax, and the duration is for a finite or a fixed duration of therapy. We can do better than this ibrutinib-venetoclax combination, because ibrutinib can cause adverse effects like atrial fibrillation and bleeding.[27] Acalabrutinib and zanubrutinib have less of these adverse effects, and it may be more effective.[28,29] Pirtobrutinib can overcome the BTK mutations that make CLL cells resistant. So I think the problem of CLL, in my view, is solved. Other people still think it's a problem, but then they use single-agent therapies with either a BTK inhibitor or with venetoclax and then they see relapses in these patients.[30]

Q: Please outline frontline therapy in patients with Ph-positive (Ph+) ALL.

KANTARJIAN: Two new leukemias have recently become highly curable. The first one is Ph+ ALL. Before the year 2000, Ph+ ALL was a diagnosis that was associated with a death sentence. Unless the patient had the option of allogeneic transplant, which cured 35% of the patients, there was no cure with intensive chemotherapy.[31,32] In 2000, we added the BCR::ABL1 TKIs to chemotherapy. We started with imatinib and then, in 2006, we added dasatinib.[33,34] In 2010, we added ponatinib, and we found that the intensive chemotherapy with ponatinib now produced an 8-year survival rate of 75% without needing allogeneic transplant.[35,36] In 2019, we started using nonchemotherapy regimens with ponatinib, which is the powerful BCR::ABL1 TKI, and then we added a new BiTE that targets CD19, which is a target on the surface of the ALL cells.[37,38]

By combining ponatinib with blinatumomab in a simultaneous regimen, we found that 100% of the patients achieve a complete response (CR), and the estimated 3-year survival rate is 95%.[39] Now, we don't have yet too many patients treated. We have about 50, and only 1 of those 50 patients needed an allogeneic transplant. So again, Ph+ ALL, which used to be one of the worst subsets of ALL, has become one of the most favorable subsets of ALL, and it is potentially curable with 2 targeted therapies and without any chemotherapy.

Q: How does ALL treatment in younger patients compare with treatment in older patients?

KANTARJIAN: The new other entity that has become potentially highly curable is pre-B ALL in the younger patients, with "younger" meaning under the age of 60 years. Using the combination of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with methotrexate and cytarabine, blinatumomab, and inotuzumab (an ADC targeting CD22, which is universally expressed on the ALL cells), we are now reporting 3-year survival rates of 85%.[40] We are tweaking the dose regimen a little bit by using less chemotherapy and by doing blinatumomab and inotuzumab simultaneously with chemotherapy and potentially adding CAR T cells at the end of 6 courses of this regimen for minimal residual disease.[41]

> Philadelphia-positive ALL, which used to be one of the worst subsets of ALL, has become one of the most favorable subsets.

Q: What are emerging therapies for patients with ALL?

KANTARJIAN: I think in pre-B ALL 5 years from now, instead of using 15 chemotherapy drugs in an intensive regimen for 3 years that is used to cure about 40%, we're going to be able, potentially, to give 6 courses of chemotherapy over 6 months. Maybe use the CAR T cells instead of allogeneic transplant after the 6 courses and be able to cure—I'm hoping—more than 80% of the patients. This would be a cure rate that's as high as the cure rate in childhood ALL, where they use the intensive chemotherapy for 3 years.[42]

Intermediate Curable Leukemias

Q: Please describe the current status and emerging therapies for treating older adults with ALL?

KANTARJIAN: We have used the same regimen—low-intensity chemotherapy (mini–hyper-CVD) with inotuzumab and blinatumomab—and we reported 5-year survival rates that improved from under 20% to 50%.[43,44] We are still having patients who die from the chemotherapy myelosuppression and some others who develop myelodysplastic syndrome or AML as a natural evolution of the disease. This is where we are going to try to use the 2 antibodies inotuzumab and blinatumomab without any chemotherapy and perhaps with the CAR T cells to see if we can cure them beyond the 50% potential 5-year survival.

Q: How effective are current therapies for treating younger adults with AML?

KANTARJIAN: Another intermediate leukemia that we see is in younger patients with AML, so this is where we are using intensive chemotherapy, which is better than the 3+7, what we call the FLAG-IDA regimen (fludarabine, high-dose cytarabine, G-CSF, and idarubicin) followed by venetoclax or the CLIA regimen (cladribine, idarubicin, and high-dose cytarabine) followed by venetoclax. We are adding venetoclax to the intensive chemotherapy and we are reporting now in the younger patients (< 60 years) a 3-year survival rate of about 60% to 70%, which is much better than what we did in the past.[45,46] In addition, in AML, we have novel therapies that target FLT3—gilteritinib, midostaurin, and, perhaps soon, quizartinib. And we have inhibitors against mutated IDH1 and IDH2.

To give you the background, *FLT3* mutations happen in 30% of the patients with AML. By adding FLT3 inhibitors to the intensive chemotherapy, we are able to produce 3-year survival rates of 70% to 75%.[4] *IDH* mutations occur in 15% to 20% of patients with AML. We have now an IDH1 inhibitor, ivosidenib, and an IDH2 inhibitor, enasidenib, and we are combining them with intensive chemotherapy and venetoclax. We think the potential cure rates with such combinations are going to go up to about 70%.[47]

More Difficult to Cure Leukemias

Q: What treatments are available for older/unfit patients with AML?

KANTARJIAN: The difficult to treat leukemia is AML in patients 60 years or older. This is where the intensive chemotherapy with 3+7—in the patients who are fit to receive intensive chemotherapy—is associated with a 3-year survival of less than 20%.[48] Since 2005, we have developed hypomethylating agents (eg, decitabine, azacitidine) as a treatment for older/unfit patients with AML. In 2018, we added venetoclax. In a randomized study, we found that azacitidine with venetoclax improves survival compared to azacitidine, but the 2- to 3-year survival is only still 35% to 40%.[49]

More recently, we developed a low-intensity regimen that incorporates azacitidine or decitabine with the nucleoside analogs cladribine and low-dose cytarabine. Then we added venetoclax. We just reported that the "triple nucleoside regimen" (cladribine, low-dose cytarabine, and azacitidine or decitabine) with venetoclax is associated with a CR rate of 85%, which is higher

than what you get with the 3+7 intensive chemotherapy in the younger patients. And we reported an estimated 2-year survival rate of about 60%.[50] So we're hoping that we'll improve on this by again adding the FLT3 and IDH inhibitors to this backbone treatment regimen.

Q: What studies are you looking forward to being presented at the American Society of Hematology (ASH) 2022 meeting?

KANTARJIAN: There are several things we are anticipating at ASH. I would like to focus on AML, because I told you this is the subset of the leukemias that is less cured than the others. The recent development that I'm excited about in AML is the development of menin inhibitors. These are new drugs that target the 11q23 translocation (t[11q23]) abnormality in AML, the mixed lineage leukemia (MLL)-AML. As single agents, they seem to produce very good response rates in MLL-AML.[51,52] So now we have to combine the menin inhibitors with the standard chemotherapy to be able to cure at a higher rate patients with MLL-AML, which is about 10% of the AMLs.

The last thing I want to mention are the immune therapies in AML, which target CD123 and CD33 on the surface of AML cells. We have ADCs that are being developed against CD123, such as IMGN632.[53,54] We are developing BiTEs that target CD33 and CD123. And we're developing CAR T cells that are targeting, again, CD33 and CD123.[55] Another type of immune therapy is agents that target CD47. Targeting CD47 will allow the stimulation of the macrophages that then can kill the leukemia cells.[56] There are several CD47 antibodies under development.

In addition to these, there is now the research with natural killer (NK) cells, autologous or allogeneic cells.[57] Also, there's a study from China that looked at CAR T cells targeting CLL1, which is present on the surface of the AML cells.[58] These forms of immune therapies—be it ADCs, BiTEs, CAR T cells, or NK cells— are new immune therapies that may help the AML subsets that are resistant to chemotherapy and to the targeted therapies. ■

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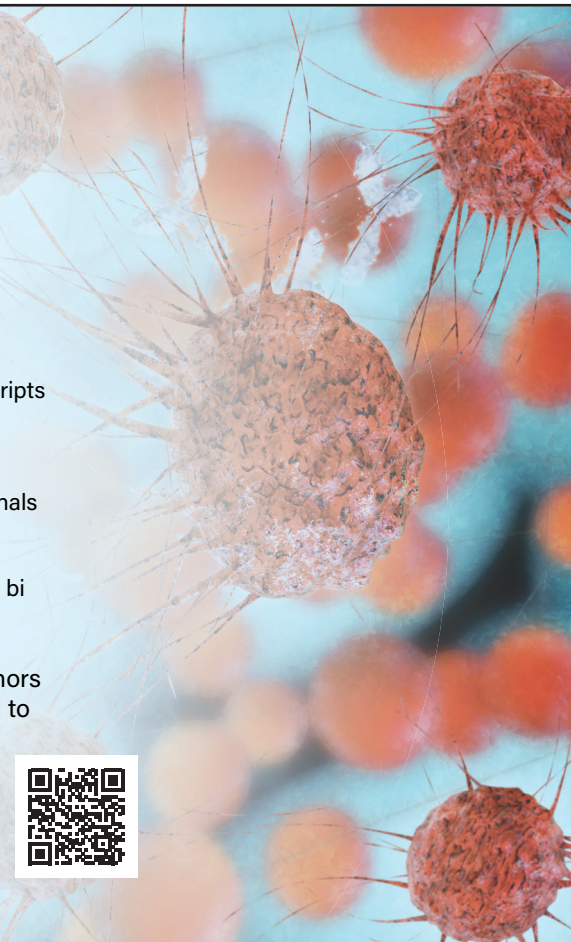

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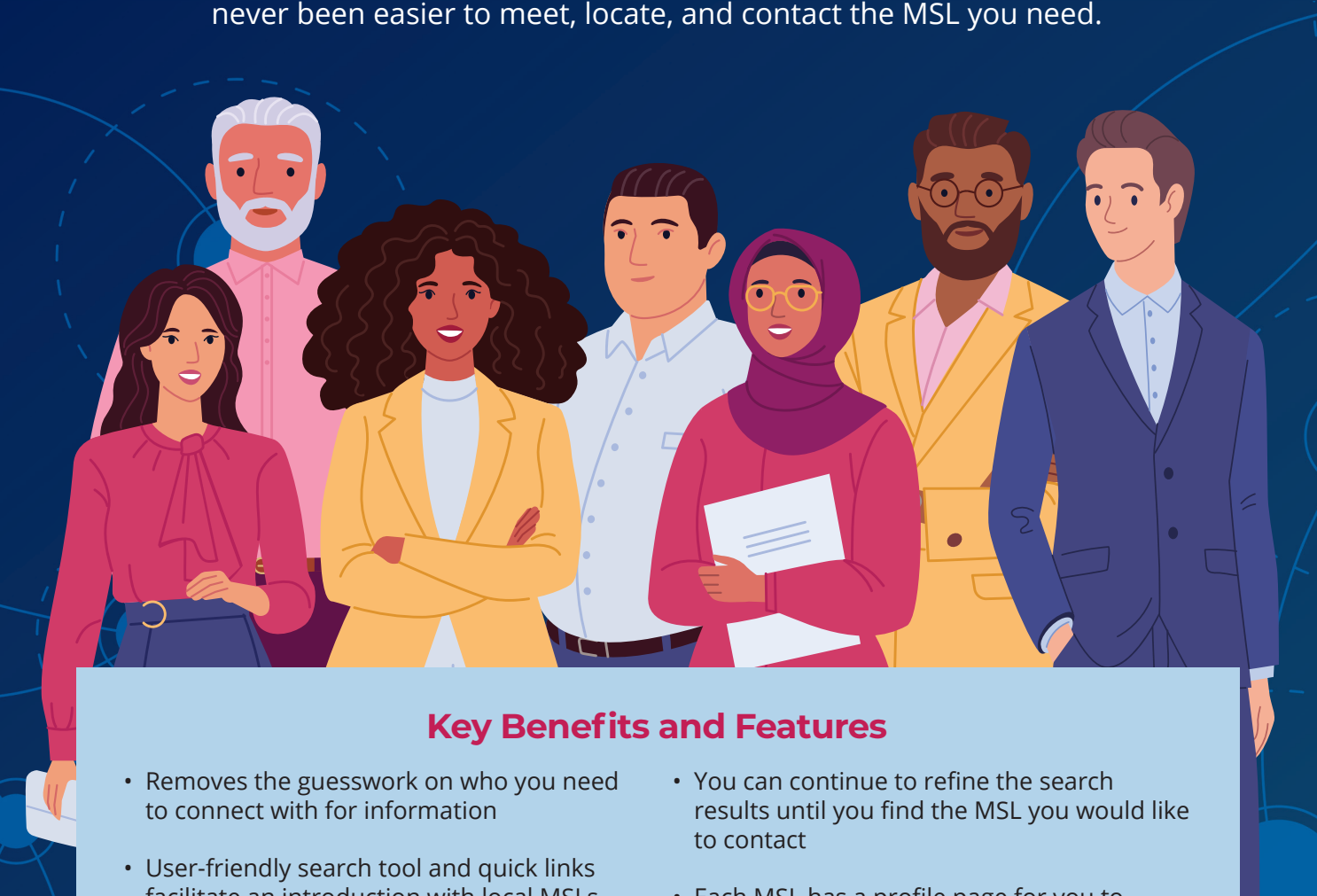

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