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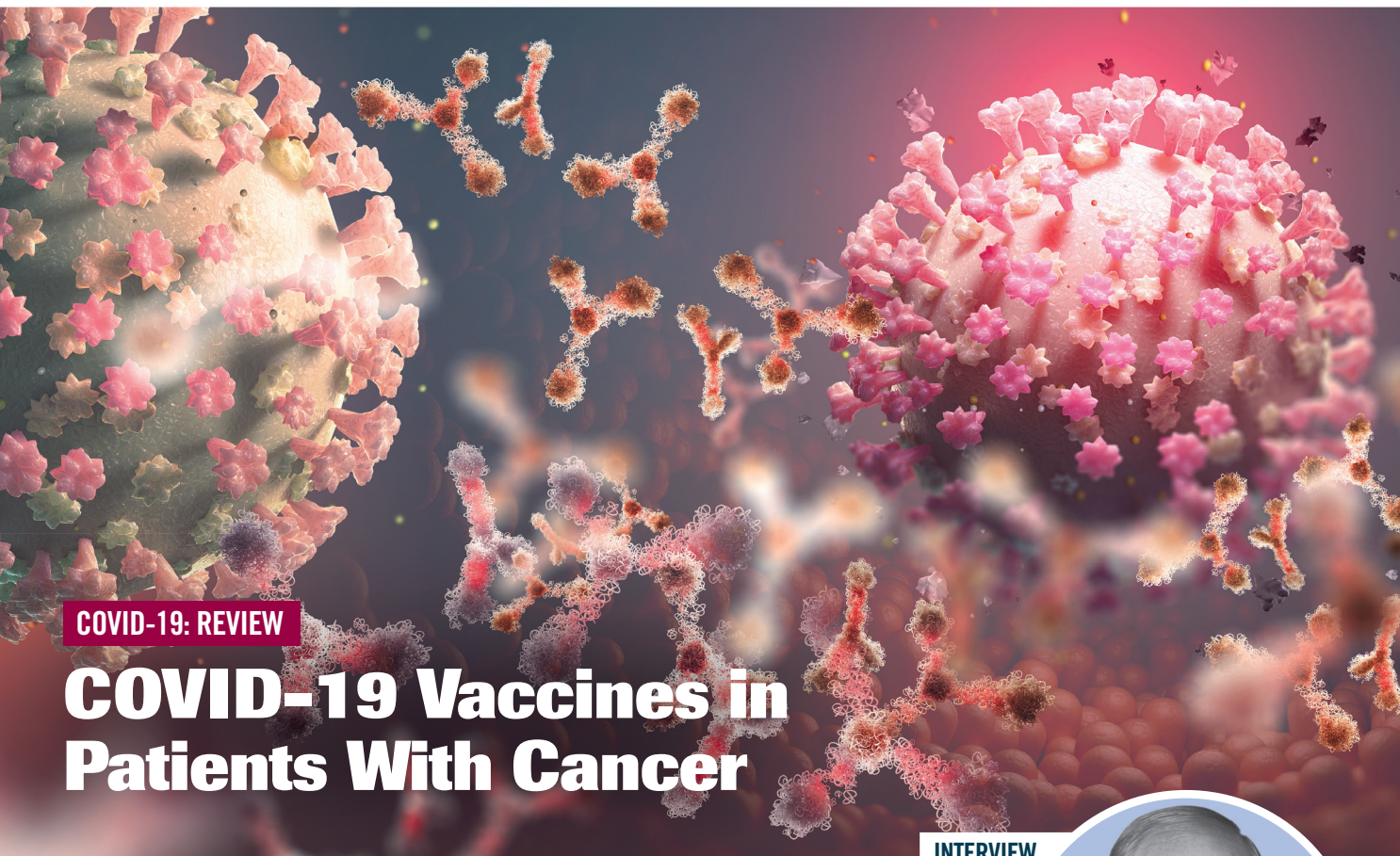

COVID-19: REVIEW

COVID-19 Vaccines in Patients With Cancer

INTERVIEW

FDA Approves Imaging Agent Designed to Target Tumors in Lung Cancer

PHILLIP S. LOW, MD, PHD

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

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

05/22 USO-IXA-0383

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

Proteasome inhibitor-based triplet regimens remain a cornerstone of treatment with optimal outcomes.[1,6]

How can you help patients on their journey to extended efficacy?

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)

Brief Summary (cont'd)

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

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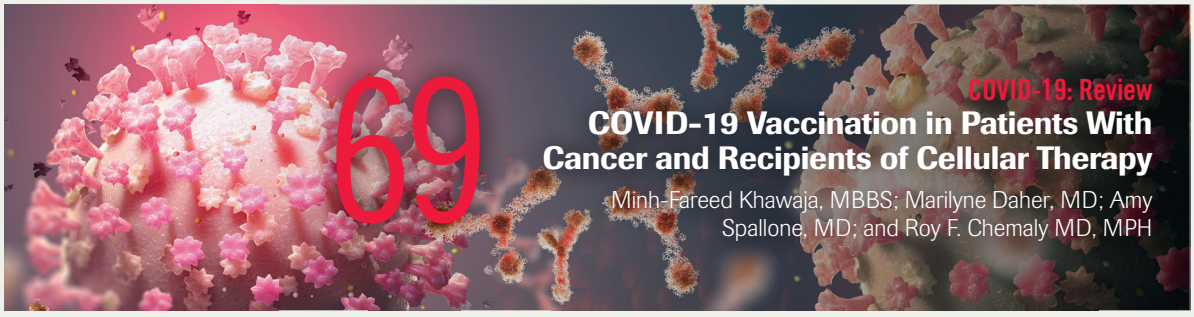

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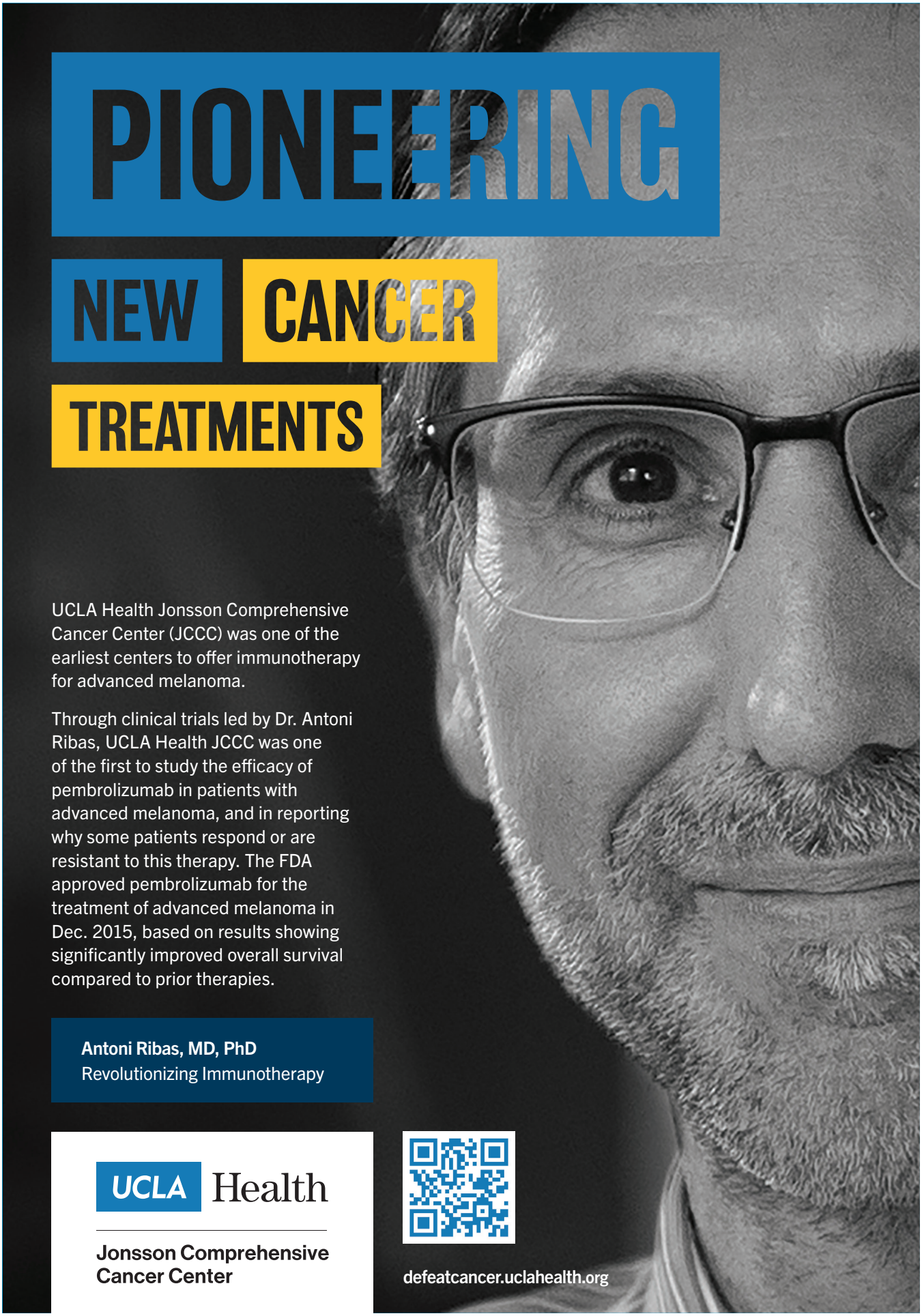
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Through clinical trials led by Dr. Antoni Ribas, UCLA Health JCCC was one of the first to study the efficacy of pembrolizumab in patients with advanced melanoma, and in reporting why some patients respond or are resistant to this therapy. The FDA approved pembrolizumab for the treatment of advanced melanoma in Dec. 2015, based on results showing significantly improved overall survival compared to prior therapies.
Antoni Ribas, MD, PhD
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UCLA Health
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Julie M. Vose, MD, MBA
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American Society of Hematology: 64th Annual Meeting Review

A variety of scientific discoveries, clinical trial results, and information about malignant and nonmalignant hematologic disorders emerged at the annual meeting of the American Society of Hematology (ASH) held last December. The plenary session consisted of several presentations and covered a wide range of topics. Martin Dreyling, MD, discussed the European MCL Network's TRIANGLE trial, a large, 3-arm study on the efficacy and safety of ibrutinib (Imbruvica) combined with standard first-line treatment as a substitute for autologous stem cell transplantation (ASCT) in younger patients with mantle cell lymphoma (MCL).[1] Results showed improved progression-free survival with ibrutinib compared with ASCT alone. Depending on the ability to obtain ibrutinib as part of the MCL patient's maintenance in first remission, this study may change the standard of care for this patient population.

Catherine Broome, MD, presented the final analysis of the ADVANCE IV trial on the efficacy and safety of intravenous efgartigimod (EFG) in adults with primary immune thrombocytopenia.[2] Compared with placebo, EFG showed an early platelet increase, higher sustained platelet response, and more weeks with a platelet count of 50×10^9/L or greater. EFG achieved the primary and all platelet-related secondary end points, and 51.2% of participants on EFG achieved IWG response criteria vs 20% of patients on placebo. EFG was well tolerated with no new safety signals.

Johannes Schetelig, MD, presented results from the ASAP trial assessing the benefit of intensive remission induction therapy prior to allogeneic hematopoietic cell transplantation in patients with relapsed/refractory acute myeloid leukemia.[3] All these abstracts may lead to changes in the standard of care for these conditions.

Perhaps more important than the presentations themselves was the ability of attendees to interact and exchange information in person. In recent years, such interactions had not been possible due to the COVID-19 pandemic. Though we all appreciate how technology allows us to connect with our peers, nothing is quite the same as in-person education and collaboration. At the same time, the ability to access the meeting online allows many more physician-scientists to learn from one another regardless of location. ASH continues to be the premier hematology meeting of the year. ■

For references visit
cancernetwork.com/Vose_2.23

MEET OUR EXPERT

Phillip S, Low, PhD.
Presidential Scholar for Drug Discovery and Ralph C. Corley Distinguished Professor of Chemistry at Purdue University

FDA Approves Imaging Agent Designed to Target Tumors in Lung Cancer

"Upon activating a fluorescent lamp, the cancer tissue glows very brightly, like stars against a black sky, and enables us to see exactly where the tumor tissue was."

Pafolacianine (Cytalux) was recently approved by the FDA as an imaging agent for patients with lung cancer.[1] The success of pafolacianine, a fluorescent imaging agent, derives from its ability to illuminate cancer cells during surgery. Previously, in November 2021, it had been approved to help detect ovarian cancer during surgery.[2] The new approval is based on the phase 3 ELUCIDATE trial (NCT04241315), which demonstrated favorable efficacy and safety in patients undergoing thoracic surgery.[3]

In an interview with *ONCOLOGY*®, the scientist who pioneered this treatment, **Philip S. Low, PhD**, discussed the drug's development. Low also talked about the use of the agent in lung cancer, how it differs from its use in ovarian cancer, and whether usage might expand to other tumor types.

Q: Can you speak about the development of pafolacianine?

LOW: Pafolacianine was developed in my laboratory at Purdue University as a tumor-targeted fluorescent dye. We tested it in animals to demonstrate that, upon injection in the tail vein of mice, for example, it would home in on malignant lesions and avoid uptake in healthy tissues. This would allow, upon activating a fluorescent lamp, the cancer tissue to glow very brightly, like stars against a black sky, and enable us to see exactly where the tumor tissue was. In mock surgeries with animals, we tested if we could locate and remove all the different metastatic lesions. If we resected a tumor or nodule out of healthy tissue, if we removed all cancer cells, and if there were residual cancer cells left, we would see fluorescence in the tumor bed. It also would tell us where to dig to find buried malignant nodules, and thereby help us avoid probing healthy tissues in places where no cancer existed. It provided multiple benefits in these mock surgeries in animals.

After demonstrating its efficacy in these animal models, it was introduced first into humans for assistance with ovarian cancer surgeries. Ovarian cancer surgeons, located at multiple sites around the world, conducted these clinical trials and demonstrated the utility of injecting the patient with this tumor-targeted fluorescent dye. It behaved very similarly to what I just described for the animal studies. After its approval for ovarian cancer, the FDA still required that we demonstrate its value in other cancers. In terms of surgery, we introduced it [in] patients with non–small cell lung cancer. [The FDA also] approved [pafolacianine] for this indication, and the data are very promising. For both ovarian and lung cancer, this suggests that it can, in fact, reveal the location and help the surgeon remove a lot more cancer than otherwise would have been possible.

Q: Is pafolacianine used in similar ways in ovarian and lung cancer?

LOW: They will essentially be used in the same way, but I think the benefit may shift between the 2 cancers. Ovarian cancer often metastasizes and has little nodules throughout the peritoneal cavity. It's not uncommon for a surgeon, upon opening a patient with ovarian cancer, to find 5 to 10, often even 20 or 30, small nodules spread [throughout] the viscera, omentum, and different structures in the peritoneal cavity. In this application, the major value is finding all these different metastatic lesions and ensuring you remove all of them.

In the case of lung cancer, it's not spread and has many little spots all over the thoracic cavity, but instead is often in 1 or 2, or 3 lumps. These are often buried deep. In this application, the major value is finding these buried lumps deep in the lungs and knowing where to dig. If you don't know where to dig, you're going to cut a lot of healthy tissue out and create a lot of damage in the lung. If you know exactly where it is, you can go straight for it and cut it out. That's one advantage.

Another advantage is when that lump is removed, [surgeons need to ask]: "has all of the cancer been removed? Is there any fluorescent tissue remaining in that tumor bed?" This has turned out to be useful.

The third advantage is finding lesions. If you find the first lump, are there others in the same lung, the opposite lung, or a different lobe of the lung? Finding these metastatic lesions—the synchronous lesions—has proven to be very useful.

Q: How can clinicians implement this in their practice?

LOW: Clinicians need to purchase the tumor-targeted fluorescent dye and a fluorescent camera that can detect the fluorescence emitted by the tumor. There are several different companies that manufacture [these kinds of] cameras. Very soon, there will be many cameras usable in combination with pafolacianine to find tumor tissue in patients with cancer.

Q: Are there any other trials currently underway to assess this agent?

LOW: There are 2 types of clinical trials. There are clinical trials initiated by a commercial entity that wishes to obtain approval from the FDA to use a drug in a particular cancer indication. [Then] there are trials initiated by investigators—[usually] surgeons working at medical schools around the country who'd like to explore the potential usefulness of pafolacianine in, let's say, kidney cancer, liver cancer, brain cancer, esophageal cancer, and so on. It turns out that there are several such investigator-sponsored trials currently underway. They're revealing a lot to us regarding the usefulness of pafolacianine for additional applications. ■

References

1. On Target Laboratories announces expanded indication of Cytalux (pafolacianine) injection for detection of lung cancer during surgery. News release. On Target Laboratories. December 16, 2022. Accessed December 19, 2022. bit.ly/3HIHo49

2. FDA approves new imaging drug to help identify ovarian cancer lesions. News release. FDA. November 29, 2021. Accessed December 19, 2022. bit.ly/3VauZZJ

3. Singhal S, et al. Randomized, multicenter phase 3 trial of the pafolacianine during intraoperative molecular imaging of cancer in the lung: results of the ELUCIDATE trial. Presented at: 102nd American Association for Thoracic Surgery Annual Meeting; May 17, 2022; Boston, MA. Abstract LB9.

Cutaneous T-Cell Lymphoma: Current and Emerging Therapies

Julia Dai, MD[1]; and Madeleine Duvic, MD[1]

ABSTRACT

Cutaneous T-cell lymphomas (CTCLs) are clinically heterogeneous T-cell lymphomas that arise in the skin and are characterized by their clinical and pathological features. This review will focus on mycosis fungoides (MF) and Sézary syndrome (SS), which represent 60% to 80% and less than 10% of CTCL cases, respectively. While most patients with MF present with patches and plaques and can be successfully treated with skin-directed therapies, a minority of patients progress from early to advanced stages or undergo large cell transformation. SS is defined as erythroderma, lymphadenopathy, and more than 1000 circulating atypical T-cells/uL with cerebriform nuclei. It has a poor overall survival of 2.5 years. Given the overall rarity of CTCLs, it is notable that clinical trials of treatments for MF/SS have been successfully completed, resulting in FDA approvals of novel therapies with increasing overall response rates. This review outlines the current multidisciplinary approach to diagnosing and treating MF/SS, with a focus on combining skin-directed therapies with emerging targeted and investigational systemic therapies. Integrating these anticancer therapies with skin care and bacterial decolonization is critical for comprehensive management. Curing patients with MF/SS may be possible by using a personalized medicine approach including novel combination strategies, restoration of T helper 1 cytokines, and avoidance of immunosuppressive regimens.

Introduction

Cutaneous T-cell lymphoma (CTCL) describes a group of clinically heterogeneous T-cell lymphomas that arise in the skin.[1] Mycosis fungoides (MF), the most common CTCL, represents 60% to 80% of all CTCLs whereas Sézary syndrome (SS), the erythrodermic and leukemic variant, affects fewer than 10% of patients with CTCL. Most patients with MF present with stage IA disease, defined as patches and plaques involving less than 10% of the body surface area (**Figure 1**). For most individuals diagnosed with early-stage disease, this is a chronic skin affliction managed with skin-directed therapy (SDT) with acceptable disease control and possible complete remissions. If the disease progresses, the treatment of MF/SS consists of sequential therapies that have increasing toxicity and potential immunosuppression.

When the first randomized study of patients with CTCL was conducted at the National Institutes of Health in 1989, no survival advantage was seen with electron beam radiation therapy (EBT) combined with chemotherapy compared with less aggressive sequential topical therapies.[2] Thus, the oncologist should be aware of the full toolbox of possible non-immunosuppressive treatments, especially skin-directed therapies and immunotherapies that can prolong the lifespan of patients with MF or SS.

Skin-Directed Therapies

SDTs are the mainstay for treatment of early-stage disease, but they also have an important role in disease palliation in patients with advanced disease. Because MF/SS is a chronic skin disease that likely requires treatment for many years, management should start out as conservatively as possible, with the goals of putting the disease in a prolonged or permanent remission and controlling pruritus.

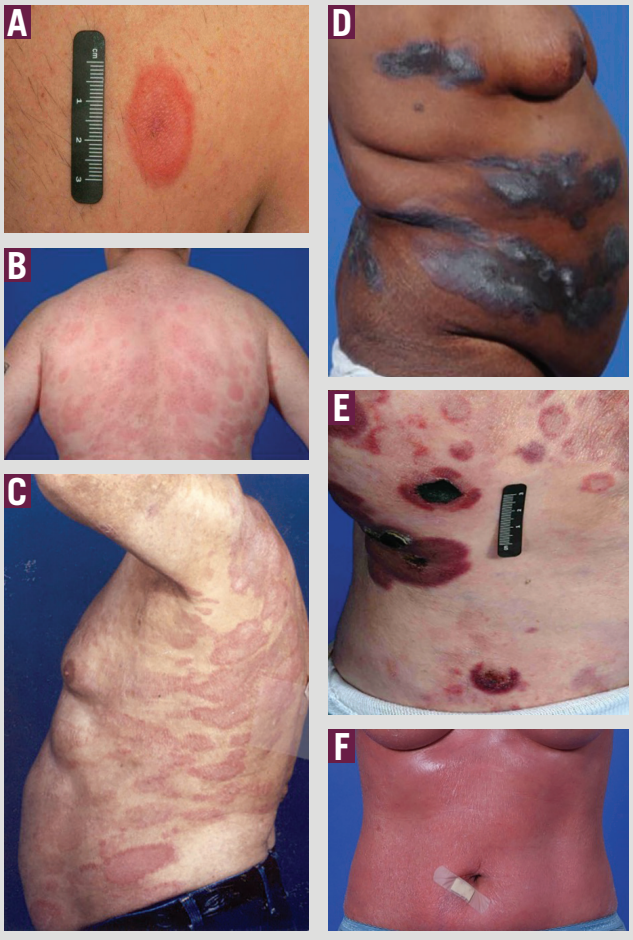

FIGURE 1. **Clinical Images of Patients With MF/SS**

Panel A: a solitary pink, annular patch (T1a) of mycosis fungoides (MF) that may be cured with radiation therapy

Panel B: multiple pink, ovoid patches covering >10% body surface area (BSA) in a patient with T2a MF

Panel C: pink, annular plaques covering >10% BSA in a patient with T2b MF

Panel D: a patient with T3 MF with indurated tumors overlying hyperpigmented plaques

Panel E: ulcerated tumors admixed with red annular patches in plaques in a patient with T3 MF with large cell transformation

Panel F: a patient with Sézary syndrome (SS) with bright pink erythroderma

Topical steroids

We use high-potency topical clobetasol 0.05% twice daily as a first-line SDT. If lesions resolve, the frequency or potency should be slowly tapered. Tapering is desirable because steroids decrease collagen production; this leads to skin atrophy, which can be severe in intertriginous areas and on the face and neck.

For patients with extensive skin involvement or erythroderma, application of topical triamcinolone 0.1% with wet warm towels for 15 minutes (wet wraps) can be helpful for controlling the itching and skin lesions for a limited period.

Topical nitrogen mustard

Topical nitrogen mustard (NM) has been used off label as a frontline SDT in MF for decades. In 2013, mechlorethamine 0.016% gel (Valchlor gel) was approved by the FDA for use in MF.[3] NM may be used as salvage therapy for patients who failed topical steroids or as a maintenance therapy following EBT. The most common adverse effect (AE) seen with NM is contact dermatitis, which is thought to elicit an inflammatory response that may lead to earlier disease clearance. Topical steroids have been used in conjunction with NM but may limit the contact dermatitis.

Topical retinoids

Vitamin A is a lipid-soluble, essential nutrient that dimerizes and binds to retinoid receptors. Its action depends on the type of retinoid: With retinoic acid receptors (RARs), it can induce T-cell or keratinocyte differentiation, and with retinoid X receptors (RXRs), it can induce apoptosis of tumor cells. Topical bexarotene (Targretin gel) is an RXR retinoid approved for the treatment of MF based on phase 1 and 2 trials.[4] The RAR retinoid tazarotene is approved for acne and psoriasis and demonstrates efficacy similar to that of bexarotene in patients with MF. Topical retinoids are especially helpful for hypertrophic, psoriatic, acral, or follicular lesions. Retinoids will cause irritation in intertriginous areas and should be used sparingly in these regions.

Topical immunotherapy

Imiquimod 5% cream (Aldara) is a Toll-like receptor (TLR)-7 agonist approved for treatment of genital warts. Several case reports observed that imiquimod 5% cream twice daily

is effective in treating tumors in MF. Topical resiquimod is a more potent TLR-7 and TLR-8 agonist and demonstrated efficacy in patients with MF in a phase 1 trial.[5] Both imiquimod and resiquimod may cause irritation and may have an abscopal effect, possibly through the generation of γ-interferon, interleukin (IL)-12, and natural killer (NK) cells.

Two steroid-sparing topical calcineurin agents (pimecrolimus and tacrolimus) have been used off label to treat areas at risk for atrophy, such as eyelids or genitalia. In a phase 2 trial evaluating topical pimecrolimus 1% cream twice daily for 16 weeks in early-stage MF, response rates of 54% and 73% were seen in patients with stage IA and IB disease, respectively.[6]

Phototherapy

Phototherapy with narrowband ultraviolet B (nbUVB) or psoralen plus ultraviolet A (PUVA) are often the first therapies considered after topical therapies have failed.[7] PUVA is a combination of oral psoralen, a photosensitizing agent, followed by UVA exposure. PUVA is more effective than nbUVB for treating more extensive plaque disease. Choice of phototherapy depends on the patient's clinical phenotype and access to phototherapy centers. Phototherapy may be used alone or combined with topical steroids as well as topical/oral retinoids; however, adjunctive treatment with NM is not recommended.

Photodynamic therapy

Photodynamic therapy is a novel treatment that combines fluorescent light and a topical photochemical (eg, hypericin) applied prior to light exposure. A phase 2 trial demonstrated safety and efficacy of topical hypericin to individual lesions followed by visible light exposure.[8] A phase 3 study of hypericin ointment with photodynamic therapy demonstrated an index lesion response rate (defined as 50% or greater improvement) in 49% of lesions after 3 cycles of therapy.[9]

Electron beam radiation (EBT) therapy

Treatment with EBT has the highest response rates, greater than 90%. Complete response rates are highest in patients with T1 and T2 disease, and early use of low-dose radiation to a solitary lesion may be curative. Low-dose (12 Gy) total skin EBT (TSEBT) can be used for disease control and palliation of symptoms in patients with disseminated skin disease,[10] whereas higher doses (up to 36 Gy) are recommended to debulk skin compartment disease prior to allogeneic hematopoietic stem cell transplantation (alloHSCT).[11,12]

TABLE 1. **Indication for and Efficacy of FDA-approved Therapies for MF/SS**

Agent (Class)	Indication	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	CTCL with 1 prior systemic therapy	Pivotal Supportive	96 71	34% 35%	15m 11m
Denileukin diftitox, discontinued (Fusion protein)	CTCL with CD25 expression	Pivotal	71	30%	4m
Bexarotene (Retinoid x-receptor activator)	CTCL with 1 prior systemic therapy	Pivotal	62	32%	5m
Vorinostat (HDAC inhibitor)	CTCL with 2 prior systemic therapies	Pivotal Supportive	74 33	30% 24%	6m 4m
Mogamulizumab (CCR4 inhibitor)	MF/SS with 1 prior systemic therapy	Pivotal	186	28%	14m
Brentuximab (CD30 inhibitor)	CTCL with 1 prior systemic therapy	Pivotal	64	55%	17m

CCR4, CC chemokine receptor 4; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; HDAC, histone deacetylase; m, months; MF/SS, mycosis fungoides/Sézary syndrome; N, number; ORR, overall response rate

First-line Systemic Therapies

Extracorporeal photopheresis

In patients with erythrodermic MF and SS, the frontline therapy is extracorporeal photopheresis (ECP), which combines phototherapy with leukapheresis.[13] ECP may be administered for 2 consecutive days every month or, if disease is progressing, every 2 weeks. ECP as monotherapy has been shown to have overall response rates (ORRs) ranging from 33% to 75%.[14,15] Studies demonstrate that ECP prolongs survival in patients with erythrodermic and advanced MF/SS, and they support the use of ECP as first-line treatment for many patients with stage III and IV disease. Photopheresis may be combined with immunomodulatory agents like oral retinoids and interferon.

Oral retinoids

Oral retinoids are often selected as first-line systemic therapy for patients who have failed SDT (**Table 2**). Two phase 2 trials led to the FDA approval of oral bexarotene based on the ORR of 48% at the optimal dose of 300 mg/m^2 daily in a combined group of patients with early and advanced-stage MF/SS.[16,17] In practice, oral bexarotene is started at 75 mg to 150 mg daily with gradual escalation to a goal dose of 300 mg/m^2 daily. Because bexarotene causes central hypothyroidism leading to hypertriglyceridemia, we initiate patients on low-dose levothyroxine (eg, 25-75 mcg daily) and fenofibrate 145 mg daily. There is a cumulative dose effect of bexarotene, and it may take 6 or more months for a response at the lower dose range. Bexarotene is the only FDA-approved retinoid for MF/SS. However, other retinoids such as acitretin and isotretinoin may be less cost-prohibitive and associated with similar efficacy.[18] Retinoids have been combined with other therapies and used for maintenance after EBT.

Interferons and interleukins

As the immune system of patients with advanced-stage MF/SS is shifted toward T-helper 2 (Th2) cytokines, treatment with interferons (IFNs) may aid in restoring the T-helper 1 (Th1)/Th2 balance.[19] IFN-α and pegylated IFN-α both have demonstrated efficacy of 64%, making them among the more effective therapies used alone or in combination with ECP or retinoids.[20] IFN-γ is as effective as IFN-α and tends to be associated with fewer AEs.

IL-12 activates NK cells and cytotoxic CD8$^+$ T cells, thereby potentiating the production of IFN-γ and reversing the drift from Th1 to Th2 cytokines. A phase 1 trial of recombinant human IL-12 (rhIL-12) administered intralesionally or subcutaneously twice weekly for up to 24 weeks demonstrated clinical response across multiple disease phenotypes.[21] Our phase 2 trial of rhIL-12 in patients with early-stage MF found that twice-weekly subcutaneous administration of rhIL-12 showed an ORR of 43%.[22] IL-12 is not commercially available, but it is a promising agent that warrants further investigation.

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACi) are small molecules that block deacetylation of tumor suppressor genes and cell cycle regulatory pathways. Vorinostat is an oral HDACi that is FDA-approved for the treatment of MF/SS; its ORR is 29%.[23,24] Vorinostat has been largely replaced by romidepsin, an FDA-approved HDACi that is given intravenously (IV) weekly for 3 consecutive weeks of a 4-week cycle. A phase 2 trial demonstrated an ORR of 34%.[25] Responses were seen across all stages and disease subtypes. Multiple clinical trials utilizing these inhibitors in combination with other treatments are under investigation.

Targeted Immunotherapies

E7777

Initially known as denileukin diftitox (Ontak), E7777 is emerging as a more stable and less toxic recombinant fusion protein. As Ontak, this agent was initially evaluated in a phase 1 study of patients with hematologic malignancies expressing CD25, and it demonstrated an ORR of 37%, including 5 complete responses.[26] A 2-dose randomized study of patients with stage IB-IVA MF/SS showed an ORR of 30%.[27] A second randomized study of patients with stage IA-III MF/SS demonstrated an ORR of 44%.[28] Patients whose skin biopsy had greater than 25% CD25 expression appeared to perform better (ORR, 78%) than patients having low to undetectable expression (ORR, 20%). These pivotal studies led to the full approval by the FDA in 2008. However, Ontak was withdrawn in 2014 for inconsistencies in the folding of the protein, and the new formulation, E7777, has since been in development. A recent phase 2 registration trial in 71 patients established a dose of 9 ug/kg/day.[29] Preliminary results show an ORR of 44%. Potential AEs are infusion reactions and capillary leak syndrome. Guidelines to prevent and manage capillary leak syndrome have been developed.[30]

Brentuximab vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate to monomethyl auristatin E that targets CD30. In a phase 2 trial, high response rates were seen in patients with MF (54%), primary cutaneous anaplastic large cell lymphoma (100%), and lymphomatoid papulosis (100%).[31] Patients with MF demonstrated similar response rates, irrespective of low, medium, or high CD30 expression (50%, 58%, and 50%, respectively). In a parallel phase 2 trial of patients with stage IB-IV MF/SS, ORR was 70%.[32] Clinical

TABLE 2. **Summary of Select Investigational Trials in Advanced MF/SS**

Category	Investigational agent	Clinicaltrials.gov ID	Phase	Status
KIR3DL2	IPH4102	NCT02593045	II	Completed
	IPH4102 + chemotherapy (TELLOMAK)	NCT03902184	II	Recruiting
	Pembro	NCT02243579	II	Completed
	Pembro + RT	NCT03385226	II	Recruiting
	Pembro + decitabine + pralatrexate	NCT03240211	I	Recruiting
	Pembro + pralatrexate	NCT03598998	I/II	Recruiting
PD1/PDL1	Pembro + romidepsin	NCT03278782	I/II	Recruiting
	Pembro + IFN-gamma	NCT03063632	II	Active, not recruiting
	Pembro + gemcitabine	NCT04960618	II	Recruiting
	Pembro + brentuximab	NCT05313243	II	Not yet recruiting
	Nivolumab + T-VEC	NCT02978625	II	Recruiting
	Nivolumab + duvelisib	NCT04652960	I	Recruiting
	Durvalumab + lenalidomide	NCT03011814	I/II	Recruiting
	TTI-621 (SIRPaFc IgG4)	NCT02663518	I	Active, not recruiting
CD47	Intratumoral TTI-621	NCT02890368	I	Terminated
	Hu5F9-G4	NCT02216409	I	Completed
	Hu5F9-G4 + mogamulizumab	NCT04541017	Ib/II	Suspended
	LB1901 (anti-CD4 CAR T)	NCT04712864	I	Active, not recruiting
CAR T	CD4CAR (anti-CD4 lentiviral vector)	NCT03829540	I	Active, not recruiting
	ATLCAR.CD30 and ATLCAR.CD30.CCR4	NCT03602157	I	Recruiting
	CTX130 (CRISPR/Cas9 targeting CD70)	NCT04502446	I	Recruiting
	Ruxolitinib (JAK1/2)	NCT02974647	II	Recruiting
JAK/STAT/SYK	Ruxolitinib + duvelisib	NCT05010005	I	Recruiting
	Cerdulatinib (JAK/SYK)	NCT01994382	I/Iia	Completed
	Tenalisib (RP6530, dual PI3K delta/gamma)	NCT02567656	I	Completed
PI3K/AKT/ mTOR	Tenalisib + romidepsin	NCT03770000	I/II	Completed
	Duvelisib (PI3K) + romidepsin or bortezomib	NCT02783625	II	Active, not recruiting
	Parsaclisib (PI3K) + romidepsin	NCT04774068	I	Recruiting

CAR T, chimeric antigen receptor T-cell therapy; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; IFN, interferon; Ig, immunoglobulin; MF/SS, mycosis fungoides/Sézary syndrome; pembro, pembrolizumab; PD1, Programmed Cell Death Protein 1; PI3K, phosphoinositide 3-kinase; RT, radiation therapy; SIRP, signal regulatory protein; T-VEC, talimogene laherparepvec

responses were seen across all levels of CD30 expression, although median $CD30_{max}$ was higher in responders than in nonresponders. The randomized phase 3 ALCANZA trial showed that BV was superior to physician's choice (oral bexarotene or methotrexate) in patients with $CD30^+$ CTCL based on an ORR lasting at least 4 months (56.3% vs 12.5%).[33] Longer median progression-free survival (PFS) intervals were observed in patients treated with BV compared with physician's choice (16.7 vs 3.5 months).

Peripheral neuropathy is the major dose-related AE, seen in 67% of patients. After discontinuing treatment, symptoms improve with time in most patients.

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody that is defucosylated to enhance antibody-dependent cellular cytotoxicity. Its target is the CC chemokine receptor 4 (CCR4), a receptor expressed by malignant cells across multiple clinical phenotypes in MF/SS and also on the surface of Th2 and regulatory T cells (Tregs).

A phase 1/2 trial in 41 patients with MF/SS demonstrated an ORR of 37%, including a response in 18 of 19 (95%) patients with B1 or greater blood involvement.[34] In the phase 3 MAVORIC registration trial, 372 patients with MF/SS were randomized to receive either mogamulizumab (1 mg/kg IV weekly for 4 weeks, then every 2 weeks) or vorinostat.[35] Global ORR was 28% for patients treated with mogamulizumab, and a higher ORR of 47% in patients with SS was observed.

Mogamulizumab-associated rash (MAR) is seen in 16% to 24% of treated patients. Skin biopsies may aid in distinguishing MAR from disease, as MAR demonstrates features of spongiotic, psoriasiform, or interface dermatitis with a predominance of $CD8^+$ T cells. Given mogamulizumab's profound effect in reducing Tregs, which are integral to successful engraftment, mogamulizumab should not be administered in the months leading up to alloHSCT.

IPH4102

KIR3DL2 (also known as CD158k) is a member of a family of inhibitory killer cell immunoglobulin-like receptors (KIRs) found on NK cells. KIR3DL2 is expressed in more than 85% of patients with SS. It has been proposed as a diagnostic and prognostic marker for SS that is superior to loss of CD26 or CD7. IPH4102, also known as lacutamab, is a fully humanized monoclonal antibody targeting KIR3DL2 that binds to receptors of target cells, inducing NK-cell mediated lysis. A phase 1, international, multicenter trial of 44 patients with MF/SS demonstrated an ORR of 43% in SS patients with minimal AEs.[36] A phase 2 trial (TELLOMAK; NCT03902184) is ongoing to study the efficacy of IPH4102 alone or in combination with chemotherapy in patients with advanced MF/SS.

Pembrolizumab and nivolumab

The use of immune checkpoint inhibitors, such as the anti–PD-1 agents pembrolizumab and nivolumab, has demonstrated how reinvigorating exhausted tumor-infiltrating lymphocytes may restore the host antitumor response in many cancers. Their role in MF/SS is less defined owing to the expression of these markers on both nonmalignant and malignant T cells. Hence, blocking PD-1 in malignant cells in T-cell lymphomas may theoretically promote tumor growth. Treatment with pembrolizumab resulted in an ORR of 38% in patients with advanced MF/SS in a phase 2 trial.[37] A transient disease flare characterized by erythroderma and pruritus was seen in more than half of patients with SS. The phase 1 study of nivolumab in patients with hematologic malignancy also demonstrated clinical responses in 15% of patients with MF/SS.[38] Ongoing trials are studying the use of checkpoint inhibitors in combination with other therapies (**Table 2**).

Single-Agent Chemotherapy

Folate antagonists

Pralatrexate is a dihydrofolate reductase inhibitor with higher activity and greater selectivity for cancer cells than methotrexate. In a dose de-escalation study in CTCL, pralatrexate 15 mg/m^2/week for 3 of 4 weeks resulted in an ORR of 45%.[39] We found that addition of oral bexarotene at 150-300 mg/m^2 based on preclinical activity enhanced the efficacy to an ORR of 61%; the safety profile was consistent with that previously seen with individual study drugs.[40] Durable responses were observed, with a median PFS of 12.8 months. We recommend pretreatment with oral folinic acid (leucovorin) at 25 mg twice daily for 3 days at the start of each pralatrexate cycle and vitamin B12 at 1 mg intramuscularly every 8 to 10 weeks.

Gemcitabine

Gemcitabine is a pyrimidine nucleoside analogue. Its use in patients with CTCL has been studied, utilizing a dose of 1000-1200 mg/m^2/week for 3 of 4 weeks.[41] A dose reduction—treatment for 2 weeks rather than 3—has been used in the elderly with good tolerability. In our phase 2 trial of patients with advanced CTCL, we observed an ORR of 68% (17 of 25 patients).[42] Gemcitabine should be administered carefully in patients with a recent history of radiation given the potential for radiation recall.

Liposomal doxorubicin

Liposomal doxorubicin (Doxil) is an anthracycline with antineoplastic effects. In the first published study of liposomal doxorubicin in patients with MF, treatment of 20 mg/m^2 once monthly resulted in an ORR of 80% (8 of 10 patients).[43]

Combination chemotherapy

Patients with advanced MF/SS, especially those with large cell transformation, may develop tumors and bulky lymphadenopathy so severe and extensive that combination chemotherapy may be considered. Several regimens have been used, but no data suggest that one is better than another. Romidepsin and E7777 have been studied in combination with CHOP (cyclophosphamide, vincristine, prednisone, and bleomycin), and studies of mogamulizumab with CHOP in other T-cell lymphomas are ongoing (**Table 2**). Response rates may be high, but responses are often short-lived without increased survival. Subsequent relapsed disease may be even more aggressive, and the risk of immunosuppression associated with chemotherapy may result in high morbidity and mortality from opportunistic infections in patients with whose skin and/or immune system are already compromised.

Other Investigational Agents

Bortezomib

Bortezomib inhibits proteasome-dependent NF-κB signaling. A phase 2 study of bortezomib in 12 patients with advanced MF or peripheral T-cell lymphoma (PTCL) with isolated skin involvement demonstrated an ORR of 67%.[44] Patients were treated with a dose of 1.3 mg/m^2 twice weekly for 2 weeks followed by 1 week off. Treatment was well tolerated and responses were durable, lasting 7 to 14 months. In vitro studies have suggested that bortezomib may also enhance the activity of HDACi.

Lenalidomide

Lenalidomide is an oral immunomodulatory agent that induces Th1 cytokine production and augments NK cell cytotoxicity. In a phase 2 exploratory trial, lenalidomide was found to be active in patients with advanced MF/SS with an ORR of 28% (9 of 32 patients, all partial responses).[45] Many patients were unable to tolerate 25 mg daily. Although doses of 10 mg daily were better tolerated, they were not as effective. In a small, sequential phase 1 study, lenalidomide demonstrated efficacy in combination with romidepsin with an ORR of 44% (4 of 9 patients).[46]

JAK-STAT inhibitors

Janus kinase-signal transducer and activator of transcription (JAK-STAT) is a signaling pathway that is critical in mediating inflammatory skin diseases, including atopic dermatitis, psoriasis, alopecia areata, and vitiligo. Mutations in the JAK-STAT pathway have been reported in SS cells by whole genome sequencing. In a phase 2 trial evaluating oral ruxolitinib, a JAK1/2 inhibitor, in patients with T-cell lymphoma with or without activating JAK-STAT mutations, 1 of 7 patients with MF/SS demonstrated a clinical response.[47]

SYK inhibitors

Overexpression of SYK, a protein tyrosine kinase, occurs in T cell lymphomas and is thought to contribute to malignant cell growth and survival. In a phase 2 study of cerdulatinib, a dual SYK/JAK inhibitor, in patients with T-cell lymphoma, ORR was 35% with the highest activity in patients with MF (ORR 45%).[48] Rapid improvements in pruritus occurred, and several patients experienced a durable response.

PI3K inhibitors

Modulation of phosphatidylinositol 3-kinase (PI3K), a lipid kinase involved in intracellular signal transduction, may contribute to the survival and differentiation of malignant tumor cells. Duvelisib and tenalisib are PI3K inhibitors with activity against the δ and γ isoforms, which are key effectors in the innate and adaptive immune response and in modulating the tumor microenvironment through tumor-associated macrophages. A phase 1 study of duvelisib demonstrated an ORR of 32% in MF/SS.[49] A phase 1/1b study of tenalisib in patients with T-cell lymphoma showed an ORR of 45% in MF/SS.[50]

Anti-CD47

CD47 has garnered much interest as a macrophage checkpoint (or "do not eat me" signal) that is overexpressed in many cancer types. In a phase 1 study of intralesional TT1-621, a CD47-SIRPα inhibitor, 35 patients with MF/SS were treated in a sequential dose escalation study with intralesional TT1-621 alone or in combination with pembrolizumab or pegylated IFN-α.[51] A response in Composite Assessment of Index Lesion Severity (CAILS) score was seen in 34% (10 of 29 evaluable patients). A phase 1 study of IV TT1-621 reported an ORR of 21% in 29 patients with MF/SS.[52]

Chimeric Antigen Receptor

Chimeric antigen receptor (CAR T) are an emerging therapy in which the patient's own CD8$^+$ T cells are engineered and expanded in culture to recognize and eliminate tumor-specific antigen, independent of MHC. In 2017, the first CAR T therapy was approved for the treatment of B-cell lymphoma using a CD19 target. However, the use of therapy in patients with T-cell lymphoma may offer unique challenges because sustained

elimination of T-cells would result in severe immunosuppression with infectious complications. To optimize "on-target, off-tumor" selection, CAR T-cells using targets CD30 and CCR4 are being studied in advanced MF/SS (**Table 2**).

Allogeneic stem cell Transplantation

AlloHSCT may result in long-term remission in a subset of patients with MF/SS and should be considered upfront for younger patients in otherwise good health who are refractory to multiple therapies or who demonstrate a high-risk profile of disease with poor life expectancy. Optimizing timing of alloHSCT when the disease is well controlled is critical, as alloHSCT administered while the patient has clinically active disease or poor immunity due to treatment toxicity may lead to relapse.

Preparatory cytoreduction with reduced-intensity or nonmyeloablative regimens is preferred as patients with advanced MF/SS are older, and posttransplant infectious complications may contribute to high morbidity and mortality in the setting of immunosuppression and skin barrier breakdown. TSEBT is often an important component because the skin is a frequent site of posttransplant relapse.

The preparatory regimen at The University of Texas MD Anderson Cancer Center incorporates TSEBT and nonmyeloablative conditioning with fludarabine and antithymocyte globulin (ATG).[53] We have observed durable remissions in patients with SS after alloHSCT (13/24 patients; 54%).[54] A Stanford University group has reported on their experience in patients with advanced MF/SS using the conditioning regimen of TSEBT, total lymphoid irradiation, and ATG, citing clinical and molecular remission in 43% of patients and 5-year OS of 56%.[13]

Treatment algorithm in advanced disease

There is no standard treatment or sequence of treatments for patients with advanced MF/SS. Treatment selection is predicated on clinical stage as well as burden of activity within each disease compartment (skin, blood, nodal, and visceral). At MD Anderson Cancer Center, we begin with therapies associated with fewer toxicities that may still offer a high response rate and durability of response. For patients with leukemic disease, treatment with oral bexarotene, ECP, and mogamulizumab are considered to be frontline therapies, with early evaluation for alloHSCT in the appropriate populations. In contrast, patients with tumors or bulky lymph node disease, especially those with large cell transformation, may be preferentially considered for treatment with BV or pralatrexate. In our experience, management with chemotherapy portends worse outcomes. Integration of relevant biomarkers, such as CD30 for BV and other next generation–sequencing mutational panels for investigational agents (eg, CCR4, KIR3DL2, JAK) should be assessed for targetable mutations. Finally, skin-directed treatment with topicals, phototherapy, and radiation (TSEBT or to individual lesions) should be incorporated to augment treatment response and enhance quality of life. Treatment within a multidisciplinary team—including dermatologists, oncologists, radiation oncologists, and bone marrow transplant specialists—is ideal for comprehensive care.

Supportive Care

Patients with erythrodermic MF or SS who are having flares are often colonized with staphylococcus aureus (*S aureus)*, which can develop into methicillin-resistant *S aureus*. Colonization must be eliminated for the patient to improve. Soaking in a bathtub of water mixed with a half-cup of bleach may help decolonize bacteria from the skin. Mupirocin 2% ointment may be useful for decolonization of nares and skin lesions.

We do not favor use of systemic corticosteroids for symptom palliation, as we frequently observe steroid dependence with resistance to subsequent therapies.

Pruritus may profoundly affect quality of life in patients with MF/SS. Effective management will lessen patients' psychological and emotional burden and also minimize secondary skin infection through less frequent manipulation of the skin. Topical steroids may offer temporary relief from pruritus and should be integrated with gentle emollients to optimize the skin barrier. Oral agents, such as gabapentin and aprepitant, may offer additional relief. Although oral antihistamines are generally ineffective for relieving severe pruritus, an evening dose may be considered for its sedating effects. ■

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CONFLICT OF INTEREST STATEMENT
MD has served on the Soligenix scientific advisory board and has received consulting fees from Bioniz, Codiac, and Citius.

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None.

For references visit
cancernetwork.com/CTCL_2.23

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In adult and pediatric patients 12 years and older

Intervene With Jakafi at the *First Sign* of Initial Systemic Treatment Failure for cGVHD

Timely Diagnosis and Early Intervention Are Critical to Prevent Potentially Irreversible Organ Damage[1]

Jakafi® (ruxolitinib) is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

REACH3 Primary Endpoint: ORR at Week 24

49.7% (82/165) with Jakafi vs 25.6% (42/164) with BAT (OR: 2.99; 95% CI, 1.86-4.80; *P*<0.0001)[2,3*†]

ORR through Week 24

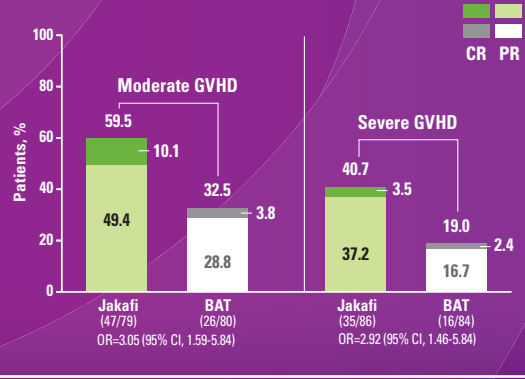
70% (116/165) with Jakafi vs 57% (94/164) with BAT[4‡]

- In the Jakafi Prescribing Information, efficacy was based on ORR through week 24 (Cycle 7 Day 1)[4]

*Overall response rate was defined as the proportion of patients with complete or partial response, according to 2014 NIH consensus criteria, at Week 24.[2]
†One-sided *P* value, odds ratio, and 95% CI were calculated using stratified Cochran-Mantel-Haenszel test, stratifying for moderate and severe cGVHD.[2]
‡Defined as proportion of patients who achieved complete or partial response, according to 2014 NIH response criteria, through Week 24 (Cycle 7 Day 1).[4]

Overall Response Rates Were Higher With Jakafi in Patients With Moderate Disease Severity at Week 24 vs BAT[3]

REACH3 Subgroup Analysis: ORR by Baseline Disease Severity at Week 24[3,5]



BAT=best available therapy; BID=twice daily; CI=confidence interval; CR=complete response; HSCT=hematopoietic stem cell transplant; GI=gastrointestinal; OR=odds ratio; ORR=overall response rate; PR=partial response.

IMPORTANT SAFETY INFORMATION

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial

Overall Response Rates Were Higher With Jakafi at Week 24 Regardless of Organs Involved at Baseline vs BAT[3]

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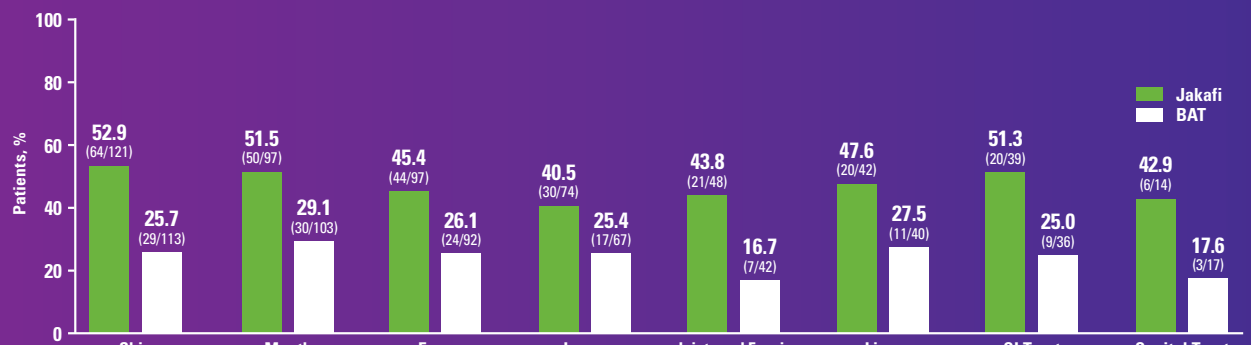
5mg • 10mg • 15mg • 20mg • 25mg

REACH3 Subgroup Analysis: ORR at Week 24 by Baseline Organ Involvement[3,a]



[a]Patients with >1 affected organ were counted in each organ subgroup. Organ involvement was defined as organ score ≥1 based on the cGVHD staging criteria.[3,6]

REACH3 was a randomized, open-label, multicenter, phase 3 study of Jakafi vs BAT in patients with steroid-refractory cGVHD (N=329).[1,2§‖¶] The starting dose for Jakafi was 10 mg BID. Crossover from BAT to Jakafi was permitted on or after Week 24 if patients progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare.[1]

[§]Patients included in the study were 12 years and older, had undergone allogeneic HSCT from any donor source/type, and had evident myeloid and platelet engraftment.[4]

[‖]BATs included ibrutinib, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, imatinib, infliximab, or pentostatin.[4]

[¶]Steroid-refractory disease was defined as lack of response or disease progression after ≥1 week of prednisone 1 mg/kg/day, disease persistence without improvement after ≥4 weeks of prednisone >0.5 mg/kg/day or 1 mg/kg every other day, or increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose.[3,5]

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infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur

- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately
- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections
- Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

References: 1. Lee SJ, Flower MED. Recognizing and managing chronic graft-versus-host disease. *Am Soc Hematol.* 2008;(1):134-141. **2.** Zeiser R, Polverelli N, Ram R, et al; for the REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3):228-238. **3.** Zeiser R, Polverelli N, Ram R, et al; for the REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3)(suppl):1-49. **4.** Jakafi [package insert]. Wilmington, DE: Incyte Corporation. **5.** Data on file. Incyte Corporation. Wilmington, DE. **6.** Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401.e1.

Incyte

Jakafi®
ruxolitinib (tablets)
5mg • 10mg • 15mg • 20mg • 25mg

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE Myelofibrosis Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. **Polycythemia Vera** Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea. **Acute Graft-Versus-Host Disease** Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older. **Chronic Graft-Versus-Host Disease** Jakafi is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary *[see Dosage and Administration (2) in Full Prescribing Information]*. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5×10^9/L) was generally reversible by withholding Jakafi until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated *[see Dosage and Administration (2) in Full Prescribing Information]*. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia *[see Dosage and Administration (2.7) in Full Prescribing Information]*, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer (NMSC)** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides *[see Adverse Reactions (6.1) in Full Prescribing Information]*. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. **Major Adverse Cardiovascular Events (MACE)** Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. **Thrombosis** Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. **Secondary Malignancies** Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers. **ADVERSE REACTIONS** The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia *[see Warnings and Precautions (5.1) in Full Prescribing Information]* • Risk of Infection *[see Warnings and Precautions (5.2) in Full Prescribing Information]* • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi *[see Warnings and Precautions (5.3) in Full Prescribing Information]* • Non-Melanoma Skin Cancer *[see Warnings and Precautions (5.4) in Full Prescribing Information]* • Lipid Elevations *[see Warnings and Precautions (5.5) in Full Prescribing Information]* • Major Adverse Cardiovascular Events (MACE) *[see Warnings and Precautions (5.6) in Full Prescribing Information]* • Thrombosis *[see Warnings and Precautions (5.7) in Full Prescribing Information]* • Secondary Malignancies *[see Warnings and Precautions (5.8) in Full Prescribing Information]*. **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.

Myelofibrosis The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200×10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200×10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia *[see Table 2]*. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache *[see Table 1]*. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	< 1	0	15	0	0
Dizziness[c]	18	< 1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	< 1	< 1
Weight Gain[e]	7	< 1	0	1	< 1	0
Flatulence	5	0	0	< 1	0	0
Herpes Zoster[f]	2	0	0	< 1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Reactions: Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50×10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation

of treatment because of thrombocytopenia occurred in < 1% of patients receiving Jakafi and < 1% of patients receiving control regimens. Patients with a platelet count of 100 × 10^9/L to 200 × 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 × 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	< 1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-Controlled Study
• 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was < 1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and < 1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was < 1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Polycythemia Vera In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy *[see Clinical Studies (14.2) in Full Prescribing Information]*. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥ 5% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Reactions	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Diarrhea	15	0	7	< 1
Dizziness[b]	15	0	13	0
Dyspnea[c]	13	3	4	0
Muscle Spasms	12	< 1	5	0
Constipation	8	0	3	0
Herpes Zoster[d]	6	< 1	0	0
Nausea	6	0	4	0
Weight Gain[e]	6	0	< 1	0
Urinary Tract Infections[f]	6	0	3	0
Hypertension	5	< 1	3	< 1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes dizziness and vertigo
[c] includes dyspnea and dyspnea exertional
[d] includes herpes zoster and post-herpetic neuralgia
[e] includes weight increased and abnormal weight gain
[f] includes urinary tract infection and cystitis

Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	< 1	< 1	58	0	0
Thrombocytopenia	27	5	< 1	24	3	< 1
Neutropenia	3	0	< 1	10	< 1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	< 1	0	16	0	0
Elevated AST	23	0	0	23	< 1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Acute Graft-Versus-Host Disease In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for aGVHD failing treatment with steroids with or without other immunosuppressive drugs *[see Clinical Studies (14.3) in Full Prescribing Information]*. The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

Table 5: Acute Graft-Versus-Host Disease: Nonhematologic Adverse Reactions Occurring in ≥ 15% of Patients in the Open-Label, Single-Cohort Study

	Jakafi (N=71)	
Adverse Reactions[a]	**All Grades[b] (%)**	**Grade 3-4 (%)**
Infections (pathogen not specified)	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

[a] Selected laboratory abnormalities are listed in Table 6 below
[b] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

Selected laboratory abnormalities during treatment with Jakafi are shown in Table 6.

Table 6: Acute Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single Cohort Study

	Jakafi (N=71)	
	Worst grade during treatment	
Laboratory Parameter	**All Grades[a] (%)**	**Grade 3-4 (%)**
Hematology		
Anemia	75	45
Thrombocytopenia	75	61
Neutropenia	58	40
Chemistry		
Elevated ALT	48	8
Elevated AST	48	6
Hypertriglyceridemia	11	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Chronic Graft-Versus-Host Disease In a Phase 3, randomized, open-label, multi-center study, 165 patients were treated with Jakafi and 158 patients were treated with best available therapy for cGVHD failing treatment with steroids with or without other immunosuppressive drugs *[see Clinical Studies (14.4) in full Prescribing Information]*; sixty-five patients crossed over from best available therapy to treatment with Jakafi, for a total of 230 patients treated with Jakafi. The median duration of exposure to Jakafi for the study was 49.7 weeks (range, 0.7 to 144.9 weeks) in the Jakafi arm. One hundred and nine (47%) patients were on Jakafi for at least 1 year. There were five fatal adverse reactions to Jakafi, including 1 from toxic epidermal necrolysis and 4 from neutropenia, anemia and/or thrombocytopenia. An adverse reaction resulting in treatment discontinuation occurred in 18% of patients treated with Jakafi. An adverse reaction resulting in dose modification occurred in 27%, and an adverse reaction resulting in treatment interruption occurred in 23%. The most common hematologic adverse reactions (incidence > 35%) are anemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence ≥ 20%) are infections (pathogen not specified) and viral infection. Table 7 presents the most frequent nonlaboratory adverse reactions occurring up to Cycle 7 Day 1 of randomized treatment.

Table 7: Chronic Graft-Versus-Host Disease: All-Grade (≥ 10%) and Grades 3-5 (≥ 3%) Nonlaboratory Adverse Reactions Occurring in Patients in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

	Jakafi (N = 165)		Best Available Therapy (N = 158)	
Adverse Reactions[b]	**All Grades[a] (%)**	**Grade ≥ 3 (%)**	**All Grades (%)**	**Grade ≥ 3 (%)**
Infections and infestations				
Infections (pathogen not specified)	45	15	44	16
Viral infections	28	5	23	5
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	18	1	13	0
General disorders and administration site conditions				
Pyrexia	16	2	9	1
Fatigue	13	1	10	2
Edema	10	1	12	1
Vascular disorders				
Hypertension	16	5	13	7
Hemorrhage	12	2	15	2
Respiratory, thoracic and mediastinal disorders				
Cough	13	0	8	0
Dyspnea	11	1	8	1
Gastrointestinal disorders				
Nausea	12	0	13	2
Diarrhea	10	1	13	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
[b] Grouped terms that are composites of applicable adverse reaction terms.

Clinically relevant laboratory abnormalities are shown in Table 8.

Table 8: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment[a]

	Jakafi (N=165)		Best Available Therapy (N=158)	
Laboratory Test	**All Grades[b] (%)**	**Grade ≥ 3 (%)**	**All Grades (%)**	**Grade ≥ 3 (%)**
Hematology				
Anemia	82	13	75	8
Thrombocytopenia	27	12	23	9
Neutropenia	58	20	54	17
Chemistry				
Hypercholesterolemia	88	10	85	8
Elevated AST	65	5	54	6
Elevated ALT	73	11	71	16
Gamma glutamyltransferase increased	81	42	75	38
Creatinine increased	47	1	40	2
Elevated lipase	38	12	30	9
Elevated amylase	35	8	25	4

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

DRUG INTERACTIONS Fluconazole Concomitant use of Jakafi with fluconazole increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Avoid concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily. Reduce the Jakafi dosage when used concomitantly with fluconazole doses of less than or equal to 200 mg *[see Dosage and Administration (2.5) in Full Prescribing Information]*. **Strong CYP3A4 Inhibitors** Concomitant use of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Reduce the Jakafi dosage when used concomitantly with strong CYP3A4 inhibitors except in patients with aGVHD or cGVHD *[see Dosage and Administration (2.5) in Full Prescribing Information]*. **Strong CYP3A4 Inducers** Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may reduce efficacy of Jakafi. Monitor patients frequently and adjust the Jakafi dose based on safety and efficacy *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **USE IN SPECIFIC POPULATIONS Pregnancy: Risk Summary** When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity *(see Data)*. There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies. **Data:** *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Lactation: Risk Summary** No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed child, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats *(see Data)*. Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. **Data:** *Animal Data* Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma. **Pediatric Use** The safety and effectiveness of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients have not been established. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults *[see Clinical Studies (14.3) in Full Prescribing Information]* and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents *[see Clinical Studies (14.3, 14.4) in Full Prescribing Information]* and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to < 17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m^2 twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults. *Juvenile Animal Toxicity Data* Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. **Geriatric Use** Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with aGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment, and ESRD (CLcr less than 15 mL/min) on dialysis *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Modify Jakafi dosage as recommended *[see Dosage and Administration (2.6) in full Prescribing Information]*. **Hepatic Impairment** Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Reduce Jakafi dosage as recommended in patients with MF or PV with hepatic impairment *[see Dosage and Administration (2.6) in full Prescribing Information]*. Reduce Jakafi dosage as recommended for patients with Stage 4 liver aGVHD. Monitor blood counts more frequently for toxicity and modify the Jakafi dosage for adverse reactions if they occur for patients with Score 3 liver cGVHD *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3) in full Prescribing Information]*. **OVERDOSAGE** There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.

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COVID-19 Vaccination in Patients With Cancer and Recipients of Cellular Therapy

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ABSTRACT

COVID-19 continues to disproportionately affect patients with cancer because of their underlying immunocompromised state. Strategies to mitigate the impact of COVID-19 on patients with cancer include vaccination, which has demonstrated some level of protection, at least against serious complications such as respiratory failure and death, with limited safety concerns. In this narrative review, we discuss the current COVID-19 vaccines that are available in the United States, the published data regarding vaccine efficacy and safety in patients with cancer, current vaccination guidelines, and future directions.

Introduction

Many millions of people have been infected with SARS-CoV-2, the causative pathogen for COVID-19, since the beginning of the pandemic, and more than 6 million people have died as a result of this infection, according to the World Health Organization.[1] SARS-CoV-2 may cause severe disease in older and immunocompromised patients, including patients with cancer.[2-5] Mortality rates for COVID-19 in patients with cancer are reported to be as high as 36%,[3,6] higher than those among the general public.[4] Risk factors associated with poor outcomes among patients with cancer who have COVID-19 include advanced age, poor functional status, use of cytotoxic chemotherapy, and having a hematologic cancer.[7-9] Recipients of hematopoietic cell transplants (HCT) and of chimeric antigen receptor (CAR) T cells are also at increased risk for COVID-19–related complications.[10] Among the multiple strategies devised to protect this vulnerable population are mass vaccinations, prompt therapy, enhanced infection control, early testing, public health protocols, and, when available, monoclonal antibodies, both pre- and post exposure.

The rapid development of the COVID-19 pandemic prompted the use of novel vaccine platforms. At present, 3 different types of COVID-19 vaccines are available: mRNA vaccines, adenoviral vector–based vaccines, and protein subunit vaccines. The FDA has approved only 2 mRNA-based vaccines (BNT162b2, Pfizer/BioNTech; and mRNA-1273, Moderna), 1 adenoviral vector–based vaccine (Ad26.COV2.S, Janssen), and 1 protein subunit–based vaccine (NVX-CoV2373, Novavax), all under formal authorization or emergency use authorization (EUA) (**Table 1**). The ChAdOx1 nCoV-19 vaccine (adenoviral vector–based platform; Oxford University-AstraZeneca) has yet to be approved in the United States but is available in the European Union and United Kingdom.

The BNT162b2 and mRNA-1273 vaccines are lipid nanoparticle–formulated mRNA vaccines encoding the SARS-CoV-2 spike protein, which mediates attachment of the virus to the host cell[11] as illustrated in **Figure 1.** Both vaccines underwent rigorous phase 3 testing in the general population and demonstrated high rates of protection against symptomatic COVID-19 (BNT162b2, 95%; mRNA-1273, 94%), with no patients experiencing severe COVID-19 after 2 doses.[12, 13] The FDA granted EUAs for BNT162b2 and mRNA-1273 on December 11, 2020, and December 18, 2020, respectively, making them the first available COVID-19 vaccines in the United States. Ad26.COV2.S is based on an adenoviral vector expressing the SARS-CoV-2 spike glycoprotein[11] as illustrated in **Figure 2.** The efficacy rate for this vaccine

TABLE 1. **The Current Status of COVID-19 Vaccines in the United States**

	BNT162b2	mRNA-1273	Ad26.COV2.S	AZD1222	NVX-CoV2373
State of development	Completed phase 3 trials (3 published studies)	Completed phase 3 trials (3 published studies)	Completed phase 3 trials (1 published study)	Completed phase 3 trials (1 published study)	Completed phase 3 trials (1 published study)
Developer	Pfizer and BioNTech	Moderna	Johnson & Johnson/Janssen Pharmaceuticals	AstraZeneca	Novavax
Vaccine platform	mRNA based	mRNA based	Adenoviral vector based	Adenoviral vector based	Protein based
Legal authorization for use in the United States	Full FDA approval: August 23, 2021	Full FDA approval: January 31, 2022	Conditional approval under EUA: February 27, 2021[a]	Not yet authorized	EUA granted: June 6, 2022
Authorized indications based on age	FDA approved: ≥5 years EUA: 6 months to 4 years	FDA approved: ≥18 years EUA: 6 months to 17 years	FDA approved: ≥18 years	NA	EUA: ≥18 years

EUA, emergency use authorization; mRNA, messenger RNA; NA, not applicable.

[a]Approved in cases in which mRNA-based vaccines are not accessible or appropriate.

has been lower than those for both mRNA-based vaccines, with a rate of 81.7% against severe to critical COVID-19 at 28 days using a 1-dose schedule.[14] All phase 3 trials of these 3 vaccines excluded patients who were immunocompromised, including patients with cancer receiving active therapy and transplant recipients. These studies did not account for the emergent new variants such as Delta, Omicron, and the Omicron subvariants, and the resultant reduction in vaccine efficacy.[15]

Because large clinical trials of COVID-19 vaccination in patients with cancer are lacking, this review focuses on pertinent data regarding vaccine efficacy and safety in this population and in cellular therapy recipients, and it discusses current vaccination guidance in the United States.

Efficacy of Vaccines by Underlying Cancer and Therapy

Various studies have assessed the efficacy of COVID-19 vaccinations in patients with different solid tumors; most focused on seroconversion as the primary outcome. Also, most highlighted the poor immunogenicity of a single dose of either the BNT162b2 or mRNA-1273 vaccine in these patients.[16-18] After a single dose of the BNT162b2 vaccine in patients with solid tumors undergoing active therapy in 2 studies in France, the seropositivity rates were 47.5% and 55%, respectively, compared with 100% in patients without cancer.[16,17] In other studies, the seropositivity rate increased significantly and was greater than 90% after the second dose of either mRNA-based vaccine in patients with solid tumors.[16,18-21] Postvaccination antibody titers in patients with solid tumors differed among studies, as some showed lower median antibody titers in patients with solid tumors than in patients without cancer,[16] whereas others showed similar titers.[19,22] These differences are likely due to differences in therapy, cancer stage, and vaccination timing in relation to cancer therapy.

Patients With Hematologic Cancer

Compared with solid tumors, hematologic cancers have been associated with worse COVID-19–related outcomes.[2,23-25] Patients with hematologic cancers were not included in large vaccine trials; however, smaller trials investigated COVID-19 vaccine efficacy in these patients.[18,19,25] Monin et al reported an increase in the seropositivity rate from 18% after the first dose of BNT162b2 to 60% after the second dose.[18] Importantly, most studies including patients with hematologic cancers showed that they had lower seropositivity rates compared with patients with solid tumors or healthy controls.[19,26,27] For example, Thakkar et al reported a seropositivity rate of 85% in patients with hematologic cancers, which was markedly lower than the rate of 98% in patients with solid tumors after 2 doses of either mRNA vaccine or 1 dose of the Ad26.COV2.S vaccine.[19] Also, in an age- and sex-matched analysis, patients with chronic lymphocytic leukemia or

small lymphocytic lymphoma had a considerably lower seropositivity rate than did patients without cancer.[27]

Patients Undergoing Cytotoxic Therapy

Recent and/or active cytotoxic chemotherapy has been associated with suboptimal serologic responses to COVID-19 vaccines in most studies.[21] Addeo et al reported that, after both the first and second mRNA vaccine doses, patients with either hematologic or solid-tumor cancer who were receiving cytotoxic therapy had lower seropositivity rates than did patients with cancer who were undergoing active surveillance (69% vs 86% and 93% vs 98%, respectively); patients with hematologic cancers had lower seroconversion rates and antibody titers than did patients with solid tumors.[21] Similarly, Thakkar et al reported that patients with solid tumors or hematologic cancer undergoing cytotoxic chemotherapy had a lower seropositivity rate after a complete series of the BNT162b2 (2 doses), mRNA-1273 (2 doses), or Ad26.COV2.S (1 dose) vaccine than did patients with cancer receiving other types of cancer therapy (eg, hormone therapy, immunotherapy; 92% vs 99%; P = .04).[19] Some study results have suggested that chemotherapy does not impact vaccine effectiveness,[19,20] but these studies had small sample size and made no clear distinction between cytotoxic therapy and other types of cancer therapy, which may explain the reported inconsistencies in response rates.

Patients Undergoing Immunotherapy

Data regarding the effects of immunotherapy on COVID-19 vaccine responses in patients with cancer have been mixed.[20] Massarweh et al evaluated the immediate humoral response to 2 doses of the BNT162b2 vaccine in 102 patients with solid tumors and in 78 healthy controls.[20] The median level of

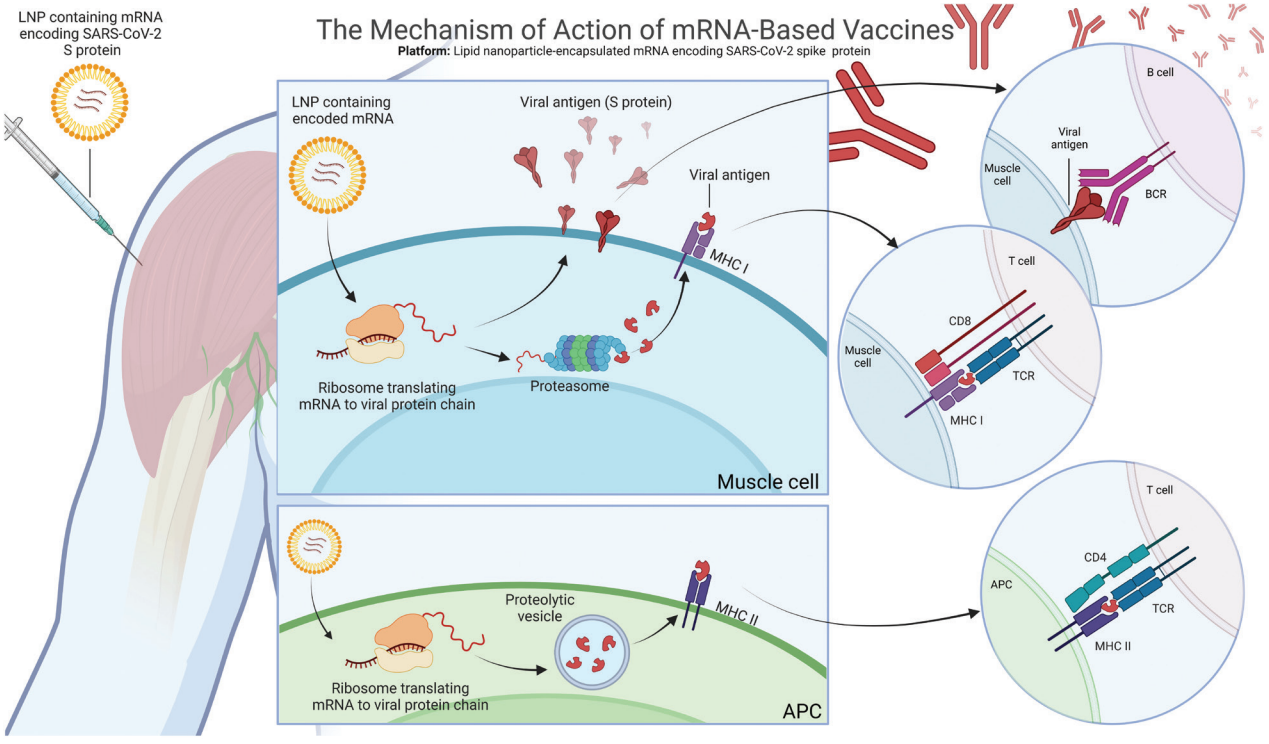

FIGURE 1. **Schematic of a COVID-19 mRNA Vaccine.**

The vaccine features mRNA that encodes the SARS-CoV-2 spike (S) protein, enveloped in a lipid nanoparticle vehicle. Upon intramuscular injection, the mRNA undergoes translation by host cell\ribosomes, resulting in a viral protein chain that is then folded to become S protein. This S protein is added to the host cell surface; there, it can interact with naïve B cells, triggering memory and plasma B-cell activation. Also, the viral protein chain can undergo proteasome degradation and presentation on major histocompatibility complex (MHC) class I molecules, triggering CD8+ T-cell response. In an APC, a viral antigen is presented on MHC class II molecules, triggering a CD4+ T-cell response.

APC, antigen-presenting cell; BCR, B-cell receptor; LNP, lipid nanoparticle; TCR, T-cell receptor.

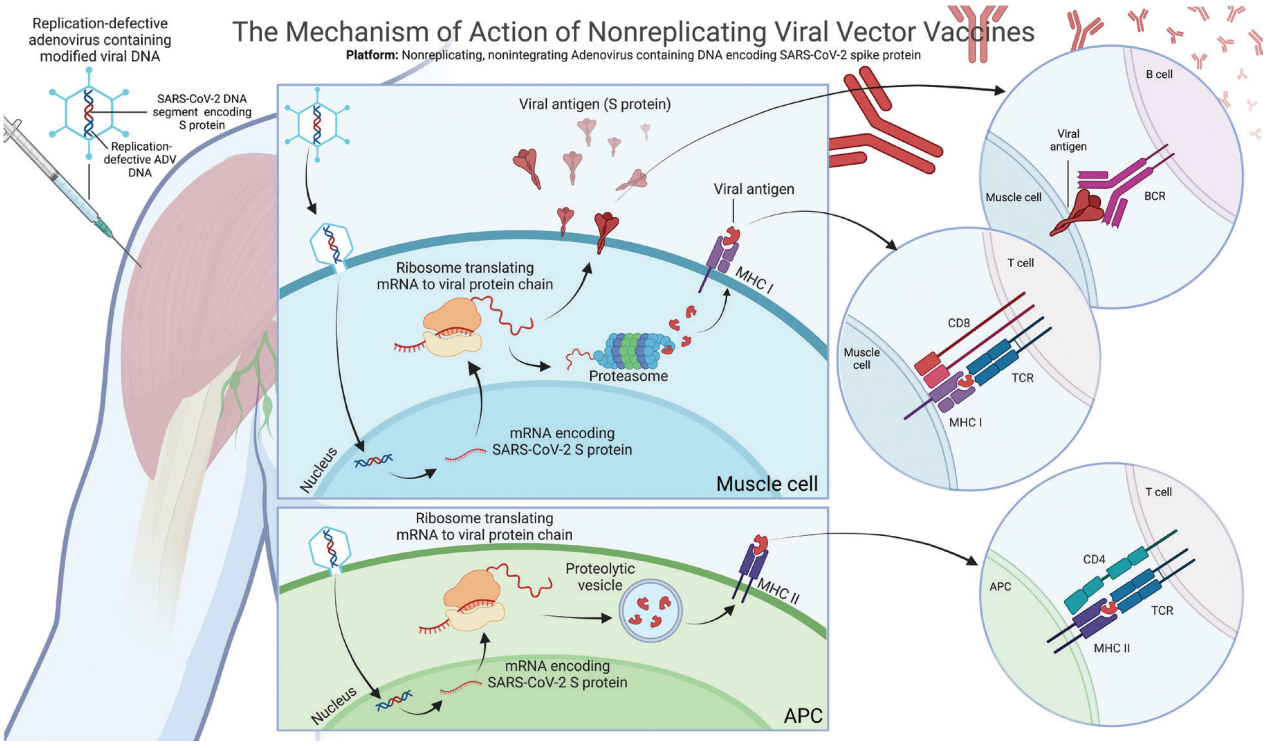

FIGURE 2. **Schematic of a COVID-19 Adenoviral Nonreplicating, Nonintegrating Virus Vaccine.**

This vaccine contains modified DNA encoding the SARS-CoV-2 spike (S) protein. Upon intramuscular injection, the ADV DNA undergoes transcription to mRNA in the host cell's nucleus. In the cytoplasm, mRNA encoding S protein is translated to a viral protein chain that is then folded to become S protein. This S protein is added to the host cell surface; there, it can interact with naïve B cells, triggering memory and plasma B-cell activation. The viral protein chain can also undergo proteasome degradation and presentation on major histocompatibility complex (MHC) class I molecules, triggering CD8+ T-cell response. In an APC, a viral antigen is presented on MHC class II molecules, triggering CD4+ T-cell response.

ADV, adenoviral; APC, antigen-presenting cell; BCR, B-cell receptor; TCR, T-cell receptor.

SARS-CoV-2 spike antibodies was lower in the patients than in the controls (1931 AU/mL [IQR, 509-4386 AU/mL] vs 7160 AU/mL [IQR, 3129-11,241 AU/mL]; $P < .001$). Also, the combination of chemotherapy and immunotherapy was the only variable associated with low antibody titers upon multivariate analysis.[27] In a follow-up study to assess the durability of antibody responses over 4 months, patients with cancer undergoing immunotherapy + chemotherapy, or immunotherapy + biologic therapy, had the lowest titers (median, 94.4 AU/mL [IQR, 49.4-191.0 AU/mL] and median, 147.0 AU/mL [IQR, 62.8-339.0 AU/mL], respectively), compared with other patients with cancer.[28] Exploratory multivariate analysis identified chemotherapy plus immunotherapy and immunotherapy plus biologic therapy as risk factors for low titers 4 months after completing a COVID-19 vaccination series. In contrast, larger, more robust studies,[29-31] such as the VOICE trial, assessed the efficacy of the mRNA-1273 vaccine in patients with cancer who were actively undergoing therapy.[29] In those studies, response rates based on serum titers were highest in the immunotherapy group (n = 130; 93%) followed by the chemotherapy/immunotherapy group (n = 143; 89%) and the chemotherapy group (n = 223; 84%). Notably, the humoral response rates of all 3 groups were not inferior to that of a group of healthy participants.[29] The discrepancies in response rates between these studies and previous ones may have resulted from smaller numbers of patients in earlier cohorts as well as the additional immunosuppression related to co-administration of agents such as cytotoxic chemotherapeutics.

Recipients of Anti-CD20 Therapy or Cellular Therapy

The results of a few studies have indicated that the use of anti-CD20 agents, such as rituximab, may be associated with reduced immunogenic responses to

TABLE 2. **Comparison of Different Guidelines for COVID-19 Vaccination in Immunocompromised Patients**

	CDC	NCCN	ASTCT
Target patient population	Moderately or severely immunocompromised persons, defined as: ▪ Those receiving active therapy for solid tumors/hematologic cancers ▪ Recipients of solid organ transplants or immunosuppressive therapy ▪ CAR T-cell/HCT recipients within 2 years of therapy or receiving immunosuppressive therapy ▪ Patients with moderate/severe primary immunodeficiencies ▪ Patients with advanced/untreated HIV infections ▪ Those receiving active treatment with high-dose steroids, alkylating agents, antimetabolites, transplant-related immunosuppressive therapy, chemotherapeutic agents classified as severely immunosuppressive, anti–tumor necrosis factor agents, biologic agents that cause immunosuppression/immunomodulation	Patients with: ▪ Solid tumors ▪ Hematologic cancers ▪ Noncancer immunocompromising conditions	HCT/CAR T-cell recipients
Recommended dosing regimen	BNT162b2 ▪ 6 months or older: 3-dose primary series with monovalent COVID-19 vaccine and 1 booster with bivalent mRNA vaccine mRNA-1273 ▪ 6 months or older: 3-dose primary series with monovalent COVID-19 vaccine and 1 booster with bivalent mRNA vaccine Ad26.COV2.S ▪ 18 years or older: 1 dose of Ad26.COV2.S followed by a dose of either mRNA vaccine to complete primary series. Booster with bivalent mRNA COVID-19 vaccine NVX-CoV2373 ▪ 18 years or older: 2 doses as the primary series followed by a booster with bivalent mRNA COVID-19 vaccine	Same as CDC	Same as CDC
Specific recommendations for cancer therapies and HCT/CAR T-cell recipients	▪ If possible, recommend ≥2 weeks prior to initiation/resumption of immunosuppressive therapy; otherwise, do not recommend delay ▪ HCT/CAR T-cell recipients: ≥3 months after HCT/CAR T-cell therapy	Same as CDC plus: ▪ Cytotoxic regimens: Delay until ANC recovers ▪ Patients with solid tumors, post surgery: Impose a waiting period of at least few days after surgery	▪ If cytotoxic or B cell–depleting therapies are planned, recommend vaccination ≥2 weeks prior to therapy

ANC, absolute neutrophil count; ASTCT, American Society of Transplant and Cellular Therapy; CAR, chimeric antigen receptor; HCT, hematopoietic cell transplantation; mRNA, messenger RNA; NCCN, National Comprehensive Cancer Network.

COVID-19 vaccines.[32,33] In the United Kingdom–based CAPTURE study of patients with cancer who received 2 doses of either the BNT162b2 or AstraZeneca AZD1222 vaccine, receipt of anti-CD20 therapy within 12 months after vaccination was associated with reduced titers among patients with hematologic cancers undergoing different treatment types.[33] In another study including 87 individuals with hematologic cancers who received anti-CD20 therapy within 12 months of 2 doses of the BNT162b2 vaccine, the patients had negligible median serologic titers, and some experienced severe breakthrough COVID-19.[34]

HCT recipients have had mixed responses to the COVID-19 vaccines. In the CAPTURE study, HCT recipients and other patients with hematologic cancers had similar antibody titers within 6 months of vaccination.[33] The timing of HCT may affect vaccine

efficacy, with study data demonstrating poorer immunologic responses in patients with recent transplants and better responses in patients vaccinated at least 12 months after HCT.[34,35] The type of transplant impacts vaccine efficacy as well, with better humoral responses after autologous HCT than after allogeneic HCT.[35,36]

Although some studies found that CAR T-cell recipients had serologic responses to COVID-19 vaccination similar to those of patients with hematologic cancer undergoing chemotherapy,[33] most found lower seropositivity rates among the patients who received CAR T-cell therapy.[19,35,37] The results of one study showed that 79% of CAR T-cell recipients had no appreciable immune responses after completing a primary vaccination series with 2 doses of either of the mRNA vaccines.[35]

Strategies to Improve COVID-19 Vaccine Efficacy in Patients With Cancer

Because of the reduced efficacy of COVID-19 vaccines in patients with cancer, new strategies are needed to increase vaccine immune responses. Additionally, the evolution of SARS CoV-2 into different variants has reduced vaccine efficacy and protection in previously vaccinated patients, resulting in part from immune evasion.[38] Breakthrough infections in patients with cancer are associated with higher mortality rates and more severe complications than in immunocompetent patients.[6,39] Optimizing the timing of vaccination, the use of additional and/or booster doses, and heterologous vaccinations are strategies that may improve vaccine immune responses.

Optimal timing of vaccination after cytotoxic therapy, anti-CD20 therapy, or cellular therapy may improve vaccine efficacy.[22,40] In a subanalysis of the phase 3 BNT162b2 vaccine trial, 3813 patients with a history of solid tumors (predominantly breast or prostate cancer) who were no longer undergoing active therapy had a vaccine efficacy rate of 94.4% at 6 months of follow-up.[22] In patients with cancer undergoing active therapy, however, timing of vaccination may prove to be more complicated, as many patients may end up getting vaccinated while receiving therapy. Vaccination at least 6 months after anti-CD20 therapy may provide better immune responses.[21] Vaccination at least 3 months after HCT or CAR T-cell therapy may provide superior immune responses,[35] especially for autologous HCT recipients.[36]

Additional or booster doses of COVID-19 vaccines have optimized serologic responses and may reduce the rate of breakthrough infections in previously vaccinated healthy adults.[41] Boosters of mRNA vaccines were also effective in preventing COVID-19 complications with the emergence of recent SARS CoV-2 variants, such as the Omicron variant.[42] Among patients with cancer, data on the efficacy of boosters are limited to the BNT162b2 vaccine.[43-46] Of 20 patients with solid tumors who received a third dose of the BNT162b2 vaccine as a booster, 16 had increased humoral but not cellular responses.[43] Other studies noted a poor seroconversion rate in patients with hematologic cancer (29.7%) after a third dose of BNT162b2.[44] Clinical studies translating the benefits of 1 or more booster doses in patients with cancer are still lacking. Additionally, due to the increased prevalence of the Omicron subvariants such as BA.4/BA.5 and subsequent immune escape to the available vaccines, 2 new bivalent vaccines that carry modified RNA from both the original Wuhan-Hu-1 strain and the Omicron BA.4/BA.5 strains were tested in clinical trials and granted FDA approval under EUA on August 29, 2022, based on preliminary data.[47] The process to produce these mRNA vaccines is the same as for the monovalent mRNA vaccines, and no new safety concerns are expected. The CDC and many professional societies, such as the American Society for Transplantation and Cellular Therapy (ASTCT) and the National Comprehensive Cancer Network (NCCN), have recommended additional and booster doses for patients with cancer after primary vaccination (**Table 2**).

Mixing COVID-19 vaccines or heterologous vaccine boosters has been considered as a potential strategy to boost immune responses to the vaccines.[48] In a recent study, vaccine response was increased in immunocompetent individuals who received heterologous booster vaccination, with an increase in titers by a factor of 6 to 73, and they had prolonged cellular responses.[48] On the other hand, among 32 patients with hematologic cancer who did not have responses to the original series of mRNA COVID-19 vaccines and had a booster dose of the Ad26.COV2.S COVID-19 vaccine,[49] 31% had serologic responses.[50] The improvement in humoral response in cancer patients is promising, but more data are needed before adopting heterologous COVID-19 vaccine boosters as a preferred strategy, as the impact of this on clinical outcomes and protection against infection with SARS-CoV-2 variants remains unclear. On the other hand, mixing booster mRNA vaccines in patients with cancer is indicated when access to specific vaccines is constrained.

Safety of COVID-19 Vaccines in Patients With Cancer

The safety of COVID-19 vaccines has been well studied. The most common adverse effects (AEs) reported in the general population include pain

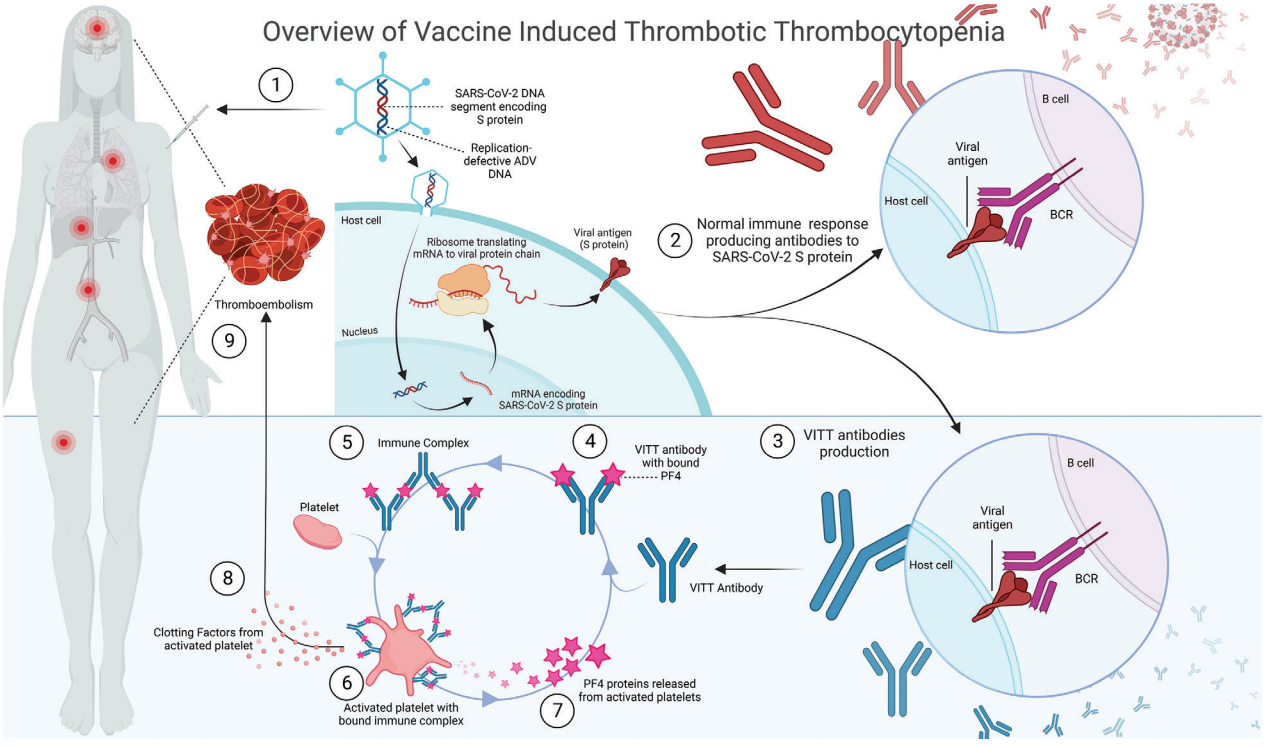

FIGURE 3. **Overview of Vaccine-Induced Thrombotic Thrombocytopenia (VITT).**

VITT can occur after administration of a replication- and integration-defective adenovirus-based COVID-19 vaccine (1). In the majority of vaccinated individuals, antibodies to SARS- CoV-2 spike (S) protein are manufactured (2). In rare cases, VITT antibodies (3) are induced that can bind to PF4, forming immune complexes that lead to platelet activation (4-6). The immune complex–activated platelets release further PF4, propagating the cycle (7). These immune complex–activated platelets cause a pathological cascade of clotting factors and a subsequent drop in the platelet count of affected patients (8), leading to the development of VITT-associated clots (9). Thromboembolic events involving the brain, lungs, abdominal viscera and veins, and limbs have been described.

ADV, adenovirus; BCR, B-cell receptor; mRNA, messenger RNA; PF4, platelet factor 4; S protein, spike protein; VITT, vaccine-induced thrombotic thrombocytopenia.

at the injection site, fever, and headaches.[12-14,51,52] Hypersensitivity related to vaccine administration is uncommon, with rates as low as 2.5 to 4.5 cases per 1 million injections.[53] Authors have reported notable AEs in few patients, including Bell palsy, idiopathic thrombocytopenia, acute disseminated encephalomyelitis, myocarditis, pericarditis, Guillain-Barré syndrome, transverse myelitis, and acute myocardial infarction.[54] Safety data for patients with cancer are limited because of their exclusion from the initial COVID-19 vaccine trials, but post marketing data are becoming available.[55-63]

Waissengrin et al compared the AEs of check point inhibitors (CPIs) in 137 patients with solid tumors and a control group of healthy participants after they received the first and second doses of the BNT162b2 vaccine. The rate of myalgia was higher in patients with cancer, but the researchers identified no CPI-mediated toxic effects during short-term follow-up.[55] On the other hand, 1 patient in a different study who underwent treatment of colorectal cancer with CPIs had cytokine release syndrome after BNT162b2 vaccination that responded to steroid-based therapy.[56] It was unclear whether CPI use contributed to this event or if it was driven by COVID-19 vaccination. Long-term safety follow-up after COVID-19 vaccination in patients receiving CPIs or other active therapy for solid tumors is necessary to better understand the associations among COVID-19 vaccination, vaccine AEs, and patient outcomes; so far, however, the COVID-19 vaccines appear to be safe in these patients.

Many patients with cancer have been administered the mRNA and adenovirus-based COVID-19 vaccines since their initial release.[57-59] In a large survey of 1094 patients with solid

tumors, the reported AEs for COVID-19 vaccines were similar to those in patients without cancer.[59] Investigators noted similar findings in prospective trials that included patients with breast cancer.[58] Similarly, multiple studies have demonstrated the safety of COVID-19 vaccines in patients with hematologic malignancies,[50,60-63] with the rate of serious AEs ranging from 0% to 7.5%.[50,61] The most common AEs have included pain at the injection site, fatigue, joint pain, and fever.[60-63] Episodes of thrombocytopenia or thrombosis have yet to be reported.[61] Immunologic responses based on antibody titers and the rate of safety events have no significant relationship, suggesting that the degree of immunologic response to the vaccines does not correlate with safety.[61,63] In addition, authors have documented the safety of heterologous COVID-19 vaccine boosters in immunocompetent recipients.[49] However, vaccine safety data for patients with hematologic cancers are currently limited to 4 to 6 weeks after vaccination, with a lack of long-term follow-up data.

Recipients of CAR T-cell therapy or of autologous or allogeneic HCT may experience toxic effects related to their specific therapies. Different transplant centers have reported limited AEs related to COVID-19 vaccinations.[64-70] Early data for HCT recipients who received 2 doses of the mRNA COVID-19 vaccines demonstrated only mild AEs, similar to those in the general population.[64,65,67] The most common AEs included pain at the injection site, headaches, fatigue, joint pain, and fever.[65,67] Among allogeneic HCT recipients, development of graft-vs-host disease (GVHD) or exacerbation of GVHD can complicate post transplantation care. Whether chronic GVHD is related to COVID-19 vaccination is unclear. No data have established a direct link; reports from some centers noted that about 6% to 12% of vaccine recipients had chronic GVHD after vaccination,[69-71] although the investigators did not study comparator groups.[68,69] Authors of one study reported graft failure in HCT recipients that was potentially related to COVID-19 vaccination, with some reports of neutropenia or lymphopenia occurring after COVID-19 vaccination.[69,70] No thrombotic AEs after vaccination have been reported.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a dreaded major AE described with the use of adenoviral vector–based COVID-19 vaccines, such as Ad26.COV2.S and ChAdOx1 nCov-19.[72,73] **Figure 3** illustrates the possible pathway of VITT based on platelet factor 4 formation. VITT events are very rare in patients with cancer after vaccination.[72,73] The few reported cases of VITT in patients with cancer occurred in those with solid tumors.[73] COVID-19–related thrombosis is more common than VITT but is still a rare AE.[74,75] The mortality rate in patients who develop sinus thrombosis as a result of COVID-19 vaccination is about 50%.[72] Because of the low risk-to-benefit ratio COVID-19 vaccines, preferably the mRNA ones, are highly recommended for patients with cancer to at least prevent severe infections and mortality.

Current Recommendations for COVID-19 Vaccination in Patients With Cancer

The CDC and NCCN have made recommendations for COVID-19 vaccination in patients with cancer.[76,77] In addition, the ASTCT has provided guidance regarding COVID-19 vaccination in HCT and CAR T-cell recipients. All these organizations agree that COVID-19 vaccination is beneficial to patients with cancer and encourage all such patients to undergo vaccination. Their guidelines are often aligned, but they do provide unique guidance for different groups. Table 2 compares the different guidelines for COVID-19 vaccination in immunocompromised patients.

As of September 2, 2022, the CDC recommends that patients with cancer and recipients of cellular therapy receive a monovalent primary series (consisting of 3 mRNA vaccine doses or 1 adenoviral vector–based and 1 mRNA vaccine dose), with an updated recommendation to include a bivalent BNT162b2 or mRNA-1273 booster dose for those 12 years or older at least 2 months after the last dose of the primary vaccine series. According to these latest guidelines, the bivalent booster dose may obviate the need for multiple booster doses. This new vaccination regimen including the bivalent booster does not have a clear clinical benefit yet, but based on prior serologic studies, it may provide better protection against COVID-19 compared with the regimen that included monovalent boosters. The CDC does not provide specific guidance for different types of cancer.

Among patients with cancer who undergo surgery, vaccination is recommended within a few days after surgery because of the patient's lack of immunosuppression. Patients with hematologic cancer are advised to undergo vaccination when their absolute neutrophil counts recover. All vaccination guidelines recommend boosters for patients with cancer, with a preference for the mRNA vaccines regardless of the primary vaccine series.[77] Specifically, the ASTCT recommends that recipients of cellular therapy receive vaccination against COVID-19 3 months after conditioning therapy. Revaccination

is also recommended for patients who were vaccinated prior to cellular therapy.[78]

Future Directions

Prevention of COVID-19 using safe, effective vaccines continues to be paramount in patients with cancer. The introduction of the new bivalent mRNA COVID-19 vaccines may lead to better protection at the time when BA.4/BA.5 subvariants are dominant,[47,79] although little is known about whether their timing in relation to cancer treatment and cellular therapy will affect humoral responses, as was described with the monovalent mRNA COVID-19 vaccines.[21] Indeed, the FDA, in their fact sheets on bivalent mRNA vaccines, provided a disclaimer that immunocompromised patients may not have effective responses to the new boosters.[47] In addition, safety data for patients with cancer have not been well investigated, and patients therefore should be observed closely post vaccination for short- and long-term adverse effects.

Other options for COVID-19 prevention in patients with cancer are monoclonal antibodies that provide passive immunity. At this time, only tixagevimab-cilgavimab (Evusheld) is approved under EUA for pre-exposure prophylaxis based on data for patients at high risk for inadequate response to COVID-19 vaccination. Very few patients with cancer were included in the original phase 3 trial of Evusheld, yet it is recommended for these patients.[80] Studies demonstrated that the effectiveness of Evusheld was retained against the SARS-CoV-2 Omicron variants with adjustments in dosing, but those studies were limited to mouse models.[81] Experience with Evusheld in immunocompromised patients has demonstrated reductions in severe COVID-19 and in hospitalization.[82,83] Because of a lack of clinical efficacy data regarding protection against the Omicron subvariants, there is some doubt regarding future use of Evusheld.[84,85] New Omicron subvariants such as BQ.1 and BQ.1.1 have demonstrated neutralizing antibody escape, imperiling the future use of Evusheld and probably bebtelovimab.[85] Monoclonal antibodies under development should provide a wider range of neutralizing capabilities for the circulating and future variants and subvariants.[86]

Stimulating the immune system to protect patients with cancer from severe COVID-19 is also a suggested prophylactic measure.[87,88] Theoretically, the use of live vaccines such as Bacille Calmette-Guérin could enhance response to COVID-19 vaccines and defend against severe COVID-19, and data from early randomized controlled trials did demonstrate some benefits of Bacille Calmette-Guérin in terms of COVID-19 protection.[88] However, live vaccines are contraindicated in patients with cancer undergoing active therapy, so a Canadian trial is investigating the use of the immunotherapeutic drug IMM-101 to stimulate the immune system of such patients.[89] So far, firm evidence supporting the use of any of these methods to enhance COVID-19 vaccination is lacking.

Conclusions

Patients with cancer and recipients of cellular therapy are at increased risk for COVID-19–related complications. Many strategies to protect these patients against COVID-19 are available, and the currently available COVID-19 vaccines provide hope. Despite reports of suboptimal serologic responses to COVID-19 vaccines, serious COVID-19–related complications may be prevented. Beyond the basic vaccine series, various strategies—such as the use of multiple boosters (homozygous or heterozygous), optimal timing of vaccination, and repeating the original vaccine series after transplantation—may provide further protection. Other strategies for protection against severe COVID-19 disease in vaccine nonresponders are needed, such as the use of pre-exposure monoclonal anti-COVID-19 antibodies. ■

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For references visit
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ONCOLOGY® Reviews Key Presentations From the
Society for Urologic Oncology (SUO) 23rd Annual Meeting

Relugolix Demonstrates Efficacy Regardless of Baseline Testosterone Levels in Advanced Prostate Cancer

Relugolix yielded positive safety and efficacy in advanced prostate cancer across all baseline testosterone levels, according to data from a subgroup analysis of the phase 3 HERO trial (NCT03085095).

In the population of 912 patients who had their baseline testosterone collected during the trial, a total of 147 patients—including 96 in the relugolix arm and 51 in the leuprolide arm—had a baseline level of less than 280 ng/dL. A total of 765 patients—including 516 in the relugolix arm and 249 in the leuprolide arm—had a level of at least 280 ng/dL. Although the median age of the population was 72 years, most patients had testosterone levels within a normal range.

At 48 weeks, the estimated castration rates were notably higher among patients treated with relugolix vs leuprolide in each respective subgroup. In the relugolix arm, patients with a level of less than 280 ng/dL and 280 ng/dL or more had rates of 97.3% and 96.5%, respectively, vs 84.1% and 89.3% in the leuprolide arm. The sustained castration rates were 96.7% and 88.8% in the overall population, respectively.

Key secondary end points also appeared to favor those treated with relugolix vs leuprolide; the exception was castration resistance–free survival, which was similar among treatment groups and subgroups.

In the relugolix cohort, 24.0% of patients with low vs high testosterone had grade 3 or higher adverse events (AEs), compared with 17.2% of those with a high level. Moreover, serious AEs occurred in 16.7% and 11.4%, respectively, and fatal AEs occurred in 2.1% and 1.0%. The most common any-grade AEs in each respective group included hot flash (52.1% and 54.8%), fatigue (30.2% and 20.2%), and diarrhea (14.6% and 11.6%).

In the leuprolide group, 21.7% of patients in the low testosterone group had high-grade AEs, vs 20.5% in the high-level group. Moreover, 17.6% and 15.3% of patients, respectively, had serious AEs and 5.9% and 2.4% had fatal AEs.

→ **For the full article, visit** Cancernetwork.com/SUO22_HERO

Novel PET Imaging Agent 18F-rHPSMA-7.3 Proves Clinically Useful Prior to Surgery in Newly Diagnosed Prostate Cancer

The use of 18F-rHPSMA-7.3 PET resulted in positive disease detection and yielded clinically important information in a population of patients with newly diagnosed prostate cancer when used prior to surgery, according to data from the phase 3 LIGHTHOUSE trial (NCT05418673).

Of the 296 patients included in the efficacy population, 7.8% to 13.0% had a 18F-rHPSMA-7.3 PET–positive pelvic lymph node, according to 3 different tests. Moreover, extrapelvic lesions were identified in 16% to 28% of patients in an extended population that included those who received 18F-rHPSMA-7.3 PET regardless of surgery (n = 352).

Investigators noted that 18F-rHPSMA-7.3 PET could be potentially labeled with 18F for use in diagnostic imaging or α-/β-emitting radiometals for systemic radiation therapy.

The study included patients with unfavorable-risk, high-risk, or very high-risk newly diagnosed disease set to undergo radical prostatectomy with regional pelvic lymph node dissection. PET/CT was performed for 50 to 70 minutes following a 296 MBq (8mCi) intravenous dose of 18F-rHPSMA-7.3.

The trial's co-primary end points were patient-level sensitivity and specificity in terms of detecting pelvic lymph node metastases. The prespecified thresholds for sensitivity and specificity

were 22.5% and 82.5%, respectively. The efficacy analysis population included patients who received 18F-rHPSMA-7.3 PET followed by surgery.

The trial did not meet the prespecified statistical threshold for sensitivity, which ranged between 23% to 30%. Investigators noted that sensitivity was higher for those with high-risk or very high-risk disease vs unfavorable-risk disease.

Additionally, investigators reported that in the safety population of 356 patients, 7.9% experienced a total of 33 treatment-emergent adverse effects (TEAEs), none of which were determined to not be serious. Of this population, 2.5% of patients experienced 10 TEAEs that were potentially related to 18F-rHPSMA-7.3 PET.

→ **For the full article, visit** Cancernetwork.com/SU022_LIGHTHOUSE

Novel PSMA/TRT-based Triplet Regimen Appears Effective in Prostate Cancer

The use of an α prostate-specific membrane antigen–targeted radionuclide therapy (PSMA-TRT; ^{225}Ac-J591), an androgen receptor (AR) signaling inhibitor, and pembrolizumab (Keytruda) elicited preliminary responses in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC), according to phase 1 data from a phase 1/2 trial (NCT04946370).

All patients experienced declines in prostate-specific antigen (PSA), and half the cohort experienced a PSA decline greater than 50%. After follow-up of 6 months or more, 4 patients (all from the 80-kBq/kg cohort) are still progression-free and on the study.

PSMA-TRT can radiate to multiple sites of disease simultaneously; AR signaling inhibitors upregulate PSMA expression, can lead to increased PD-L1 expression, and can also radiosensitize prostate cancer.

The study enrolled patients with progressive mCRPC as defined by Prostate Cancer Working Group 3 criteria (at least 1 AR pathway inhibitor and no chemotherapy in the mCRPC setting). During the phase 1 portion of the study, 2 cohorts included 6 patients each. All patients received physician's choice of AR signaling inhibitor along with pembrolizumab at 400 mg every 6 weeks, along with a single infusion of ^{225}Ac-J591—one cohort received the infusion at a dose of 65 KBq/kg, and the other at 80-kBq/kg.

Based on the phase 1 findings, the investigators selected the 80 KBq/kg dose of ^{225}Ac-J591 for the phase 2 portion of the study.

→ **For the full article, visit** Cancernetwork.com/SU022_PSMA

ONCOLOGY® Reviews Key Presentations From the **2022 San Antonio Breast Cancer Symposium (SABCS)**

Long-term Data Show Neoadjuvant Olaparib Combination Does Not Outperform Carboplatin/Paclitaxel for HER2-Negative Early Breast Cancer

A combination of neoadjuvant olaparib (Lynparza) plus paclitaxel and carboplatin does not appear to improve outcomes in patients with HER2-negative, homologous recombination deficient (HRD) early breast cancer vs paclitaxel and carboplatin alone, according to long-term findings from the phase 2 GeparOLA trial (NCT02789332).

At a median follow-up of 49.8 months, the 4-year invasive disease-free survival rate with olaparib plus paclitaxel and carboplatin (n = 69) was 76.0% vs 88.5% among 37 patients who received chemotherapy. The unadjusted HR between the arms was 2.86 (95% CI, 0.83-9.90) and the adjusted HR for nodal status and germline mutational status was 3.6 (95% CI, 1.02-12.7).

Further, the 4-year locoregional recurrence rates were higher following treatment with olaparib and chemotherapy (10.3%) compared with paclitaxel and carboplatin (4.9%).

Additional long-term efficacy end points included distant disease-free survival (DDFS) and overall survival (OS). The 4-year DDFS rate with olaparib/paclitaxel/carboplatin was 81.2% vs 93.4% with paclitaxel/carboplatin (HR, 3.03; 95% CI, 0.67-13.67; log-rank P = .1290). The 4-year OS rate was 89.2% with the olaparib combination vs 96.6% with paclitaxel/carboplatin alone (HR, 3.27; 95% CI, 0.39-27.20; log-rank P = .2444).

Germline/somatic *BRCA* mutations were reported among 55.9% of patients in the olaparib arm (n = 38) and 56.8% of patients in the paclitaxel/carboplatin arm (n = 21). With long-term follow-up in this subgroup, outcomes were comparable for the olaparib combination vs paclitaxel/carboplatin (HR, 1.16; 95% CI, 0.30-4.49; log-rank P = .8303).

Of the enrolled population, 96 patients had a high HRD score. Of these, 46.2% had a mutation, 43.4% were intact, and 1 patient had insufficient quality or quantity of DNA available

for measurement. Further, 3 patients had low HRD scores, all of whom had *BRCA*-mutant disease, and 7 patients were not measurable for HRD status.

→ **For the full article, visit** Cancernetwork.com/SABCS22_olaparib

Early Efficacy Is Observed With Trastuzumab Deruxtecan With or Without Pertuzumab for HER2+ Metastatic Breast Cancer

Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) with or without pertuzumab (Perjeta) demonstrated promising preliminary efficacy and a tolerable safety profile in patients diagnosed with HER2-positive metastatic breast cancer, according to findings from the phase 1b/2 DESTINY-Breast07 trial (NCT04538742).

With a median follow-up of 11 months, patients in the monotherapy module (n = 23) achieved an unconfirmed objective response rate (ORR) of 87.0% (80% CI, 73.2%-95.1%) and a confirmed ORR of 69.6% (80% CI, 54.1%-82.2%). Those who were assigned to the T-DXd plus pertuzumab module (n = 22) had a median follow-up of 10 months and achieved an unconfirmed ORR of 81.8% (80% CI, 66.9%-91.8%) and a confirmed ORR of 72.7% (80% CI, 57.0%-85.0%). The median duration of treatment between both arms was 9.1 months and 9.2 months, respectively.

No grade 3 or higher nausea or vomiting adverse events (AEs) were reported, and interstitial lung disease/pneumonitis was experienced by 1 patient with T-DXd given as a single agent. One patient died from disease progression in each study arm.

The safety profiles of the agents were similar to those previously reported and all patients in both the monotherapy and combination arms experienced any-grade AEs. Grade 3 or higher AEs were reported in 30.4% and 40.9% of patients in the monotherapy and combination arms, respectively, and serious AEs occurred in 8.7% and 13.6% of patients. Treatment remains ongoing for 73.9% of patients in the T-DXd arm and for 72.7% of patients in the T-DXd plus pertuzumab module.

→ **For the full article, visit** Cancernetwork.com/SABCS22_trastuzumab

Camizestrant Elicits Superior Treatment Responses, Survival Benefit vs Fulvestrant in HER2-Negative Advanced Breast Cancer Subset

The use of 2 separate camizestrant monotherapy doses was associated with a more than doubling of progression-free survival (PFS) vs standard-of-care fulvestrant in patients with estrogen receptor (ER)–positive, HER2-negative advanced breast cancer, according to data from the phase 2 SERENA trial (NCT04214288).

The study included several treatment arms assessing different dose levels of camizestrant—300 mg (n = 20), 75 mg (n = 74), and 150 mg (n = 73)—as well as a fulvestrant cohort (n = 173). Of note, the study authors have not formally analyzed the data from the 300 mg subset as patient enrollment to that treatment arm ended early.

The 75-mg dose (median follow-up, 16.6 months) demonstrated a superior median PFS of 7.2 months (95% CI, 3.7-10.9), compared with 3.7 months (95% CI, 2.0-6.0) with fulvestrant (median follow-up, 17.4 months), for an HR of 0.58 (95% CI, 0.41-0.81; P = .0124). Similarly, the 150-mg dose (median follow-up, 16.6 months) doubled median PFS at 7.7 months (95% CI, 5.5-12.9), vs fulvestrant, for an HR of 0.67 (95% CI, 0.48-0.92; P= .0161).

The benefit of camizestrant was determined to be both statistically significant and clinically meaningful at both dose levels and further confirmed via blinded independent central review sensitivity analysis.

PFS was also assessed in several patient subgroups. Among patients who received a previous CDK4/6 inhibitor, the median PFS was 5.5 months (95% CI, 3.7-10.9; HR, 0.49; 95% CI, 0.31-0.75) in the 75-mg cohort and 3.8 months (HR, 0.68; 95% CI, 0.44-1.04) in the 150-mg camizestrant dose cohorts, vs 2.1 months (95% CI, 1.9-3.7) in the fulvestrant arm.

In those with lung and/or liver metastases, the median PFS was 7.2 months (95% CI, 3.6-11.1; HR, 0.43; 95% CI, 0.28-0.66) in the 75-mg dose group, 5.6 months (95% CI, 3.7-9.1; HR, 0.55; 95% CI, 0.37-0.82) in the 150-mg dose group, and 2.0 months (95% CI, 1.9-3.6) in the fulvestrant group.

Moreover, the median PFS was 6.3 months (95% CI, 3.4-12.9; HR, 0.33; 95% CI, 0.18-0.68), 9.2 months (95% CI, 3.7-12.9; HR, 0.55; 95% CI, 0.33-0.89), and 2.2 months (95% CI, 1.9-3.6) in each respective cohort in a population of patients with *ESR1*-mutant disease.

In those with evidence of ER-driven disease, the median PFS was 7.4 months (95% CI, 4.5-11.1; HR, 0.55; 95% CI, 0.35-0.79), 12.0 months (95% CI, 5.6-14.6; HR, 0.55; 95% CI, 0.39-0.86), and 3.2 months in the 75-mg, 150-mg, and fulvestrant arms, respectively.

→ **For the full article, visit** Cancernetwork.com/SABCS22_camizestrant

ONCOLOGY® Reviews Key Presentations From the
2022 American Society of Hematology (ASH) Annual Meeting

MYELOMA

Teclistamab Combination Therapy Produces Promising Safety Profile in Relapsed/Refractory Multiple Myeloma

Teclistamab (Tecvayli) plus daratumumab (Darzalex) and lenalidomide (Revlimid) was well tolerated and demonstrated promising early clinical activity among patients with relapsed/refractory multiple myeloma, according to a presentation of data from the phase 1b MajesTEC-2 trial (NCT04722146).

In the hematologic safety profile of the combination therapy, the most common grade 3/4 hematologic adverse effect (AE) was neutropenia, which occurred among 78.1% of patients. Additionally, 15.6% had thrombocytopenia and 12.5% had febrile neutropenia. Most nonhematologic AEs were low grade, with any-grade cytokine release syndrome occurring among 81.3% (n = 26) of patients and lasting on average 2 days.

Most infections among patients during treatment were low grade. The most common grade 3/4 infections included pneumonia (15.6%), COVID-19 (12.5%), and sepsis (9.4%). Two fatal AEs occurred among patients, including 1 related to COVID-19 within 77 days following the last treatment dose, and another involving multiorgan failure due to sepsis.

At a median follow-up of 8.4 months, the overall response rate was 93.5%. The median time to first response among patients was 1 month, and the median time to complete response or better was 3 months. In total, 80.6% of patients remained progression free and were on treatment at the time of data cutoff. Patient responses deepened over time, and the median duration of response had not been reached.

→ **For the full article, visit** Cancernetwork.com/ASH22_MajesTEC

Improvement of HRQOL Is Observed With Daratumumab Quadruplet in Newly Diagnosed, Transplant-Eligible Multiple Myeloma

Based on patient-reported outcomes from the phase 2 GRIFFIN study (NCT02874742), the quadruplet regimen of daratumumab (Darzalex) with bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (DRVd) induction/consolidation therapy plus lenalidomide maintenance was found to produce enhanced health-related quality of life (HRQOL), specifically a reduction in pain symptoms, compared with RVd alone.

At a median follow-up of 49.6 months, the median time to worsening disease symptoms (HR, 0.75; 95% CI, 0.43-1.30) and utility scores (HR, 0.49; 95% CI, 0.30-0.81) were not reached in the daratumumab plus DRVd arm. Further, DRVd reduced the risk for worsening of treatment adverse effects, compared with RVd alone, by 18% (HR, 0.82; 95% CI, 0.57-1.18).

Patients who received DRVd also reported worsening global health score symptoms 30 months later than patients who received RVd (HR, 0.71; 95% CI, 0.46-1.10). Moreover, there was no difference between treatment arms for median time to worsening of EQ-5D-5L visual analogue scores (HR, 0.86; 95% CI, 0.56-1.33).

→ **For the full article, visit** Cancernetwork.com/ASH22_GRIFFIN

Talquetamab Continues to Elicit High Treatment Responses in a Heavily Pretreated Multiple Myeloma Population

Updated findings from the phase 1/2 MonumenTAL-1 trial (NCT04634552), which is investigating the recommended phase 2 doses of talquetamab, showed that treatment with the agent resulted in an overall response rate (ORR) exceeding 70% in a population of patients with heavily pretreated relapsed/refractory multiple myeloma.

Study data indicated that patients treated with the subcutaneous agent had an ORR of 74.1% at the 0.4 mg/kg weekly dose and 73.1% with the 0.8 mg/kg twice weekly dose.

This included a stringent complete response rate (sCR) of 23.8%, a CR rate of 9.8%, a very good partial response rate (VGPR) of 25.9%, and a PR rate of 14.7% in the 0.4 mg/kg cohort, as well as rates of 20.0%, 12.4%, 24.8%, and 15.9%, respectively, in the 0.8 mg/kg group. ORR was notably consistent across all patient subgroups. As of the data cut-off, the median duration of response (DOR) was not reached in either group.

The investigators also reported that the median progression-free survival was 7.5 months (95% CI, 5.7-9.4) and 11.9 months (95% CI, 8.4 to not estimable) in the 0.4 mg/kg and 0.8 mg/kg groups, respectively.

The most common high-grade hematologic adverse effects (AEs) were cytopenias. In both the 0.4 mg/kg and 0.8 mg/kg cohorts, common grade 3/4 AEs were anemia (31.5% and 24.8%, respectively), neutropenia (30.8% and 22.1%), lymphopenia (25.9% and 25.5%), and thrombocytopenia (20.3% and 16.6%).

Most of the patient population (70.6%) had been previously treated with chimeric antigen receptor T-cell therapy, 35.3% had received a prior bispecific antibody, and 7.8% were refractory to belantamab (Blenrep). Patients in both arms who received prior T-cell redirection achieved an ORR of 62.7%, including an sCR rate of 17.6%, a CR rate of 5.9%, a VGPR rate of 29.4%, and a PR rate of 9.8%. Additionally, the median DOR among these patients was 12.7 months.

→ **For the full article, visit** Cancernetwork.com/ASH22_MonumenTAL-1

Belantamab Mafodotin Monotherapy Produces Durable Responses in DREAMM-2 Final Analysis in R/R Multiple Myeloma

Belantamab mafodotin (Blenrep) was found to stimulate sustained, deep, and durable responses in patients with relapsed/refractory multiple myeloma who had relapsed after 3 or more lines of therapy, according to results from the phase 2 DREAMM-2 trial (NCT03525678).

Final results from the open-label, 2-arm study of single-agent belantamab showed that responses to the drug were both rapid and durable. The median time to response was 1.5 months (95% CI, 1.0-2.1) in the patient cohort given 2.5 mg/kg of belantamab (n = 97), compared with 1.4 months in the 3.4 mg/kg cohort (n = 99). Moreover, the median duration of response was 12.5 months (95% CI, 4.2-19.3) in the 2.5 mg/kg cohort and 6.2 months (95% CI, 4.8-18.7) in the 3.4 mg/kg cohort.

The overall response rate remained consistent with previous reports at 32% in the 2.5 mg/kg cohort (97.5% CI, 21.7%-43.6%) compared with 35% (97.5% CI, 24.8%-47.0%) in the 3.4 mg/kg cohort; however, there were more complete responses, factoring for stringent complete responses, in the analysis cohort vs the comparator arm at 9 patients vs 5 patients, respectively.

For patients who had a VGPR or greater, the median progression-free survival (PFS) was 14.0 months (95% CI, 9.7 to not reached [NR]) in the 2.5 mg/kg cohort compared with 16.8 months (95% CI, 7.7-NR) in the 3.4 mg/kg cohort. Median PFS among the rest of the patients was 2.8 months (95% CI, 1.6-3.6) in the 2.5 mg/kg cohort compared with 3.9 months (95% CI, 2.0-5.8) in the 3.4 mg/kg arm.

The minimal residual disease (MRD) negativity rates also remained consistent with previous reports but were ultimately stronger in the 2.5 mg/kg cohort. The MRD negativity rate for patients with a VGPR or more was 36% (95% CI, 12.8%-64.9%) in the 2.5 mg/kg cohort vs 23% (95% CI, 5.0%-53.8%) in the 3.4 mg/kg cohort. Among the 14 patients with a VGPR in the 2.5 mg/kg cohort, 5 were MRD negative compared with 3 of 13 patients with VGPR in the 3.5 mg/kg cohort.

→ **For the full article, visit** Cancernetwork.com/ASH22_DREAMM-2

LEUKEMIA

Ziftomenib Demonstrates Activity and Tolerability in Relapsed/Refractory AML

According to updated data from a phase 1/2 trial (NCT04067336), ziftomenib monotherapy had a tolerable toxicity profile and provided pronounced antileukemic activity when given at a 600-mg dose in heavily pretreated patients with relapsed/refractory acute myeloid leukemia (AML).

When given at this dose, patients with *NPM1*-mutated disease were enrolled into phases 1a and 1b of the trial (n = 20), and the menin-KMT2A inhibitor elicited a complete remission (CR) rate of 30.0%. Notably, 2 of these patients had a concurrent *IDH1/2* mutation, and 2 patients had both *IDH1/2* and *FLT3*-ITD/TKD mutations. Of the 7 patients who had *IDH1/2* co-mutations, 57% achieved a CR with ziftomenib.

In the overall population, the CR/CR with partial hematologic recovery (CRh) rate with the agent was 30.0% and the composite CR (CRc) rate was 35.0%. The minimal residual disease (MRD) negativity rate was 42.9%. Ziftomenib elicited an overall response rate (ORR) of 40.0% in those who harbored this mutation.

Activity was also observed in patients with *KMT2A*-rearranged disease who were enrolled in the phase 1a and 1b portions of the trial and received the agent at 600 mg (n = 18).

In this group, the CR/CRh rate achieved with ziftomenib was 5.6%, and the CRc rate was 11.1%. The MRD negativity rate achieved with the agent was 100.0%. Moreover, ziftomenib produced an ORR of 16.7% in this population.

→ **For the full article, visit** Cancernetwork.com/ASH22_ziftomenib

Blinatumomab Prolongs Survival in MRD-Negative B-Cell Acute Lymphoblastic Leukemia

According to findings of the phase 3 ECOG-ACRIN E1910 trial (NCT02003222), blinatumomab (Blincyto) followed by consolidation chemotherapy led to a 58% reduction in the risk of death compared with standard consolidation chemotherapy alone in adult patients with newly diagnosed minimal residual disease (MRD)–negative B-cell acute lymphoblastic leukemia.

Results showed that the median overall survival (OS) with blinatumomab plus chemotherapy was not reached compared with 71.4 months with chemotherapy alone (HR, 0.42; 95% CI, 0.24-0.75; *P* = .003). OS rates at a median of 3.5 years were 83% and 65%, respectively.

Stratification factors included age, CD20 status, rituximab (Rituxan) use, and hematopoietic stem cell transplantation (yes vs no). Twenty-two patients in each arm proceeded to allogeneic hematopoietic stem cell transplant.

Seventeen deaths occurred on the blinatumomab arm (relapse, n = 8; nonrelapse mortality [NRM], n = 9) vs 39 on the chemotherapy-alone arm (relapse, n = 20; NRM, n = 17; unknown, n = 2).

→ **For the full article, visit** Cancernetwork.com/ASH22_ECOG-ACRIN

Lintuzumab-Ac225 May Produce Efficacy Benefit in R/R AML

Residual leukemia cells and a good safety profile were observed when lintuzumab-Ac225 (Actimab-A) was added to salvage therapy for patients with relapsed/refractory acute myeloid leukemia (AML), according to results from a phase 1 trial (NCT03441048).

Investigators of the regimen—cladribine, cytarabine, filgrastim, and mitoxantrone chemotherapies, combined with lintuzumab-Ac225—met their primary objective of finding the maximum tolerated dose and recommended phase 2 dose. Favorable response and survival rates were observed, as well as high minimal residual disease (MRD) negativity rates in patients with composite complete remission.

The 1- and 2-year overall survival (OS) rates were 53% and 32%, respectively, in all patients. In patients with composite complete remission and MRD negativity (n = 9), there was an 89% OS rate at 1 year and 48% OS rate at 2 years. Patients with *TP53* mutations had 51% and 19% OS rates at 1 and 2 years, respectively, and patients who received prior venetoclax (Venclexta) had 59% and 32% OS rates, respectively.

→ **For the full article, visit** Cancernetwork.com/ASH22_lintuzumab

Zanubrutinib Produces Superior Efficacy Over Ibrutinib in Relapsed/Refractory CLL/SLL

The risk of progression or death was reduced by 35% when patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma were treated with zanubrutinib (Brukinsa) vs ibrutinib (Imbruvica), according to results from the phase 3 ALPINE study (NCT03734016).

The findings met the criteria for noninferiority and superiority for zanubrutinib vs ibrutinib for objective response rate (ORR) and progression-free survival (PFS) by independent review committee. The 24-month investigator-assessed PFS rate was 79.5% with zanubrutinib vs 67.3% with ibrutinib. The ORR, the study's primary end point, was 86.2% with zanubrutinib compared with 75.7% for ibrutinib (*P* = .0007).

Atrial fibrillation/flutter, assessed as a secondary end point, was significantly less common with zanubrutinib vs ibrutinib (5.2% vs 13.3%, respectively; *P* = .0004). There were no fatal cardiac events reported with zanubrutinib compared with 6 events in the ibrutinib arm.

After 29.6 months of follow-up, the median PFS was not yet reached in the zanubrutinib arm compared with 35.0 months in the ibrutinib arm (95% CI, 33.2-44.3). In patients with deletion 17p or *TP53* mutations (n = 75 in each arm), by independent assessment, the 24-month PFS rates were 77.6% vs 55.7% for zanubrutinib and ibrutinib, respectively (HR, 0.52; 95% CI, 0.30-0.88; *P* = .0134). PFS favored zanubrutinib across other major subgroups analyzed.

The investigator-assessed PFS rates were similar to those of the independent review committee. At 24 months, PFS rates were 78.4% with zanubrutinib and 65.9% for ibrutinib-treated patients. The PFS also favored zanubrutinib over ibrutinib by investigator review for the deletion 17p/*TP53*-mutant subgroup (HR, 0.53; 95% CI, 0.31-0.88).

AEs of any grade or cause were experienced by 98.1% and 99.1% of patients in the zanubrutinib and ibrutinib groups, respectively. Grade 3 to 5 AEs were seen in 67.3% of those treated with zanubrutinib, with 10.2% of patients having a grade 5 AE. In the ibrutinib arm, 70.4% of patients experienced a grade 3 to 5 AE, with grade 5 events seen in 11.1% of patients. Serious AEs were experienced by 42.0% and 50.0% of patients in the zanubrutinib and ibrutinib arms, respectively.

→ **For the full article, visit** Cancernetwork.com/ASH22_ALPINE

LYMPHOMA

Second-Line Liso-Cel May Be Preferred Treatment vs SOC in LBCL

The reduction in the risk of an event occurring was 64.4% in patients with high-risk relapsed/refractory large B-cell lymphoma treated with lisocabtagene maraleucel (liso-cel; Breyanzi) vs standard-of-care (SOC) chemoimmunotherapy induction and autologous stem cell transplantation, according to results from the phase 3 TRANSFORM study (NCT03575351).

After a median follow-up of 17.5 months in the open-label study, the median event-free survival (EFS) was not yet reached in the liso-cel arm compared with 2.4 months for SOC (HR, 0.356; 95% CI, 0.243-0.522). The 18-month EFS rate was 52.6% with liso-cel (95% CI, 42.3%-62.9%) vs 20.8% with SOC (95% CI, 12.2%-29.5%). EFS findings were consistent across subgroups, with HRs ranging from 0.10 to 0.46.

The median progression-free survival (PFS) was not yet reached with liso-cel (95% CI, 12.6 to not reached) compared with 6.2 months with SOC (95% CI, 4.3-8.6), with a 60% reduction seen in the risk of progression or death with the CAR T-cell therapy (HR, 0.4; 95% CI, 0.261-0.615; P <.0001). The 18-month PFS rate was 58.2% with liso-cel (95% CI, 47.7%-68.7%) compared with 28.8% with SOC (95% CI, 17.7%-40.0%).

The objective response rate was 87% with liso-cel (95% CI, 78.3%-93.1%) vs 49% with SOC (95% CI, 38.3%-59.6%). The complete response (CR) rate was 74% with liso-cel (95% CI, 63.7%-82.5%) compared with 43% with SOC (95% CI, 33.2%-54.2%), demonstrating a statistically significant improvement with the CAR T-cell therapy (P <.0001). The duration of CR was not yet reached with liso-cel compared with 9.3 months with SOC (HR, 0.483; 95% CI, 0.262-0.890).

The median overall survival (OS) was not yet reached in the liso-cel arm with 17.5 months of follow-up. The median follow-up was 29.9 months in the SOC arm, with the bar for statistical superiority not yet reached between the arms (HR, 0.724; 95% CI, 0.443-1.183; P = .0987). The 18-month OS rate was 73.1% with liso-cel (95% CI, 63.9%-82.3%); it was 60.6% with SOC (95% CI, 50.2%-71.1%).

→ **For the full article, visit** Cancernetwork.com/ASH22_TRANSFORM

Durable Survival Benefit Observed Following HDC-ASCT vs Nonmyeloablative Chemoimmunotherapy for Primary CNS Lymphoma

Treatment with consolidation high-dose chemotherapy (HDC) plus autologous stem cell transplantation (ASCT) resulted in improved survival outcomes vs nonmyeloablative chemoimmunotherapy in those diagnosed with primary central nervous system (CNS) lymphoma, according to data from the phase 3 MATRix/IELSG43 trial (NCT02531841).

High-dose methotrexate–based induction immunochemotherapy followed by consolidation HDC-ASCT is the current standard of care for primary CNS lymphoma. There was no research showing that conventional-dose nonmyeloablative immunochemotherapy can overcome chemotherapy resistance, eliminate minimal residual disease, and cross the blood-brain barrier. Determining the full capability of this treatment strategy was the main purpose of MATRix/IELSG43.

In the HDC-ASCT arm, the complete response (CR) and unconfirmed CR rates were 40.0% before consolidation and 65.2% after consolidation compared with 39.5% and 67.5%, respectively, in the control arm. The partial response rate was 60.0% before consolidation in the HDC-ASCT arm and 15.7% after consolidation vs 60.5% and 21.1%, respectively, in the ifosfamide and carboplatin-based therapy (R-DeVIC) arm. After consolidation in the HDC-ASCT arm, 8.7% of patients had stable disease (SD) and 8.7% had progressive disease (PD). In comparison, the control arm had a 5.3% rate of SD and a 6.2% rate of PD.

Results for the primary end points favored the HDC-ASCT arm. The progression-free survival (PFS) rate was 79% (95% CI, 71%-86%) vs 53% (95% CI, 44%-62%) with the control (HR, 0.404; 95% CI, 0.252-0.650; P = .0002). The PFS benefit was also seen across most subgroups in the HDC-ASCT arm.

Regarding the key secondary end point of overall survival

(OS), HDC-ASCT led to a 54.4% reduction in the risk of death. The OS rate was 86% (95% CI, 78%-91%) with HDC-ASCT vs 71% (95% CI, 61%-78%) with R-DeVIC (HR, 0.456; 95% CI, 0.256-0.812; *P* = .0077).

→ **For the full article, visit** Cancernetwork.com/ASH22_MATRix

Addition of Ibrutinib to CRT/ASCT Appears to Improve Outcomes for MCL

A younger population of patients with mantle cell lymphoma derived statistically significant improvements in outcomes when treated with ibrutinib (Imbruvica), standard chemoimmunotherapy induction, and autologous stem cell transplantation (ASCT) plus maintenance ibrutinib for 2 years vs standard chemoimmunotherapy induction and ASCT alone, according to data from the phase 3 TRIANGLE study (NCT02858258).

The primary end point of the 2-arm study was failure-free survival (FFS); stable disease following induction, any progression, and death all counted as events. The 3-year FFS rate was 72% with standard induction and ASCT compared with 88% with ibrutinib added to induction, ASCT, and 2 years of ibrutinib maintenance (HR, 0.52; *P* = .0008).

Moreover, standard chemoimmunotherapy induction and ASCT failed to show superior FFS compared with ibrutinib plus chemoimmunotherapy as induction and 2 years of ibrutinib maintenance without ASCT, a regimen with far fewer adverse events (AEs). The 3-year FFS rate was 72% for chemoimmunotherapy/ASCT compared with 86% for ibrutinib alone (HR, 1.77; *P* = .9979). Rituximab (Rituxan) maintenance was permitted across all arms, with about half of patients receiving this treatment; however, subgroup analyses found that its use did not alter the main results.

Grade 3 to 5 AEs were similar between chemoimmunotherapy induction groups following induction therapy. The most common AEs in those receiving chemoimmunotherapy alone vs the addition of ibrutinib for maintenance were thrombocytopenia (59% vs 61%, respectively), neutropenia (47% vs 49%), anemia (22% vs 24%), leukopenia (15% in both), febrile neutropenia (9% vs 12%), infections 9% vs 12%), and cardiac disorders (2% vs 3%). There were three grade 5 events in induction therapy with 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone)/R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) followed by ASCT; two grade 5 events occurred in ibrutinib-containing arms.

→ **For the full article, visit** Cancernetwork.com/ASH22_TRIANGLE

Zanubrutinib Continues to Be Safe, Efficacious in Advanced Marginal Zone Lymphoma

The Bruton tyrosine kinase inhibitor zanubrutinib (Brukinsa) continued to elicit effective results at the 2-year mark for patients with relapsed/refractory marginal zone lymphoma (MZL), according to the final analysis of the phase 2 MAGNOLIA trial (NCT03846427). Preliminary findings from MAGNOLIA led to the FDA approval of zanubrutinib in 2021.

Now, data from a median follow-up of 28 months and a median treatment duration of 24.2 months showed that the independent review committee-assessed overall response rate (ORR) was 68.2% (95% CI, 55.6%-79.1%)—including a 25.8% complete response (CR) rate—in the overall study population, which included 66 patients with relapsed/refractory MZL who were treated with at least 1 CD20-directed regimen.

The ORRs were 64.0%, 76.0%, 66.7%, and 50.0% for patients with extranodal, nodal, splenic, and unknown subtypes of MZL, respectively. The corresponding CR rates were 40.0%, 20.0%, 8.3%, and 25.0%, respectively.

A sensitivity analysis using only CT-based criteria found the ORR and CR rates to be 66.7% and 24.2%, respectively.

At the time of study completion, 45.6% of patients (n = 31) benefited from rolling over to a long-term extension study of zanubrutinib. While all patients experienced at least 1 adverse effect (AE), no new safety signals were observed with zanubrutinib.

The most common treatment-emergent AEs that occurred in 10% or more of patients were bruising (23.5%), diarrhea (22.1%), constipation (17.6%), arthralgia (14.7%), pyrexia (14.7%), upper respiratory tract infection (13.2%), and abdominal pain and back pain (each 11.8%).

→ **For the full article, visit** Cancernetwork.com/ASH22_MAGNOLIA

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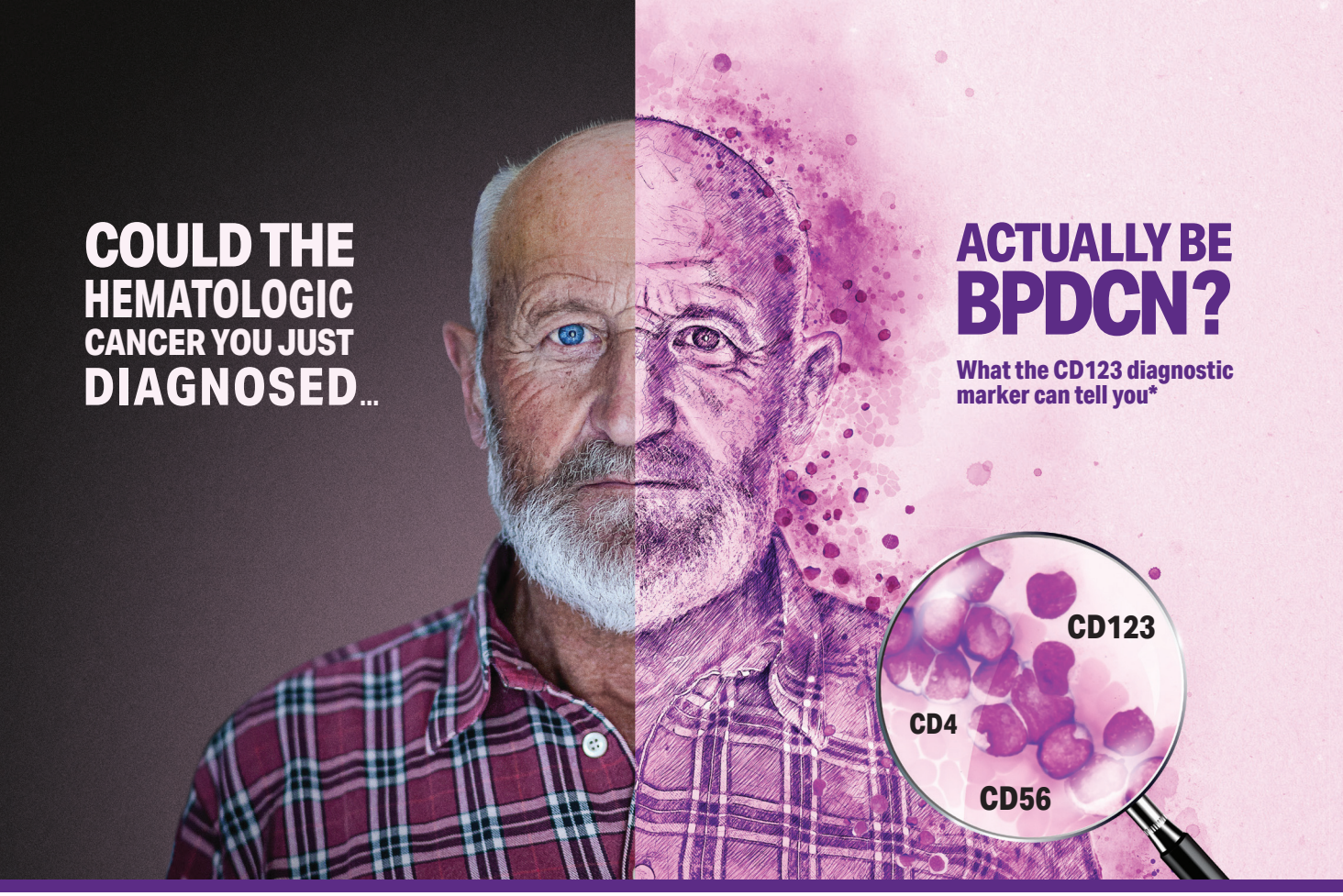

CD123 is a rapidly emerging therapeutic target in hematologic cancer.[1,2]

A signature triad of diagnostic markers, including CD123, may help identify Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN), an aggressive and deadly hematologic cancer.[1,2] Similarity to other malignancies may contribute to misdiagnosis.[1,7]

BPDCN may be mistaken for other hematologic cancers, including:[1,3–5]

- AML
- ALL
- Leukemia cutis
- MDS
- Myeloid sarcoma
- CMML
- NK/T-cell lymphoma
- CTCL

Consider CD123, CD4, and CD56 when BPDCN is suspected.[1,2,7,*]

Visit BPDCNinfo.com to learn more

* BPDCN can include other markers, such as TCL1, TCF4, and CD303 (BDCA2).[1,6,7]

AML = acute myeloid leukemia; NK = natural killer; ALL = acute lymphoblastic leukemia; MDS = myelodysplastic syndrome; CMML = chronic myelomonocytic leukemia; CTCL = cutaneous T-cell lymphoma.

References: **1.** Pagano L, Valentini CG, Grammatico S, Pulsoni A. *Br J Haematol.* 2016;174(2): 188–202. **2.** Pemmaraju N, Konopleva M. The Hematologist website. http://www.hematology.org/Thehematologist/Ask/8927.aspx. Published August 28, 2018. Accessed February 5, 2020. **3.** Riaz W, Zhang L, Horna P, Sokol L. *Cancer Control.* 2014;21(4):279–289. **4.** Laribi K, Denizon N, Besançon A, et al. *Biol Blood Marrow Transplant.* 2016;22(8):1357–1367. **5.** Goyal A, Carter JB, Duncan LM. In: Carter JB, Goyal A, Duncan LM, eds. *Atlas of Cutaneous Lymphomas: Classification and Differential Diagnosis.* 2015:193–203. **6.** Ceribelli M, Hou ZE, Kelly PN, et al. *Cancer Cell.* 2016;30(5):764–778. **7.** Khoury JD, Solary E, Abla O. The 5th edition of the World Health Organization classification of Haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. *Leukemia.* 2022;36(7):1703-1719. doi:10.1038/s41375-022-01613-1

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