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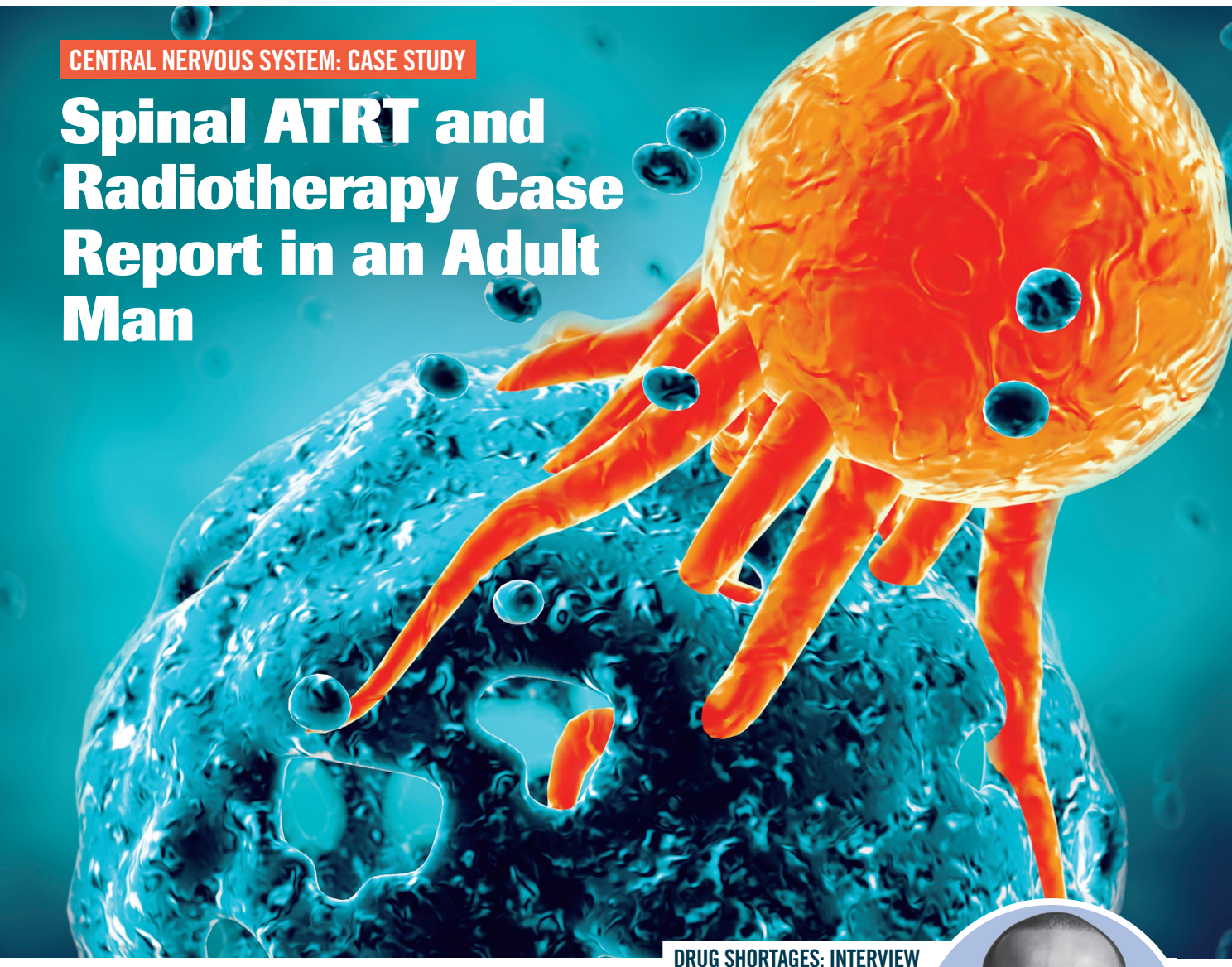

CENTRAL NERVOUS SYSTEM: CASE STUDY

Spinal ATRT and Radiotherapy Case Report in an Adult Man

DRUG SHORTAGES: INTERVIEW

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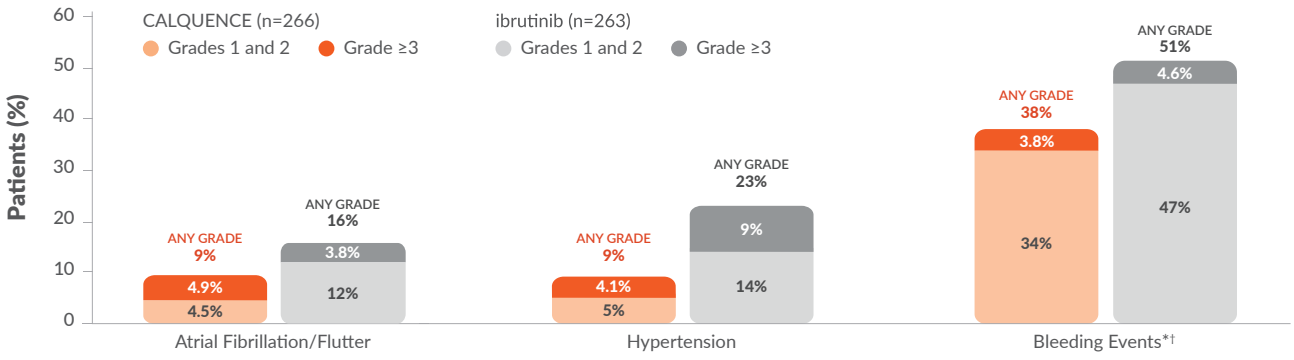
CALQUENCE® (acalabrutinib) IN RELAPSED/REFRACTORY CLL

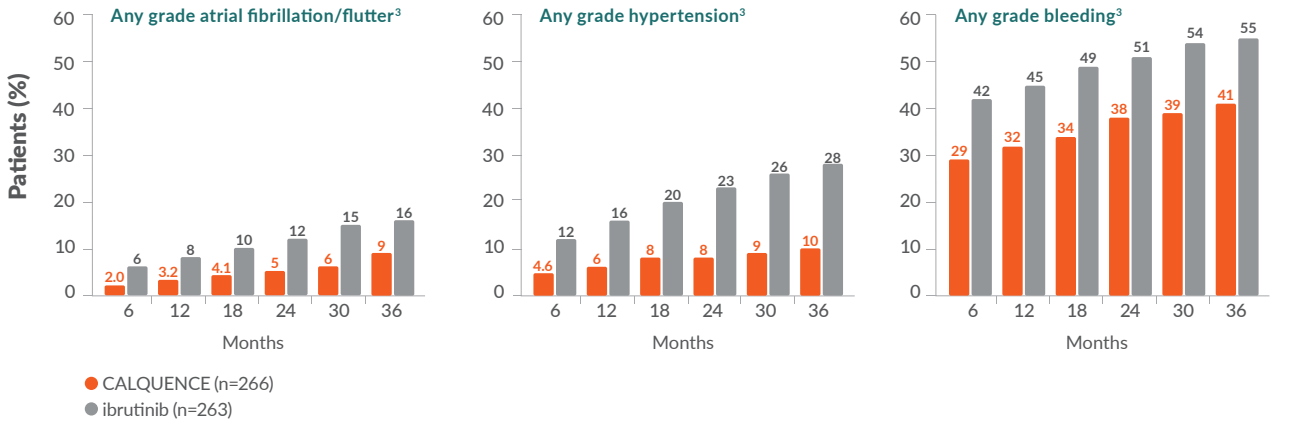
LOW RATES OF ATRIAL FIBRILLATION/FLUTTER, HYPERTENSION, AND GRADE ≥3 BLEEDING EVENTS[1,2]

ELEVATE-RR: CALQUENCE VS IBRUTINIB

ELEVATE-RR: Select AEs with CALQUENCE and ibrutinib at 40.9-month median follow-up[1]



Post hoc analysis of cumulative incidence‡ of select AEs of clinical interest[3]



The ELEVATE-RR data have not been reviewed by the FDA and are not included in the prescribing information for CALQUENCE.

*Includes major bleeding events, which were defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or that was a central nervous system hemorrhage (any grade), occurred in 4.5% of CALQUENCE patients and 5% of ibrutinib patients.[1]

†Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis.[1,3]

‡Investigator-selected cumulative incidences of events of clinical interest and common adverse events were assessed using Kaplan-Meier methods and a Cox proportional-hazards model.[1,3]

SELECT SAFETY INFORMATION

INDICATION AND USAGE

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets

Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE. Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

CALQUENCE®

acalabrutinib 100 mg tablets

ELEVATE-RR: CALQUENCE VS IBRUTINIB

The first head-to-head study of a BTKi vs ibrutinib in R/R CLL[1]

ELEVATE-RR was a Phase 3, open-label, randomized, multicenter trial in 533 patients with relapsed/refractory CLL and the presence of 17p deletion and/or 11q deletion. Patients received either CALQUENCE 100 mg orally approximately every 12 hours (n=268) or ibrutinib 420 mg orally once daily (n=265) until disease progression or unacceptable toxicity. The primary endpoint was IRC-assessed PFS (non-inferiority*; tested after ~250 events). Secondary endpoints included incidence of any grade atrial fibrillation, incidence of Grade ≥3 infections, incidence of Richter's transformation, and OS.[1]

Safety and tolerability data at 40.9-month median follow-up[1]

Most common AEs (>15%, any grade) in ELEVATE-RR[1]

	CALQUENCE (n=266)		ibrutinib (n=263)	
Adverse event	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Headache	35	1.5	20	0
Diarrhea	35	1.1	46	4.9
Cough	29	0.8	21	0.4
Upper respiratory tract infection	27	1.9	25	0.4
Pyrexia	23	3.0	19	0.8
Anemia	22	12	19	13
Neutropenia	21	20	25	23
Fatigue	20	3.4	17	0
Pneumonia	18	11	16	9
Nausea	18	0	19	0.4
Arthralgia	16	0	23	0.8
Thrombocytopenia	15	10	13	7
Contusion	12	0	18	0.4
Atrial fibrillation	9†	4.5	16†	3.4
Hypertension	9	4.1	23	9

- Adverse events of clinical interest (any grade) in patients receiving CALQUENCE included infections (78%), cytopenias (41%), bleeding events (38%), cardiac events (24%), and second primary malignancies, excluding non-melanoma skin cancers (9%)[1]
- The median duration of CALQUENCE exposure was 38.3 months (range: 0.3-55.9); the median duration of ibrutinib exposure was 35.5 months (range: 0.2-57.7)[1]

*Derivation of the non-inferiority margin (upper bound of HR two-sided 95% CI <1.429) was based on the results of one ibrutinib study. Therefore, it may be difficult to verify the constancy assumption of the historical control.[1]

†Select secondary endpoint.[1]

AEs=adverse events; BR=bendamustine + rituximab; BTKi=Bruton tyrosine kinase inhibitor; CI=confidence interval; CLL=chronic lymphocytic leukemia; HR=hazard ratio; IdR=idelalisib + rituximab; INV=investigator; IRC=Independent Review Committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory.

ASCEND: RELAPSED/REFRACTORY CLL

The first study of a BTKi vs IdR or BR in R/R CLL[2,4]

ASCEND was a Phase 3, open-label, randomized, multicenter trial in 310 patients with relapsed/refractory CLL. Patients received either CALQUENCE monotherapy 100 mg approximately every 12 hours until disease progression or unacceptable toxicity (n=155) or investigator's choice of IdR or BR (n=155). Primary endpoint at the interim analysis (median follow-up of 16.1 months) was IRC-assessed PFS. After the interim analysis at 16.1-month median follow-up, PFS was INV-assessed only. Select secondary endpoints were ORR, OS, and safety.[2,4]

Safety and tolerability data at 46.5-month median follow-up[2]

Most common AEs (>15%, any grade) in ASCEND[2]

	CALQUENCE (n=154)		IdR (n=118)		BR (n=35)	
Adverse event	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Infection	68	29	73	34	49	11
Upper respiratory tract infection	20	1.9	17	3.4	11	2.9
Pneumonia	19	10	14	10	6	2.9
Hemorrhage	31	2.6	8	2.5	6	2.9
Major hemorrhage*	3.2	2.6	2.5	2.5	2.9	2.9
Neutropenia	24	19	47	40	34	31
Headache	23	0.6	6	0	0	0
Diarrhea	21	1.9	53	26	14	0
Anemia	18	13	11	7	11	9
Cough	18	0	15	0.8	6	0
Pyrexia	16	3.2	19	7	17	2.9

- The median duration of CALQUENCE exposure was 44.2 months (range: 1.1-54.2)[2]

- **At 16.1-month median follow-up**, the most common adverse reactions (≥20%) of any grade in patients receiving CALQUENCE were infection (56%), neutropenia (48%), anemia (47%), thrombocytopenia (33%), lymphocytosis (26%), and headache (22%)[4]
  - Events of clinical interest (any grade; Grade ≥3) included infection (56%; 15%), bleeding (26%; 1.9%), atrial fibrillation (5%; 1.3%), and hypertension (3.2%; 1.9%)[4,5]
  - The median duration of CALQUENCE exposure was 15.7 months (range: 1.1-22.4)[4,5]

The median 46.5-month follow-up data from ASCEND have not been reviewed by the FDA and are not included in the Prescribing Information for CALQUENCE.

*Major hemorrhage was defined as any serious or Grade ≥3 hemorrhage or central nervous system hemorrhage of any grade, excluding immune thrombocytopenic purpura.[2]

VIEW HEAD-TO-HEAD TRIAL RESULTS AT CALQUENCEHCP.COM

SELECT SAFETY INFORMATION (cont'd)

Atrial Fibrillation and Flutter

Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (eg, palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

Please see Brief Summary of full Prescribing Information on adjacent pages.

You are encouraged to report the negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

References: 1. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol.* 2021;39(31):3441-3452 and supplementary appendix. **2.** Ghia P, Pluta A, Wach M, et al. Acalabrutinib versus investigator's choice in relapsed/refractory chronic lymphocytic leukemia: final ASCEND trial results. *Hemasphere.* 2022;6(12):e801. **3.** Seymour JF, Byrd JC, Hillmen P, et al. Characterization of Bruton tyrosine kinase inhibitor (BTKi)-related adverse events in a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia (CLL). Poster presented at the American Society of Hematology (ASH) Annual Meeting; December 11-14, 2021. Abs 3721. **4.** CALQUENCE® (acalabrutinib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022. **5.** Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2020;38(25):2849-2861 and supplementary appendix.

AstraZeneca

CALQUENCE® (acalabrutinib) tablets, for oral use
Initial U.S. Approval: 2017

Brief Summary of Prescribing Information.
For full Prescribing Information consult official package insert.

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

DOSAGE AND ADMINISTRATION

Recommended Dosage

CALQUENCE as Monotherapy
For patients with CLL, or SLL, the recommended dosage of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

CALQUENCE in Combination with Obinutuzumab
For patients with previously untreated CLL or SLL, the recommended dosage of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE prior to obinutuzumab when given on the same day.

Advise patients to swallow tablet whole with water. Advise patients not to chew, crush, dissolve, or cut the tablets. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

Recommended Dosage for Drug Interactions

Dosage Modifications for Use with CYP3A Inhibitors or Inducers
These are described in Table 1 *[see Drug Interactions (7) in the full Prescribing Information]*.

Table 1: Recommended Dosage Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid co-administration. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE.
	Moderate CYP3A inhibitor	Reduce the CALQUENCE 100 mg every 12 hours dosage to 100 mg once daily.
Induction	Strong CYP3A inducer	Avoid co-administration. If co-administration is unavoidable, increase CALQUENCE dosage to 200 mg approximately every 12 hours.

Dosage Modifications for Adverse Reactions
Recommended dosage modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dosage Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE.

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious and Opportunistic Infections
Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%) *[see Adverse Reactions (6.1) in the full Prescribing Information]*. These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jirovecii* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

Second Primary Malignancies
Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter
Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Hemorrhage *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Cytopenias *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Atrial Fibrillation and Flutter *[see Warnings and Precautions (5.5) in the full Prescribing Information]*

Clinical Trials Experience
As 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 data in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

Chronic Lymphocytic Leukemia
The safety data described below reflect exposure to CALQUENCE (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.2) in the full Prescribing Information]*.

The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

ELEVATE-TN
The safety of CALQUENCE plus obinutuzumab (CALQUENCE+G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomized, multicenter, open-label, actively controlled trial in 526 patients with previously untreated CLL *[see Clinical Studies (14.2) in the full Prescribing Information]*.

Patients randomized to the CALQUENCE+G arm were treated with CALQUENCE and obinutuzumab in combination for six cycles, then with CALQUENCE as monotherapy until disease progression or unacceptable toxicity. Patients initiated obinutuzumab on Day 1 of Cycle 2, continuing for a total of 6 cycles. Patient randomized to CALQUENCE monotherapy received CALQUENCE approximately every 12 hours until disease progression or unacceptable toxicity. The trial required age ≥ 65 years of age or 18 to < 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min, hepatic transaminases ≤ 3 times ULN and total bilirubin ≤1.5 times ULN, and allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

During randomized treatment, the median duration of exposure to CALQUENCE in the CALQUENCE+G and CALQUENCE monotherapy arms was 27.7 months (range 0.3 to 40 months), with 95% and 92% and 89% and 86% of patients with at least 6 months and 12 months of exposure, respectively. In the obinutuzumab and chlorambucil arm, the median number of cycles was 6 with 84% of patients receiving at least 6 cycles of obinutuzumab, 70% of patients received at least 6 cycles of chlorambucil. Eighty-five percent of patients in the CALQUENCE+G arm received at least 6 cycles of obinutuzumab.

In the CALQUENCE+G and CALQUENCE monotherapy arms, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE+G arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (2.8% to 7%).

In the CALQUENCE+G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE in 7% of patients. In the CALQUENCE monotherapy arm, adverse reactions led to discontinuation in 10% and dose reduction in 4% of patients.

Tables 5 and 6 present adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

Table 5: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ELEVATE-TN)

Body System Adverse Reaction*	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection†	69	22‡	65	14‡	46	13‡
Upper respiratory tract infection§	39	2.8	35	0	17	1.2
Lower respiratory tract infection[a]	24	8	18	4.5	7	1.8
Urinary tract infection	15	1.7	15	2.8	5	0.6
Blood and lymphatic system disorders[b]						
Neutropenia[c]	53	37	23	13	78	50
Anemia[d]	52	12	53	10	54	14
Thrombocytopenia[e]	51	12	32	3.4	61	16
Lymphocytosis[f]	12	11	16	15	0.6	0.6
Nervous system disorders						
Headache	40	1.1	39	1.1	12	0
Dizziness	20	0	12	0	7	0
Gastrointestinal disorders						
Diarrhea	39	4.5	35	0.6	21	1.8
Nausea	20	0	22	0	31	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[g]	37	2.2	32	1.1	16	2.4
Arthralgia	22	1.1	16	0.6	4.7	1.2
General disorders and administration site conditions						
Fatigue[h]	34	2.2	23	1.1	24	1.2
Skin and subcutaneous tissue disorders						
Bruising[i]	31	0	21	0	5	0
Rash[j]	26	2.2	25	0.6	9	0.6
Vascular disorders						
Hemorrhage[k]	20	1.7	20	1.7	6	0

* Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia
‡ Includes 3 fatal cases in the CALQUENCE plus obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm

§ Includes upper respiratory tract infection, nasopharyngitis and sinusitis
[a] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
[b] Derived from adverse reaction and laboratory data
[c] Includes neutropenia, neutrophil count decreased, and related laboratory data
[d] Includes anemia, red blood cell count decreased, and related laboratory data
[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data
[f] Includes lymphocytosis, lymphocyte count increased, and related laboratory data
[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain
[h] Includes asthenia, fatigue, and lethargy
[i] Includes bruise, contusion, and ecchymosis
[j] Includes rash, dermatitis, and other related terms
[k] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:

- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

Table 6: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)

Laboratory Abnormality*, [a]	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	29	29	22	22	37	37
ALT increase	30	7	20	1.1	36	6
AST increase	38	5	17	0.6	60	8
Bilirubin increase	13	0.6	15	0.6	11	0.6

*Per NCI CTCAE version 4.03
[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) *[see Clinical Studies (14.2) in the full Prescribing Information]*. The trial enrolled patients with relapsed or refractory CLL after at least one prior therapy and required hepatic transaminases ≤ 2 times ULN, total bilirubin ≤ 1.5 times ULN, and an estimated creatinine clearance ≥ 30 mL/min. The trial excluded patients having an absolute neutrophil count < 500/µL, platelet count < 30,000/µL, prothrombin time or activated partial thromboplastin time > 2 times ULN, significant cardiovascular disease, or a requirement for strong CYP3A inhibitors or inducers. Patients were allowed to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonist.

In ASCEND, 154 patients received CALQUENCE (100 mg approximately every 12 hours until disease progression or unacceptable toxicity), 118 received idelalisib (150 mg approximately every 12 hours until disease progression or unacceptable toxicity) with up to 8 infusions of a rituximab product, and 35 received up to 6 cycles of bendamustine and a rituximab product. The median age overall was 68 years (range: 32-90); 67% were male; 92% were white; and 88% had an ECOG performance status of 0 or 1.

In the CALQUENCE arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE, permanent discontinuation due to an adverse reaction occurred in 10% of patients, most frequently due to second primary malignancies followed by infection. Adverse reactions led to dosage interruptions of CALQUENCE in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and dose reduction in 3.9% of patients.

Selected adverse reactions are described in Table 7 and non-hematologic laboratory abnormalities are described in Table 8. These tables reflect exposure to CALQUENCE with median duration of 15.7 months with 94% of patients on treatment for greater than 6 months and 86% of patients on treatment for greater than 12 months. The median duration of exposure to idelalisib was 11.5 months with 72% of patients on treatment for greater than 6 months and 48% of patients on treatment for greater than 12 months. Eighty-three percent of patients completed 6 cycles of bendamustine and rituximab product.

Table 7: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND)

Body System Adverse Reaction*	CALQUENCE N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection†	56	15‡	65	28‡	49	11
Upper respiratory tract infection§	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection[a]	23	6	26	15	14	6
Blood and lymphatic system disorders[b]						
Neutropenia[c]	48	23	79	53	80	40
Anemia[d]	47	15	45	8	57	17
Thrombocytopenia[e]	33	6	41	13	54	6
Lymphocytosis[f]	26	19	23	18	2.9	2.9
Nervous system disorders						
Headache	22	0.6	6	0	0	0
Gastrointestinal disorders						
Diarrhea[g]	18	1.3	49	25	14	0
Vascular disorders						
Hemorrhage[h]	16	1.3	5	1.7	6	2.9
General disorders						
Fatigue[i]	15	1.9	13	0.8	31	6
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[j]	15	1.3	15	1.7	2.9	0

* Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia
‡ Includes 1 fatal case in the CALQUENCE monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm
§ Includes upper respiratory tract infection, rhinitis and nasopharyngitis
[a] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
[b] Derived from adverse reaction and laboratory data
[c] Includes neutropenia, neutrophil count decreased, and related laboratory data
[d] Includes anemia, red blood cell decreased, and related laboratory data
[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data
[f] Includes lymphocytosis, lymphocyte count increased and related laboratory data
[g] Includes colitis, diarrhea, and enterocolitis
[h] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis
[i] Includes asthenia, fatigue, and lethargy
[j] Includes back pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, pain in extremity, myalgia, spinal pain and bone pain

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:

- *Skin and subcutaneous disorders:* bruising (10%), rash (9%)
- *Neoplasms:* second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders:* arthralgia (8%)
- *Cardiac disorders:* atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection:* herpesvirus infection (4.5%)

Table 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)

Laboratory Abnormality [a]	CALQUENCE N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	15	15	11	11	23	23
ALT increase	15	1.9	59	23	26	2.9
AST increase	13	0.6	48	13	31	2.9
Bilirubin increase	13	1.3	16	1.7	26	11

Per NCI CTCAE version 5
[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to animals during organogenesis resulted in dystocia in rats and reduced fetal growth in rabbits at maternal exposures (AUC) 2 times exposures in patients at the recommended dose of 100 mg approximately every 12 hours (*see Data*). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9 times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2 times the AUC in patients at 100 mg approximately every 12 hours.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2 times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5 times the AUC in patients at 100 mg approximately every 12 hours.

Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for 2 weeks after the last dose.

Females and Males of Reproductive Potential

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 1 week following the last dose of CALQUENCE. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Pediatric Use

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

Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

Hepatic Impairment

Avoid use of CALQUENCE in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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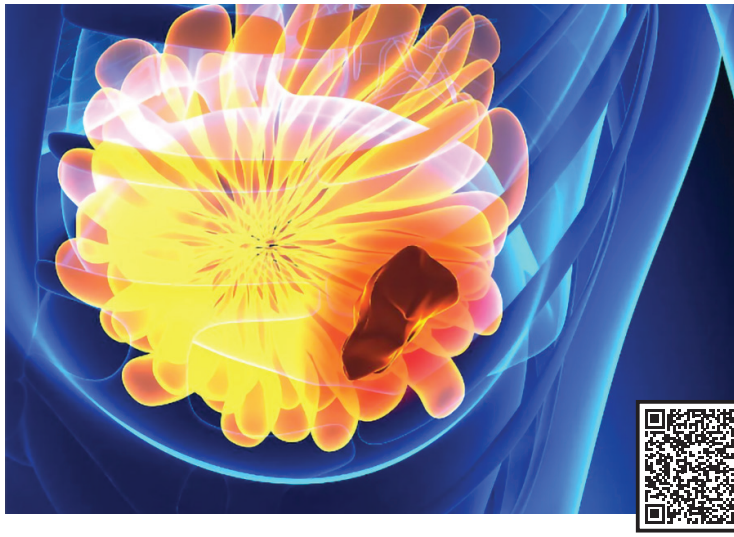

WEB FEATURE

Endocrine Therapy Break May Allow for Conception in HR+ Breast Cancer

Results from the POSITIVE trial have left the breast cancer community pondering an essential question: Can endocrine therapy be temporarily paused in patients with hormone receptor–positive disease long enough to allow for pregnancy and childbirth? Data from the trial, which analyzed the risk of breast cancer events associated with pausing treatment in those with hormone receptor–positive, early breast cancer, showed that it may be possible.

Cancernetwork.com/POSITIVE_Trial

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TAZVERIK®
(tazemetostat) tablets
200 mg

CHANGE THE TUNE

CONSIDER TAZVERIK® (tazemetostat) FOR YOUR APPROPRIATE ADULT PATIENTS WITH R/R FOLLICULAR LYMPHOMA[1]

Indication

TAZVERIK is indicated for the treatment of:

- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[1]

EZH2=enhancer of zeste homolog 2.

Important Safety Information

Warnings and Precautions

- **Secondary Malignancies**

The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

- **Embryo-Fetal Toxicity**

Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

Important Safety Information continued on back page of this insert. Please see Brief Summary of the Prescribing Information on the adjacent pages.

TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

• TAZVERIK® (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

• TAZVERIK is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies]*. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

Patient Selection - Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens *[see Clinical Studies]*. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Swallow tablets whole. Do not cut, crush, or chew tablets. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions, and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

Dose Reduction	Dosage
First	600 mg orally twice daily
Second	400 mg orally twice daily*

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Neutropenia *[see Adverse Reactions]*	Neutrophil count less than 1 x 10^9/L	• Withhold until neutrophil count is greater than or equal to 1 x 10^9/L or baseline. • For first occurrence, resume at same dose. • For second and third occurrence, resume at reduced dose. • Permanently discontinue after fourth occurrence.
Thrombocytopenia *[see Adverse Reactions]*	Platelet count less than 50 x 10^9/L	• Withhold until platelet count is greater than or equal to 75 x 10^9/L or baseline. • For first and second occurrence, resume at reduced dose. • Permanently discontinue after third occurrence.
Anemia *[see Adverse Reactions]*	Hemoglobin less than 8 g/dL	• Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.
Other adverse reactions *[see Adverse Reactions]*	Grade 3	• Withhold until improvement to at least Grade 1 or baseline. • For first and second occurrence, resume at reduced dose. • Permanently discontinue after third occurrence.
	Grade 4	• Withhold until improvement to at least Grade 1 or baseline. • For first occurrence, resume at reduced dose. • Permanently discontinue after second occurrence.

Dosage Modifications for Drug Interactions

Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor *[see Drug Interactions, Clinical Pharmacology]*.

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

Current Dosage	Adjusted Dosage
800 mg orally twice daily	400 mg orally twice daily
600 mg orally twice daily	400 mg for first dose and 200 mg for second dose
400 mg orally twice daily	200 mg orally twice daily

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS

Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [$AUC_{0\text{-}45h}$]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies *[see Warnings and Precautions]*.

Clinical Trial Experience - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in two cohorts (Cohorts 4 and 5) of Study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma *[see Clinical Studies]*. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 87 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The median number of prior therapies was 3 (range 1 to 11). Patients were required have a creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in ≥2% of patients was second primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in ≥3% of patients were thrombocytopenia and fatigue. Dose reduction due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions (≥20%) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

Adverse Reaction	TAZVERIK N=99	
	All Grades (%)	Grade 3 or 4 (%)
General		
Fatigue[a]	36	5
Pyrexia	10	0
Infections		
Upper respiratory tract infection[b]	30	0
Lower respiratory tract infection[c]	17	0
Urinary tract infection[d]	11	2
Gastrointestinal		
Nausea	24	1
Abdominal pain[e]	20	3
Diarrhea	18	0
Vomiting	12	1
Musculoskeletal and connective tissue		
Musculoskeletal pain[f]	22	1
Skin and subcutaneous tissue		
Alopecia	17	0
Rash[g]	15	0
Respiratory and mediastinal system		
Cough[h]	17	0
Nervous system		
Headache[i]	13	0

Table 6 continues on the next page

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101 (continued)

[a]Includes fatigue and asthenia

[b]Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper repiratory tract infection, viral upper respiratory tract infection

[c]Includes bronchitis, lower respiratory tract infection, tracheobronchitis

[d]Includes cystitis, urinary tract infection, urinary tract infection staphylococcal

[e]Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper

[f]Includes back pain, limb discomfort, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, spinal pain

[g]Includes erythema, rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation

[h]Includes cough and productive cough

[i]Includes headache, migraine, sinus headache

Clinically relevant adverse reactions occurring in <10% of patients who received TAZVERIK included:
- Infection: sepsis (2%), pneumonia (2%), and herpes zoster (2%)

Table 7 summarizes select laboratory abnormalities in patients with follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 7. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

Laboratory Abnormality	TAZVERIK*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	57	18
Decreased hemoglobin	50	8
Decreased platelets	50	7
Decreased white blood cells	41	9
Decreased neutrophils	20	7
Chemistry		
Increased glucose	53	10
Increased aspartate aminotransferase	24	0
Increased alanine aminotransferase	21	2.3
Increased alkaline phosphatase	18	1.0
Increased creatinine	17	0

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

DRUG INTERACTIONS

Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A Inhibitors: Coadministration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations *[see Clinical Pharmacology]*, which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose *[see Dosage and Administration]*. Strong and Moderate CYP3A Inducers: Coadministration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations *[see Clinical Pharmacology]*, which may decrease the efficacy of TAZVERIK. Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK.

Effect of TAZVERIK on Other Drugs - CYP3A Substrates: Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates *[see Use in Specific Populations, Clinical Pharmacology]*.

USE IN SPECIFIC POPULATIONS

Pregnancy - Risk Summary: Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology]*, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [$AUC_{0\text{-}45h}$] at the 800 mg twice daily dose *(see Data)*. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data - Animal Data: In pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses of ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose). At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

Lactation - Risk Summary: There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Females and Males of Reproductive Potential - Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK *[see Use in Specific Populations]*. Risk Summary: TAZVERIK can cause fetal harm when administered to pregnant women *[see Use in Specific Populations]*. Contraception: *Females* - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective *[see Drug Interactions]*. *Males* - Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

Pediatric Use - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

Juvenile Animal Toxicity Data - In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:
- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Distended testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

Geriatric Use - Clinical studies of TAZVERIK did not include sufficient numbers of patients with relapsed or refactory follicular lymphoma aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment - No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease *[see Clinical Pharmacology]*.

Hepatic Impairment - No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN). TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment *[see Clinical Pharmacology]*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs *[see Use in Specific Populations]*.

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

Secondary Malignancies - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity - Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose *[see Use in Specific Populations]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose *[see Use in Specific Populations, Nonclinical Toxicology]*.

Lactation - Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose *[see Use in Special Populations]*.

Drug Interactions - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, grapefruit, and grapefruit juice while taking TAZVERIK *[see Drug Interactions]*.

Epizyme®

Brief Summary [07/2020]
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EFFICACY IN CONCERT WITH TOLERABILITY[1]

NCCN recommended

Tazemetostat (TAZVERIK®) is included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas with a category 2A recommendation as an option for appropriate patients with R/R FL.[2]

Learn more about why you should consider TAZVERIK for your next R/R follicular lymphoma patient.[1]

Visit **ExploreTAZVERIK.com** today

Important Safety Information *(continued)*

- **Embryo-Fetal Toxicity** *(continued)*
  Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC0-45h]) at the 800 mg twice daily dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions

Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.

Avoid coadministration of moderate and strong

CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.

Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation

Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Before prescribing TAZVERIK, please read the Brief Summary of the Prescribing Information on the adjacent pages.

EZH2=enhancer of zeste homolog 2; MT=mutant type; WT=wild type.

References: 1. TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July 2020. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V4.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed, June 13, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way

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SEPTEMBER 2023 ▪ VOL. 37 ▪ NO. 9

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

Christopher R. Flowers, MD, MS
Hematologic Malignancies Editorial Board Member
Flowers was recently promoted to head of the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston. He currently works in the Department of Lymphoma & Myeloma at the institution.

Linda E. Carlson, RPsych, PhD
Integrative Oncology Editorial Board Member
Carlson was lead author on the recently published update for the Society of Integrative Oncology titled "Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults With Cancer: Society for Integrative Oncology–ASCO Guideline." These new guidelines will help clinicians better recommend ways to limit anxiety and depression in patients with cancer.

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Drug Price Negotiations: One Long-Overdue "Small Step" for the American Health Care Consumer

With the Inflation Reduction Act of 2022 signed into law, President Joseph R. Biden and the previous Congress established a new process for limiting federal expenditures on drugs, using the leverage of the largest consumer of health care services in the United States (US)—Medicare. Currently, from Medicare's 2022 budget of $747 billion, Part D drug expenditure accounts for $216 billion (28%).[1] Even a 5% saving on these drugs would amount to $10 billion yearly.

Before the Inflation Reduction Act, Medicare was not permitted to negotiate drug pricing with drug manufacturers. Any FDA-approved drug has been reimbursed at the price set by the manufacturer without negotiation. The Inflation Reduction Act seeks to level the playing field for American taxpayers, as most high-income countries have some level of price negotiation before their health care plans agree to reimburse for a new drug.[2]

In England, drugs are approved by the health regulatory authorities but are not reimbursed until a second effectiveness review is conducted by the National Institute for Health and Care Excellence and a drug price is set.[3] If the manufacturer does not come to an agreement, the National Health Service will not pay for the drug, though it may be available to some patients via private payment or insurance. Other countries consider cost-effectiveness when deciding whether new drugs should be added to the essential basket of health care. In the US, the Veterans Health Administration negotiates drug prices when they purchase the large quantities necessary.[3] The result of this worldwide situation is that US patients bear a disproportionate burden regarding the costs of drug development and manufacture. The new law will, to a small extent, redress this inequality for the US consumer compared with the rest of the world.

The new law is set to take effect in September 2023 with Medicare proposing 10 drugs for negotiation, with cost reductions to start in 2026.[4] In 2024 and 2025, 15 drugs will be added, and in 2026 and after, 20 drugs per year. The drugs on the list for the first negotiation were announced on August 29, 2023. These include Eliquis (apixaban) with $16.5 billion in Medicare expenditures; Jardiance (empagliflozin) at $7 billion; Xarelto (rivaroxaban), at $6 billion, Januvia (sitagliptin), Farxiga (dapagliflozin), Entresto (sacubitril/ valsartan), Enbrel (etanercept), Stelara (ustekinumab), Novolog (insulin aspart), and the cancer drug Imbruvica (ibrutinib)at $2.7 billion.[5]

This seems to be a modest step forward. We already give drug manufacturers at least 20 years of exclusivity through patent protection, which constitutes the basic incentive to develop new drugs. When drugs are widely used "blockbusters," patent protection against generics and 9 years of full reimbursement issues seem like a modest request of the pharmaceutical industry.

Nonetheless, 6 pharmaceutical giants (AstraZeneca, Bristol Myers Squibb, Merck, Pfizer, Johnson & Johnson, and Astellas) have filed suit against the US government to stop this process on the basis of infringement of their freedom of commerce and unconstitutional price controls.[6] As physicians, however, it is hard to sympathize when we have been under price controls since Medicare set its rates in the 1980s, and managed care has followed suit. Little has been done to fix the situation, resulting in primary care physicians commonly losing money on Medicare patients due to failure to update reimbursement levels.

In addition, we should also recognize the role of the US government and taxpayers in drug development. Essentially, every new targeted agent and every new biologic has benefited from the National Institutes of Health (NIH)-supported research at US universities and even biotechnology companies. NIH grants have led to major advances such as restriction enzymes, DNA sequencing, monoclonal antibody production technology, gene editing, and CRISPR plus its more recent innovations.

These advances have led to amazing new drugs in cancer, hypertension, rheumatologic diseases, and now obesity, and a new biotechnology industry. For example, US taxpayers invested approximately $337 million (from NIH, Biomedical Advanced Research and Development Authority) in the development of RNA vaccine technology, prior to the COVID-19 epidemic, with the interest mainly in the potential for cancer vaccines and for Zika virus. Fortunately, the technology was sufficiently developed to pivot for manufacturing COVID-19 vaccines when needed. With the advent of COVID-19, the US government (we, the taxpayers) invested another $29 billion. Yet Moderna, BioNTech, and Pfizer all made massive profits from the COVID-19 vaccines ($90 billion in pretax profits in 2021 and 2022).[7]

We certainly must recognize the extensive costs to the pharmaceutical manufacturers in bringing all these discoveries from the laboratory to clinical trials and FDA approval. Nonetheless, it is unfair that the US taxpayer shoulders most of the costs of basic research leading to drugs, then pays more than any other health care consumer in the world. Drug price negotiations are starting now, and it is only fair to the US consumer that some relief in drug costs is on the horizon. We recognize the efforts of the current administration to bring this process forward for the first time. ■

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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

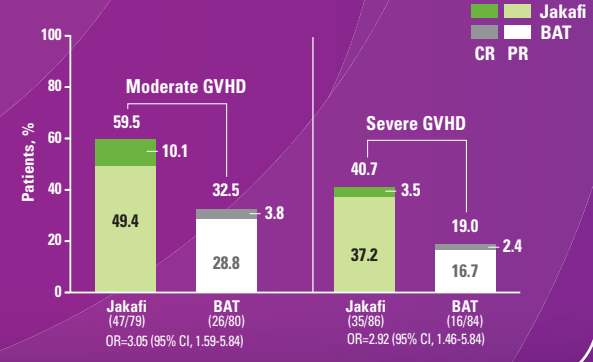
70% (116/165) with Jakafi vs 57% (94/164) with BAT[4‡]

- 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.

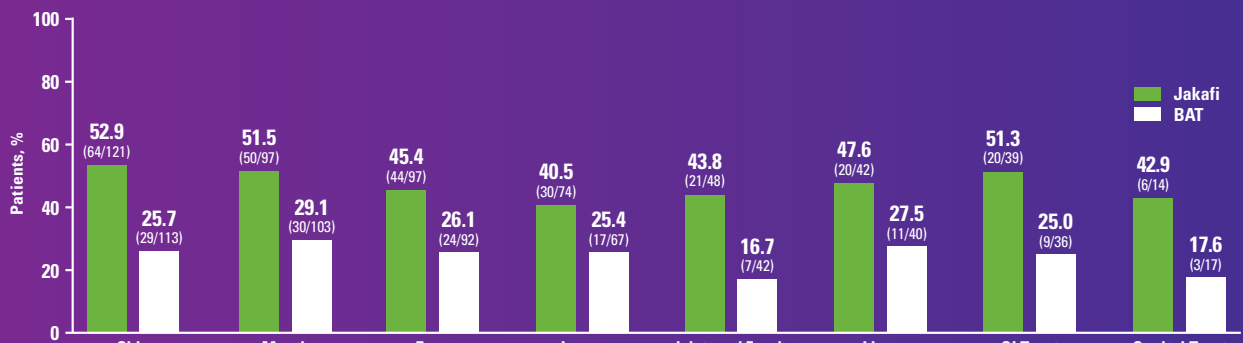
IMPORTANT SAFETY INFORMATION

- Treatment with Jakafi® (ruxolitinib) 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
- Herpes zoster infection has been reported in patients receiving Jakafi. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines
- 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

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

Jakafi® ruxolitinib (tablets)
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]

Intervene with Jakafi in your appropriate patients with cGVHD.

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- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial 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.

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 and Herpes Simplex* Herpes zoster infection has been reported in patients receiving Jakafi *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi *[see Adverse Reactions (6.2) in Full Prescribing Information]*. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines. *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 (2.8) 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 $\times 10^9$/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
Neutropenia	27	12	23	9
Thrombocytopenia	58	20	54	17

	Jakafi (N = 165)		Best Available Therapy (N = 158)	
Laboratory Test	All Grades[b] (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
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

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of Jakafi. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: • Infections and Infestations: Herpes simplex virus reactivation and/or dissemination.

DRUG INTERACTIONS: Effect of Other Drugs on Jakafi: 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 (2.6) 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 (2.6) 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:** Myelofibrosis The safety and effectiveness of Jakafi for treatment of myelofibrosis in pediatric patients have not been established. Polycythemia Vera The safety and effectiveness of Jakafi for treatment of polycythemia vera in pediatric patients have not been established. Acute Graft-Versus-Host Disease The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of pediatric patients 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. Chronic Graft-Versus-Host Disease 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 pediatric patients 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 (14.4) 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. Other Myeloproliferative Neoplasms, Leukemias, and Solid Tumors The safety and effectiveness of ruxolitinib were assessed but not established in a single-arm trial (NCT01164163) in patients with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms. The patients included 18 children (age 2 to < 12 years) and 14 adolescents (age 12 to < 17 years). Overall, 19% of patients received more than one cycle. No new safety signals were observed in pediatric patients in this trial. The safety and effectiveness of ruxolitinib in combination with chemotherapy for treatment of high-risk, de novo CRLF2 rearranged or JAK pathway–mutant Ph-like acute lymphoblastic leukemia (ALL) were assessed but not established in a single-arm trial (NCT02723994). The patients included 2 infants (age < 2 years), 42 children (age 2 to < 12 years) and 62 adolescents (age 12 to < 17 years). No new safety signals were observed in pediatric patients in this trial. 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 (2.7) 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 (2.7) 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 (2.7) 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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MEET OUR EXPERT

Kirollos Hanna, PharmD, BCPS, BCOP, FCCC, is the director of pharmacy at Minnesota Oncology and an assistant professor of pharmacy at Mayo Clinic College of Medicine and Science in Rochester, Minnesota

Legislation Needed to Overcome Chemotherapy Shortage; Expert Discusses Impact in GU Cancers

"During the most intense parts of the shortage around cisplatin, we were conserving utility in 2 patient populations—curative intent for bladder cancer and curative intent for testicular cancer—because of the limited opportunity."

Although the ongoing cisplatin shortage hasn't largely affected the genitourinary cancer space,[1] bladder cancer has proven to be an area of critical need, especially for patients with muscle-invasive bladder cancer, where the agents are used with curative intent, according to Kirollos Hanna, PharmD, BCPS, BCOP, FCCC.

In an interview with CancerNetwork, Hanna emphasized that there are few alternative treatment options for the population. However, he explained that several strategies may help to lessen the impact of the shortage in the bladder cancer space, including reducing doses where appropriate to preserve cisplatin, as well as importing platinum-based chemotherapy agents from China through the help of the FDA.[2] Hanna discussed the differences these strategies have made.

Q: Can you discuss the impact of the chemotherapy shortage in the bladder cancer space?

HANNA: When you're talking about bladder cancer, specifically in terms of GU [genitourinary] cancers, [drugs such as] cisplatin and carboplatin play a critical role at different stages for these patients. When you talk about something like kidney cancer, platinum agents and some of the drugs we've seen shortages [for] haven't played a significant role in the GU space, but bladder [cancer] has certainly been our No. 1 [space in need]. Most critically and recently have been these platinum agents that have been in shortage.

There are 3 key stages of bladder cancer. There are patients who have non–muscle-invasive disease, where we try to resect the tumors. Once these patients move into the muscle-invasive space, something like a cisplatin-containing regimen is the gold standard. It's recommended across guidelines, and across most of the literature in the data.[3] We are still trying to cure patients with muscle-invasive disease. Moving away from cisplatin-containing regimens is a significant disservice to these patients [because] carboplatin has inferior data.

For patients with muscle-invasive disease, we have 2 modalities to treat them with. There's dose-dense MVAC [methotrexate, vinblastine, doxorubicin, and cisplatin], then there's gemcitabine with cisplatin. You'll find that many GU experts try to push the envelope with dose-dense MVAC. It's a more intensive regimen but does lead to better surgical outcomes. We generally administer neoadjuvant treatment for these patients and take them to surgery. Often, a good portion of these patients do well; I would say 70% to 75% of these patients are considered cured.

When you talk about metastatic disease, even though we can get away from cisplatin in the metastatic setting, carboplatin has still

played a significant role for these patients with metastatic disease. We're still utilizing similar regimens, but we can substitute carboplatin. What we're finding in the oncology space is that the shortage of cisplatin has now led to a shortage of carboplatin due to some therapeutic interchanges across many tumor types, which has even trickled into the GU space.

For our system, when we were going through phases—we're still going through the shortage phase—[and] were in critical supply, we had patients with bladder cancer [as] one of the diagnoses where we were conserving cisplatin just because of the importance of curing [the disease]. Those were some of the strategies we've been utilizing.

[Regarding] therapeutic alternatives, if you look at [patients with] muscle-invasive [disease], there aren't many alternatives you're going to provide this population that have as good of data...outside of platinum agents, especially cisplatin-containing regimens. In the metastatic setting, though, bladder cancer has had a lot of exciting updates. Even if you do have to move away from maybe a carboplatin, or a cisplatin-based regimen in the frontline setting, a study just recently reported out—EV-103—looking at the combination of pembrolizumab with enfortumab vedotin, which is an antibody-drug conjugate with exciting outcomes for this patient population.

Now, the cohort that reported out was patients who were platinum ineligible, but regardless of that, we still saw some great responses. Again, this was an early study with early data, but within the metastatic setting, among immunotherapy, among antibody-drug conjugates, as well as a targeted therapeutic. We have a few more options, but [treating] a curative-intent patient [is] very hard for us right now.

Q: How can the importation of cisplatin from China help to alleviate the shortage in the United States?

HANNA: It's exciting to see the FDA thinking of unique strategies to bring in drug supply to alleviate some of the things we're seeing here in the United States. It makes you think, "Why haven't we been doing this over time to try to improve the supply chain in any type of drug shortages? How long have drug shortages been impacting us here in the United States?" This is an exciting opportunity for patients.

The FDA has also partnered with Apotex. They are one of the biotech companies that is responsible for the distribution of this inventory. They're working with our wholesale distributors like McKesson and Cardinal Health to get this [product] out. For patients, this is an exciting opportunity [to help] alleviate the shortage to some extent, as well as some small supply that has also been released by many of our generic manufacturers here in the United States. I don't think, in terms of manufacturing and quality assurance, that there are any major concerns greater than the state of the shortage. Although [the treatments are] coming and not vetted through the normal channels we have here in the United States with our manufacturing, certainly the shortage in terms of patient impact is much greater. I am happy we're able to bring this in.

The drug is the same concentration; what we have in the United States is a 50-mg vial. There will be a temporary [national drug code] number generated for this product as well to help in terms of billing and processing insurance claims.

Q: How has your institution responded to the shortage?

HANNA: Early in March 2023, when we started to hear about the shortage of cisplatin, [we started to think about] what's going to happen next or the implications that are going to come of this. We put ourselves [at Minnesota Oncology] in a comfortable situation around carboplatin at that time. We kept what we call in the pharmacy world par levels, or minimum levels; we kept them at a much higher level than what we would generally be accustomed to on a day-in/day-out basis. We then started to implement strategies to help utilize a little less of the drug where it didn't clinically impact our patients. This was both for carboplatin and cisplatin. Strategies like dose rounding [were utilized]. If we can dose round down to a vial size or a billing unit, we did that. We informed providers if there's a clinically appropriate situation where instead of giving a patient a 21-day cycle to go to a 28-day cycle, to do that, around carboplatin.

In many situations, it's very hard for a patient to tolerate an area under the curve [AUC] of 6, so we as providers, instead of an AUC of 6, went down to an AUC of 5. We implemented all these strategies to try to conserve some supply. We also have clinical pharmacists who evaluate all our new start regimens. One of the initiatives that we also implemented with our clinical pharmacists is [to use] a therapeutic alternative deemed to be clinically equivalent [if] it's not taking away from the impact for that patient. Our clinical pharmacists worked with our providers to determine if a patient is on a cisplatin-containing regimen or carboplatin-containing regimen, [and asked for their] opinion on the potential opportunity to conserve what we have. We've been doing well, and we're still sitting on a very good supply of carboplatin. Our planning strategies and efforts have put us in a good spot for our patients.

Q: What are potential solutions for avoiding a shortage of this magnitude in the future?

HANNA: This cisplatin shortage stemmed from [a quality-control issue with] a manufacturer, one of the largest manufacturers that make approximately 70% to 80% of the cisplatin in the country. The FDA had to shut down that plant, and they're working

with them. All of a sudden, other generic manufacturers that were generally responsible for making approximately 20% of allocations for the country, the ask is much higher, but they can't produce accordingly. We have seen numerous things that have led to shortages—sometimes [COVID-19] pandemic related, sometimes prepandemic. We've been dealing with shortages for years now.

What I find interesting is if you look at Keytruda [pembrolizumab], Opdivo [nivolumab], or Darzalex [daratumumab], if you look at these branded therapeutics, these monoclonal antibodies where so much money is invested from these larger pharmaceutical companies, we will never find a shortage of these drugs. We have never seen a shortage of these drugs. Why is it that these critical therapeutics that in many areas are tied to curative-intent regimens [have shortages]? Why do we not invest in those plants or organizations [that produce generic drugs] to keep the situation from ever happening?

Why don't we partner with different manufacturers outside of the United States, similar to what we did with China, to alleviate the cisplatin shortage? Why do we wait until it gets so critical? For something of this magnitude, for there to be a true resolution, there needs to be something that comes down from legislation that is national and governs all. I'm working with the FDA and the government to invest and fund some type of manufacturers and plants to address all of this.

Sometimes, because of the cheap cost of generic therapeutics, a lot of time, money, and effort aren't invested in that because your [return on investment] isn't there [like] you see with your big, branded products. That's what I think needs to happen at a national level for this situation to resolve. As practices and health care providers, the number of times we've seen this should have people think a little differently about shortages. ■

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†≥CR: sCR+CR.

INDICATION AND USAGE

TECVAYLI™ (teclistamab-cqyv) is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI™. Initiate treatment with TECVAYLI™ step-up dosing schedule to reduce risk of CRS. Withhold TECVAYLI™ until CRS resolves or permanently discontinue based on severity.

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and serious and life-threatening reactions, can occur in patients receiving TECVAYLI™. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold TECVAYLI™ until neurologic toxicity resolves or permanently discontinue based on severity.

TECVAYLI™ is available only through a restricted program called the TECVAYLI™ Risk Evaluation and Mitigation Strategy (REMS).

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome - TECVAYLI™ can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions. In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI™ at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%).

Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI™. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days. Clinical signs and symptoms of CRS included, but were not limited to, fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation).

Initiate therapy according to TECVAYLI™ step-up dosing schedule to reduce risk of CRS. Administer pretreatment medications to reduce risk of CRS and monitor patients following administration of TECVAYLI™ accordingly. At the first sign of CRS, immediately evaluate patient for hospitalization. Administer supportive care based on severity and consider further management per current practice guidelines. Withhold or permanently discontinue TECVAYLI™ based on severity.

TECVAYLI™ is available only through a restricted program under a REMS.

Neurologic Toxicity including ICANS - TECVAYLI™ can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

In the clinical trial, neurologic toxicity occurred in 57% of patients who received TECVAYLI™ at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most frequent neurologic toxicities were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%). With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI™.

In the clinical trial, ICANS was reported in 6% of patients who received TECVAYLI™ at the recommended dose. Recurrent ICANS occurred in 1.8% of patients. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). Less than 3% of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI™. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose with a median duration of 3 (range: 1 to 20) days. The most frequent clinical manifestations of ICANS reported were confusional state and dysgraphia. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Please see Brief Summary of full Prescribing Information, including Boxed WARNING on adjacent pages.

Choose TECVAYLI™, the first bispecific BCMA × CD3 T-cell engager given as an off-the-shelf subcutaneous injection for adult patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody[1,2]

Learn more at TECVAYLIHCP.com

MajesTEC-1 study design:

The efficacy of TECVAYLI™ was evaluated in patients with RRMM in a single-arm, open-label, multi-center, phase 1/2 study. The study included patients who had previously received at least 3 prior therapies, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

CD3, cluster of differentiation 3; CD38, cluster of differentiation 38; CI, confidence interval; CR, complete response; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or permanently discontinue TECVAYLI™ based on severity per recommendations and consider further management per current practice guidelines.

Due to the potential for neurologic toxicity, patients are at risk of depressed level of consciousness. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI™ step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves.

TECVAYLI™ is available only through a restricted program under a REMS.

TECVAYLI™ REMS - TECVAYLI™ is available only through a restricted program under a REMS called the TECVAYLI™ REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Hepatotoxicity - TECVAYLI™ can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI™ at the recommended dose in the clinical trial, there was one fatal case of hepatic failure. Elevated aspartate aminotransferase (AST) occurred in 34% of patients, with Grade 3 or 4 elevations in 1.2%. Elevated alanine aminotransferase (ALT) occurred in 28% of patients, with Grade 3 or 4 elevations in 1.8%. Elevated total bilirubin occurred in 6% of patients with Grade 3 or 4 elevations in 0.6%. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI™ or consider permanent discontinuation of TECVAYLI™ based on severity.

Infections - TECVAYLI™ can cause severe, life-threatening, or fatal infections. In patients who received TECVAYLI™ at the recommended dose in the clinical trial, serious infections, including opportunistic infections, occurred in 30% of patients, with Grade 3 or 4 infections in 35%, and fatal infections in 4.2%. Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI™ and treat appropriately. Administer prophylactic antimicrobials according to guidelines. Withhold TECVAYLI™ or consider permanent discontinuation of TECVAYLI™ based on severity.

Monitor immunoglobulin levels during treatment with TECVAYLI™ and treat according to guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Neutropenia - TECVAYLI™ can cause neutropenia and febrile neutropenia. In patients who received TECVAYLI™ at the recommended dose in the clinical trial, decreased neutrophils occurred in 84% of patients, with Grade 3 or 4 decreased neutrophils in 56%. Febrile neutropenia occurred in 3% of patients.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines. Monitor patients with neutropenia for signs of infection. Withhold TECVAYLI™ based on severity.

Hypersensitivity and Other Administration Reactions - TECVAYLI™ can cause both systemic administration-related and local injection-site reactions. Systemic Reactions - In patients who received TECVAYLI™ at the recommended dose in the clinical trial, 1.2% of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue. Local Reactions - In patients who received TECVAYLI™ at the recommended dose in the clinical trial, injection-site reactions occurred in 35% of patients, with Grade 1 injection-site reactions in 30% and Grade 2 in 4.8%. Withhold TECVAYLI™ or consider permanent discontinuation of TECVAYLI™ based on severity.

Embryo-Fetal Toxicity - Based on its mechanism of action, TECVAYLI™ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECVAYLI™ and for 5 months after the last dose.

Adverse Reactions - The most common adverse reactions (≥20%) were pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, upper respiratory tract infection, nausea, headache, pneumonia, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥20%) were decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.

cp-322928v1

References: 1. TECVAYLI™ (teclistamab-cqyv) Prescribing Information. Janssen Biotech, Inc., Horsham, PA 19044. **2.** US Food and Drug Administration. FDA approves teclistamab-cqyv for relapsed or refractory multiple myeloma. Accessed November 9, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma

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Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Brief Summary of Prescribing Information for TECVAYLI™ (teclistamab-cqyv)

TECVAYLI™ (teclistamab-cqyv) injection, for subcutaneous use

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI. Initiate treatment with TECVAYLI step-up dosing schedule to reduce risk of CRS. Withhold TECVAYLI until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and serious and life-threatening reactions, can occur with TECVAYLI. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold TECVAYLI until neurologic toxicity resolves or permanently discontinue based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Because of the risk of CRS and neurologic toxicity, including ICANS, TECVAYLI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TECVAYLI REMS *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

TECVAYLI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome

TECVAYLI can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions *[see Adverse Reactions]*.

In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days.

Clinical signs and symptoms of CRS included, but were not limited to, fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation).

Initiate therapy according to TECVAYLI step-up dosing schedule to reduce risk of CRS *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information]*. Administer pretreatment medications to reduce risk of CRS and monitor patients following administration of TECVAYLI accordingly *[see Dosage and Administration (2.2, 2.4) in Full Prescribing Information]*.

At the first sign of CRS, immediately evaluate patient for hospitalization. Administer supportive care based on severity and consider further management per current practice guidelines. Withhold or permanently discontinue TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

TECVAYLI is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Neurologic Toxicity including ICANS

TECVAYLI can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) *[see Adverse Reactions]*.

In the clinical trial, neurologic toxicity occurred in 57% of patients who received TECVAYLI at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most frequent neurologic toxicities were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%).

With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI.

In the clinical trial, ICANS was reported in 6% of patients who received TECVAYLI at the recommended dose *[see Adverse Reactions]*. Recurrent ICANS occurred in 1.8% of patients. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). Less than 3% of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose with a median duration of 3 (range: 1 to 20) days. The most frequent clinical manifestations of ICANS reported were confusional state and dysgraphia. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or permanently discontinue TECVAYLI based on severity per recommendations and consider further management per current practice guidelines *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Due to the potential for neurologic toxicity, patients receiving TECVAYLI are at risk of depressed level of consciousness *[see Adverse Reactions]*. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

TECVAYLI is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

TECVAYLI REMS

TECVAYLI is available only through a restricted program under a REMS called the TECVAYLI REMS because of the risks of CRS and neurologic toxicity, including ICANS *[see Warnings and Precautions]*.

Notable requirements of the TECVAYLI REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving TECVAYLI about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with Patient Wallet Card.
- Pharmacies and healthcare settings that dispense TECVAYLI must be certified with the TECVAYLI REMS program and must verify prescribers are certified through the TECVAYLI REMS program.
- Wholesalers and distributers must only distribute TECVAYLI to certified pharmacies or healthcare settings.

Further information about the TECVAYLI REMS program is available at www.TECVAYLIREMS.com or by telephone at 1-855-810-8064.

Hepatotoxicity

TECVAYLI can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI at the recommended dose in the clinical trial, there was one fatal case of hepatic failure. Elevated aspartate aminotransferase (AST) occurred in 34% of patients, with Grade 3 or 4 elevations in 1.2%. Elevated alanine aminotransferase (ALT) occurred in 28% of patients, with Grade 3 or 4 elevations in 1.8%. Elevated total bilirubin occurred in 6% of patients with Grade 3 or 4 elevations in 0.6%. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Infections

TECVAYLI can cause severe, life-threatening, or fatal infections. In patients who received TECVAYLI at the recommended dose in the clinical trial, serious infections, including opportunistic infections, occurred in 30% of patients, with Grade 3 or 4 infections in 35%, and fatal infections in 4.2% *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI and treat appropriately. Administer prophylactic antimicrobials according to guidelines *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor immunoglobulin levels during treatment with TECVAYLI and treat according to guidelines, including infection precautions and antibiotic or antiviral prophylaxis *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Neutropenia

TECVAYLI can cause neutropenia and febrile neutropenia. In patients who received TECVAYLI at the recommended dose in the clinical trial, decreased neutrophils occurred in 84% of patients, with Grade 3 or 4 decreased neutrophils in 56%. Febrile neutropenia occurred in 3% of patients *[see Adverse Reactions]*.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines.

Monitor patients with neutropenia for signs of infection.

Withhold TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Hypersensitivity and Other Administration Reactions

TECVAYLI can cause both systemic administration-related reactions and local injection-site reactions.

Systemic Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, 1.2% of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue.

Local Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, injection-site reactions occurred in 35% of patients with Grade 1 injection-site reactions in 30% and Grade 2 in 4.8%.

Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action, TECVAYLI may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECVAYLI and for 5 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are also described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions]*
- Neurologic Toxicity including ICANS *[see Warnings and Precautions]*
- Hepatotoxicity *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Neutropenia *[see Warnings and Precautions]*
- Hypersensitivity and Other Administration Reactions *[see Warnings and Precautions]*

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

MajesTEC-1

The safety of TECVAYLI was evaluated in MajesTEC-1 *[see Clinical Studies (14) in Full Prescribing Information]* which included adult patients with relapsed or refractory multiple myeloma. Patients received step-up doses of 0.06 mg/kg and 0.3 mg/kg of TECVAYLI followed by TECVAYLI 1.5 mg/kg, subcutaneously once weekly (N=165). Among patients who received TECVAYLI, 47% were exposed for 6 months or longer and 7% were exposed for one year or longer.

The median age of patients who received TECVAYLI was 64 years (range: 33 to 84 years); 58% were male; 81% were White, 13% were Black or African American, and 2% were Asian.

Serious adverse reactions occurred in 54% of patients who received TECVAYLI. Serious adverse reactions in >2% of patients included pneumonia (15%), cytokine release syndrome (8%), sepsis (6%), general physical health deterioration (6%), COVID-19 (6%), acute kidney injury (4.8%), pyrexia (4.8%), musculoskeletal pain (2.4%), and encephalopathy (2.4%).

Fatal adverse reactions occurred in 5% of patients who received TECVAYLI, including COVID-19 (1.8%), pneumonia (1.8%), septic shock (0.6%), acute renal failure (0.6%), and hemoperitoneum (0.6%).

Permanent discontinuation of TECVAYLI due to adverse reactions occurred in 1.2% of patients. Adverse reactions resulting in permanent discontinuation of TECVAYLI included pneumonia (adenoviral and pneumocystis jirovecii pneumonia in the same patient) and hypercalcemia.

Dosage interruptions of TECVAYLI due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in >5% of patients included neutropenia, pneumonia, pyrexia, cytokine release syndrome, upper respiratory tract infection, and COVID-19.

The most common adverse reactions (≥20%) were pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, upper respiratory tract infection, nausea, headache, pneumonia, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥20%) were decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.

Table 1 summarizes the adverse reactions in MajesTEC-1.

Table 1: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1

Adverse Reactions	TECVAYLI (N=165)	
	Any Grade (%)	Grade 3 or 4 (%)
General disorders and administration site conditions		
Pyrexia	76	3#
Injection site reaction[1]	37	0.6#
Fatigue[2]	33	2.4#
Chills	16	0
Pain[3]	15	1.8#
Edema[4]	13	0
Immune system disorders		
Cytokine release syndrome	72	0.6#
Hypogammaglobulinemia[5]	11	1.2#
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[6]	44	4.2#
Bone pain	16	3#
Infections		
Upper respiratory tract infection[7]	26	2.4#
Pneumonia[8*]	24	15
Urinary tract infection[9]	11	5#

TECVAYLI™ (teclistamab-cqyv) injection

Table 1: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1 (continued)

Adverse Reactions	TECVAYLI (N=165)	
	Any Grade (%)	Grade 3 or 4 (%)
Gastrointestinal disorders		
Nausea	25	0.6#
Diarrhea	21	2.4#
Constipation	18	0
Vomiting	12	0.6#
Nervous system disorders		
Headache	25	0.6#
Motor dysfunction[10]	16	0
Sensory neuropathy[11]	15	1.2#
Encephalopathy[12]	13	0
Vascular disorders		
Hypotension	18	1.2#
Hemorrhage[13*]	12	1.8
Hypertension[14]	12	4.8#
Respiratory, thoracic, and mediastinal disorders		
Hypoxia	18	1.8
Cough[15]	15	0
Cardiac disorders		
Cardiac arrhythmia[16]	16	1.8
Metabolism and nutrition disorders		
Decreased appetite	11	0.6#
Renal and urinary disorders		
Acute kidney injury[17]	11	3.6

Adverse reactions were graded based on CTCAE Version 4.03, with the exception of CRS, which was graded per ASTCT 2019 criteria.

[1] Injection site reaction includes application site erythema, injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site edema, injection site pruritus, injection site rash, injection site reaction and injection site swelling.

[2] Fatigue includes asthenia and fatigue.

[3] Pain includes ear pain, flank pain, groin pain, oropharyngeal pain, pain, pain in jaw, toothache and tumor pain.

[4] Edema includes face edema, fluid overload, fluid retention, edema peripheral and peripheral swelling.

[5] Hypogammaglobulinemia includes hypogammaglobulinemia and hypoglobulinemia.

[6] Musculoskeletal pain includes arthralgia, back pain, muscle discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain and pain in extremity.

[7] Upper respiratory tract infection includes bronchitis, influenza like illness, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tracheitis, upper respiratory tract infection and viral upper respiratory tract infection.

[8] Pneumonia includes COVID-19 pneumonia, enterobacter pneumonia, lower respiratory tract infection, metapneumovirus pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia klebsiella, pneumonia moraxella, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia staphylococcal and pneumonia viral.

[9] Urinary tract infection includes cystitis, cystitis escherichia, cystitis klebsiella, escherichia urinary tract infection, urinary tract infection and urinary tract infection bacterial.

[10] Motor dysfunction includes cogwheel rigidity, dysgraphia, dysphonia, gait disturbance, hypokinesia, muscle rigidity, muscle spasms, muscular weakness, peroneal nerve palsy, psychomotor hyperactivity, tremor and VIth nerve paralysis.

[11] Sensory neuropathy includes dysesthesia, hypoesthesia, hypoesthesia oral, neuralgia, paresthesia, paresthesia oral, peripheral sensory neuropathy, sciatica and vestibular neuronitis.

[12] Encephalopathy includes agitation, apathy, aphasia, confusional state, delirium, depressed level of consciousness, disorientation, dyscalculia, hallucination, lethargy, memory impairment, mental status changes and somnolence.

[13] Hemorrhage includes conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemoperitoneum, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage and subdural hematoma.

[14] Hypertension includes essential hypertension and hypertension.

[15] Cough includes allergic cough, cough, productive cough and upper-airway cough syndrome.

[16] Cardiac arrhythmia includes atrial flutter, cardiac arrest, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia and ventricular tachycardia.

[17] Acute kidney injury includes acute kidney injury and renal impairment.

Only grade 3 adverse reactions occurred.

* Includes the following fatal adverse reactions: hemorrhage (n=1), pneumonia (n=3).

Clinically relevant adverse reactions in <10% of patients who received TECVAYLI included febrile neutropenia, sepsis, ICANS, seizure, Guillain-Barré syndrome, hepatic failure, and new onset or reactivated viral infections (including adenovirus, hepatitis B virus (HBV), cytomegalovirus (CMV), varicella zoster virus (VZV), and herpes simplex virus (HSV)).

Table 2 summarizes laboratory abnormalities in MajesTEC-1.

Table 2: Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1

Laboratory Abnormality	TECVAYLI (N=165[1]) All Grades (%)	TECVAYLI (N=165[1]) Grade 3 or 4 (%)
Hematology		
Lymphocyte count decreased	92	84
White blood cell decreased	86	41
Neutrophil count decreased	84	56
Platelet count decreased	71	22
Hemoglobin decreased	67	33
Chemistry		
Albumin decreased	68	6
Alkaline phosphatase increased	42	2.4
Phosphorus decreased	38	13
Gamma-glutamyl transferase increased	37	8
Sodium decreased	35	10
Aspartate aminotransferase increased	34	1.2
Calcium (corrected) decreased	31	1.2
Creatinine increased	30	3

[1] The denominator used to calculate the rate varied from 164 to 165 based on the number of patients with a baseline value and at least one post-treatment value.

Laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

DRUG INTERACTIONS

TECVAYLI causes release of cytokines *[see Clinical Pharmacology (12.2) in Full Prescribing Information]* that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of TECVAYLI step-up dosing schedule up to 7 days after the first treatment dose and during and after CRS *[see Warnings and Precautions]*. Monitor for toxicity or concentrations of drugs that are CYP substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant CYP substrate drug as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action, TECVAYLI may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on the use of TECVAYLI in pregnant women. No animal reproductive or developmental toxicity studies have been conducted with TECVAYLI. Teclistamab-cqyv causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, teclistamab-cqyv has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

TECVAYLI is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI should be considered.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation

Risk Summary

There are no data on the presence of teclistamab-cqyv in human milk, the effect on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to TECVAYLI are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with TECVAYLI and for 5 months after the last dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

TECVAYLI™ (teclistamab-cqyv) injection

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 5 months after the last dose of TECVAYLI.

Pediatric Use

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

Geriatric Use

Of the 165 patients with relapsed or refractory multiple myeloma treated with TECVAYLI in MajesTEC-1 at the recommended dosage, 48% were 65 years of age or older, and 15% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients 65 to 74 years of age compared to younger patients. There is an insufficient number of patients 75 years of age or older to assess whether there are differences in safety or effectiveness.

PATIENT COUNSELING INFORMATION

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

Cytokine Release Syndrome (CRS)

Discuss the signs and symptoms associated with CRS, including fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of CRS. Advise patients that they will be hospitalized for 48 hours after administration of all doses within the TECVAYLI step-up dosing schedule *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neurologic Toxicity including ICANS

Discuss the signs and symptoms associated with neurologic toxicity, including ICANS, including headache, confusion, dysgraphia, motor dysfunction, neuropathy, or encephalopathy. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of neurologic toxicity. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

TECVAYLI REMS

TECVAYLI is available only through a restricted program called TECVAYLI REMS. Inform patients that they will be given a TECVAYLI Patient Wallet Card that they should carry with them at all times and show to all of their healthcare providers. This card describes signs and symptoms of CRS and neurologic toxicity which, if experienced, should prompt the patient to immediately seek medical attention *[see Warnings and Precautions]*.

Hepatotoxicity

Advise patients that liver enzyme elevations may occur and that they should report symptoms that may indicate liver toxicity, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions]*.

Infections

Discuss the signs and symptoms of infection *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neutropenia

Discuss the signs and symptoms associated with neutropenia and febrile neutropenia *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Hypersensitivity and Other Administration Reactions

Advise patients to immediately seek medical attention for any signs and symptoms of systemic administration-related reactions. Advise patients that local injection-site reactions may occur and to report any severe reactions *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with TECVAYLI and for 5 months after the last dose *[see Warnings and Precautions and Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with TECVAYLI and for 5 months after the last dose *[see Use in Specific Populations]*.

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cp-337020v1

Spinal ATRT and Radiotherapy Case Report in an Adult Man

Fatma Betül Ayrak[1], Süheyla Aytaç Arslan[1,2], Yılmaz Tezcan[1,2]

ABSTRACT

Atypical teratoid/rhabdoid tumor (ATRT) is usually seen in children and is usually located intracranially; it generally has a poor prognosis. Due to this tumor's rarity and the lack of randomized controlled trials, it has been challenging to define optimal therapy and to make treatment advances. Treatment options are surgery, chemotherapy, and radiotherapy.[1] This is a case report of a man with spinal ATRT, aged 44 years, who was treated with radiotherapy.

FIGURE 1. **Preoperative MRI Cervical (Axial and Sagittal)**

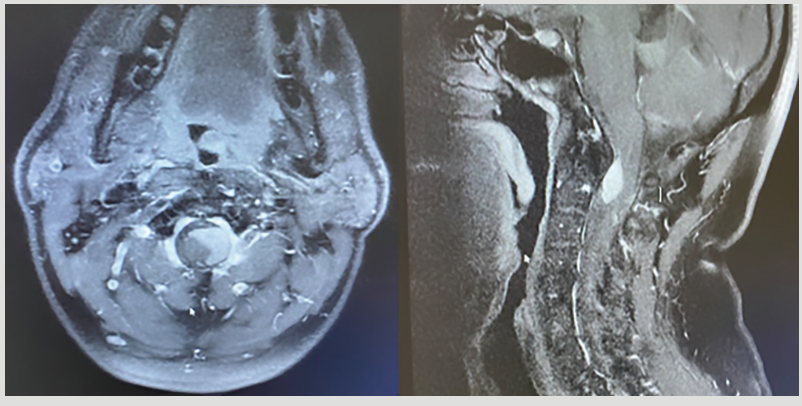
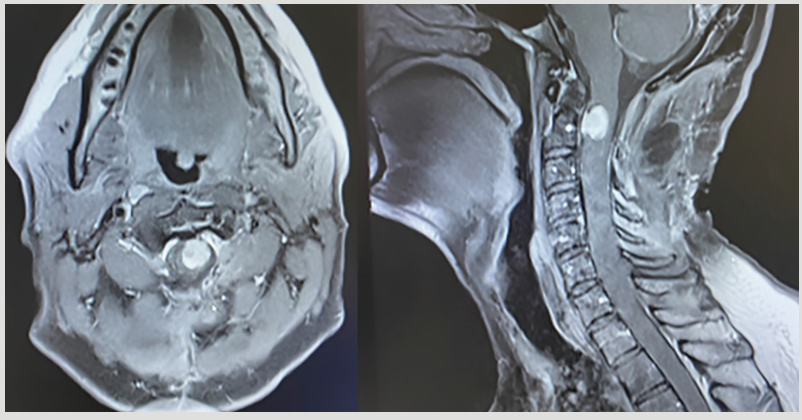


FIGURE 2. **Postoperative MRI Cervical, Recurrence of Mass (Axial and Sagittal)**



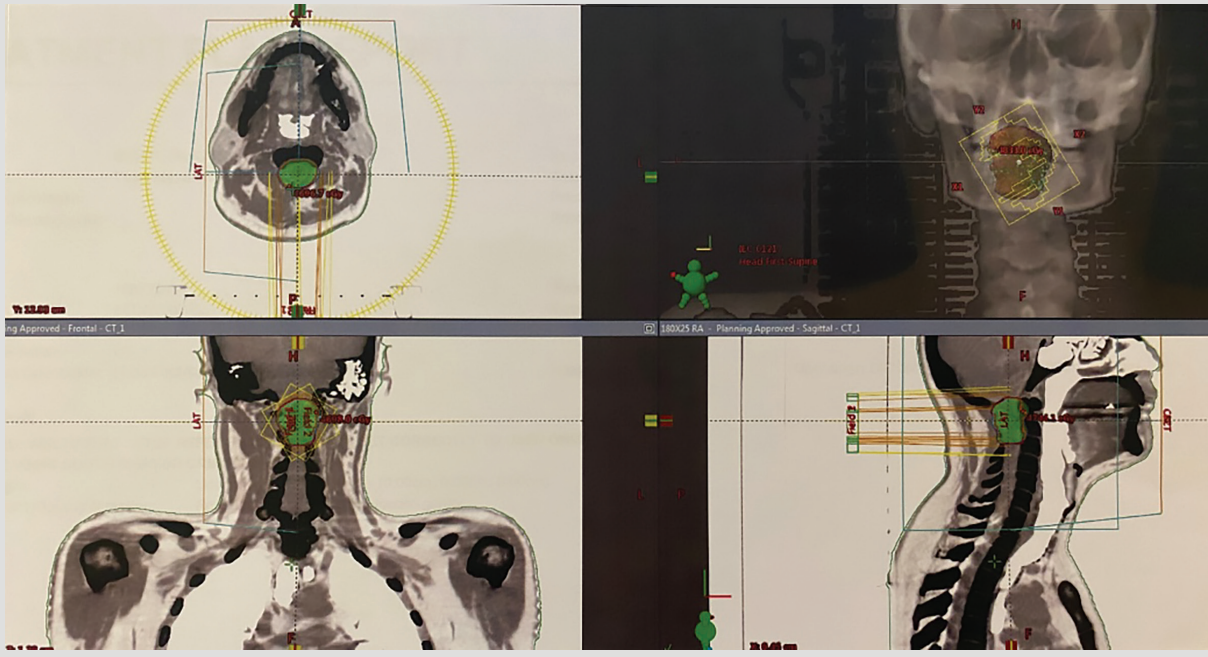
Introduction

Atypical teratoid/rhabdoid tumor (ATRT) is a malignant embryonal tumor of the central nervous system (CNS) that is composed of rhabdoid cells, with or without fields resembling classical primitive neuroectodermal tumor. This tumor typically affects children younger than 3 years, and cases in individuals older than 18 years are rare, with an estimated lifetime risk of less than 1 in 1,000,000.[2-4]

Typically, a patient presents with an intracranial lesion. Approximately two-thirds of these tumors are located in the posterior fossa and one-fourth of them reside supratentorially; spinal involvement is very uncommon. The most suggestive radiographic feature of an ATRT is a posterior fossa mass, especially in the cerebellopontine angle, in a child younger than 2 years, showing intense enhancement, hyperdensity on CT scans, and hemorrhagic foci on T1-weighted MRI.[5,6]

The prognosis for patients with ATRT remains dismal, with historic median overall survival (OS) ranging from 6 to 18 months.[1] In the 10 adult

FIGURE 3. **Radiotherapy Plan Images**



patients whose survival data have been reported in the literature, median survival was 15 to 18 months, although it ranged from 2 weeks to more than 17 years.[7]

Due to this tumor's rarity and the lack of randomized controlled trials, it has been challenging to define optimal therapy and to make treatment advances. Radiation is an effective component of therapy, but it is avoided in patients younger than 3 years due to long-term neurocognitive sequelae. Most long-term survivors undergo radiation therapy as a part of their upfront or salvage therapy, and it has been suggested that sequencing the radiation earlier in therapy may improve outcomes. There is no standard curative chemotherapeutic regimen, but anecdotal reports advocate the use of intensive therapy with alkylating agents, high-dose methotrexate, or therapy that combines high-dose chemotherapy with stem cell transplant.[8]

Case Report

History and Examination

A male patient, aged 44 years, presented with neck pain and bilateral upper extremity paralysis. He had no previous known disease. In the preoperative MRI, a 25 x 17 x 19 mm intradural extramedullary mass extending from the cervicomedullary junction to the cervical (C) 2 to C3 vertebra level, causing compression on the left ventrolateral [side] of the spinal cord, was observed.

The lesion appeared isointense with gray matter on the T1 to T2 images. There was intense contrast enhancement in the lesion after the application of an intravenous contrast agent (**Figure 1**).

Initial Treatment: Surgery

The tumor was entered with a median suboccipital incision; C1 partial and C2 to C3 total laminectomy was performed. The intradural tumor was totally excised.

Pathological Findings

In serial sections of the material, on the background of thin-walled abundant vascular structures and thin muscle fibrotic bands, there was relatively narrow, vesicular, or slightly eosinophilic cytoplasm; it was interspersed with fine eosinophilic granular cytoplasmic inclusions, and it was coarse, round or oval, vesicular, pleomorphic, nucleolar prominent and irregular in contour. A hypercellular tumoral lesion consisting of atypical cells, some with nuclei showing frequent mitotic activity, was observed. In the immunohistochemical study, tumor cells were found to be diffuse positive with vimentin and CD99; diffuse negative (staining loss) with INI-1; PAN-CK focal positive; EMA rare weak positive; CD 138 focal weak positive; SALL-4 weak positive; and GFAP, CD34, ERG, S-100, HMB-45, SOX-10, SMA, desmin, CD117, and LCA were all negative. The tumor gave 40% to 45% positive reaction with Ki-67 in the most intense area.

FIGURE 4. **Postradiotherapy MRI Cervical**

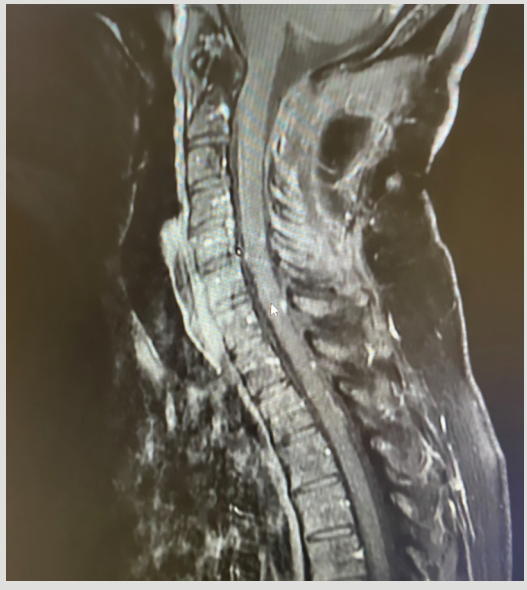
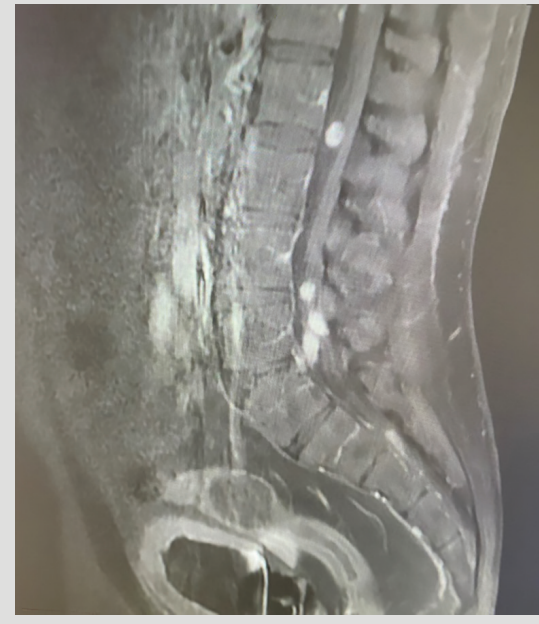


FIGURE 5. **Postradiotherapy MRI Sacral**



Diagnosis: Atypical Teratoid Rhabdoid Tumor

Postoperative Process

Six months after the surgery, the patient presented with quadriparesis that had developed within the previous week. He had stool and urinary incontinence as well as swallowing dysfunction. The MRI showed nodular mass lesions at the C2 level, located in the intradural extramural; they showed intense contrast enhancement, involving a segment of approximately 2 cm and reaching 0.8 cm at the widest part (**Figure 2**).

Surgery was not considered for the patient in his current state; instead, radiotherapy treatment was planned.

Radiotherapy

The CT simulation of the patient was performed in the supine position with a head-neck mask (**Figure 3**). We contoured the gross total volume (GTV) and all gross disease on the MRI. We created the clinical target volume (CTV) by giving a 1-cm margin to the GTV. We calculated the planning target volume by giving a 2-mm margin to CTV. Using the Hyperarc technique, we planned radiotherapy treatments totaling 4860 cGy: 180 cGy x 27 fractions. The medulla spinalis maximum dose was 49 Gy.

Radiotherapy Process

The patient started to move his fingers and felt urine and stool after the fourth fraction. He started walking with a walker after the 14th fraction. When treatment was completed, upper and lower extremity motor strength was 4/5 bilaterally. Additionally, 4 x 4-mg steroid treatment had begun at the same time as radiotherapy started, but as the symptoms regressed, the dose was reduced by half and then, later, stopped altogether.

Postradiotherapy Process

The patient, who came to the control after 2 months, had no adverse effects. No residual disease was found on the cervical MRI (**Figure 4**). However, nodular-shaped tumoral implants, all smaller than 1 cm, were noted on the spinal cord surface. Continuity of the implants was observed, starting from the distal thoracic spine segments on the thoracic, lumbar, and sacral MRIs and continuing up to the conus, suggesting the leptomeningeal spread of the existing tumor. In addition, leptomeningeal implants of neoplastic nature, the largest of which was approximately 1.1 cm in diameter, were observed within the fibers of the cauda equina in the distal conus medullaris (**Figure 5**).

The patient was started on a chemotherapy protocol of vincristine, doxorubicin, and cyclophosphamide. Craniospinal irradiation was also planned for the patient, because regression in the leptomeningeal involvement areas were seen in the MRI that was taken after 6 cycles of chemotherapy.

Craniospinal Irradiation

The CT simulation of the patient was performed in the supine position with

a head-neck mask. The target volume was to the craniospinal area. Radiotherapy was planned at a dose of 36 Gy/20 fx with an intensity-modulated radiotherapy technique.

Post Craniospinal Irradiation

The patient, who came to the control 3 months after treatment, had no adverse effects. No pathological finding was seen on the craniospinal MRI.

Discussion

Spinal ATRTs in adults are more than just rare: Only 10 patients—including the present one—have been reported in the literature.[6] Case reports and case series report an overall poor prognosis for such patients, with a median survival of 20 months. However, there are cases of adult patients with ATRT who have survived beyond 17 years from diagnosis. Preliminary results from the first prospective clinical trial in children with ATRT indicate that intensive multimodality treatment, including resection, CNS radiotherapy, and chemotherapy—based on the Intergroup Rhabdomyosarcoma Study Group III protocol—may lead to longer survival, with an estimated mean (SD) 2-year OS rate of 70% (10%). Although the use of radiotherapy has been controversial, given the associated risk of adverse effects on the neurocognitive development of young children, emerging nonrandomized evidence indicates that radiotherapy may be important to achieve long-term survival in patients with ATRT.[2,9,10]

In a prospective study of 25 patients (median age, 26 months; range, 2.4 months to 19.5 years) by Chi et al, all received intensive multimodal treatment including surgery, induction chemotherapy, chemoradiotherapy, consolidation, and continuous chemotherapy. The study results indicated that this intensive multimodality treatment regimen led to improvement in OS and progression-free survival. However, the disease recurred in 8 patients between 2 weeks and 2.2 years after diagnosis.[11]

Because adult ATRT is so rare, a consistent treatment protocol has not yet been established. Currently, the management of ATRT in adults is based on data extrapolated from the pediatric literature. However, a multimodal approach that includes surgical resection, radiation, and chemotherapy has been taken

TABLE. **Adult Spinal ATRT in the Literature[13-20]**

Year	Study authors	Patient age (years)	Gender	Vertebral level	Surgery	Radiotherapy	Relapses
2007	Zarovnaya et al	43	F	C4-C6	STR	5000 cGy/25 fx	Yes
2013	Kanoto et al	60	M	C5-T1	Unknown	Unknown	Unknown
2014	Sinha et al	65	M	T12	STR	5100 cGy/30 fx	Yes
2015	Gotti et al	19	F	L4-5	STR	5400 cGy/30 fx	Yes
2016	Li et al	23	F	L2-4	Inoperable	36 Gy to craniospinal axis, 20 Gy to lumbar region	Yes
2017	McGinity et al	43	F	C1-3	GTR	5400 cGy/28 fx	No
2019	Neromyliotis et al	19	F	L4-S2	STR	5400 cGy/30 fx	Yes
2022	Zarei et al	17	F	L2	STR	36 Gy to craniospinal axis and localization to the tumor bed, to a total dose of 5220 cGy	No
2022	Broggi et al	Unknown	Unknown	L4-5	Unknown	Unknown	Yes

C, cervical; F, female; fx, fraction; GTR, gross total resection; L, lumbar; M, male; STR, subtotal resection; T, thoracic.

in treating adult sellar region ATRT.[2,10]

ATRTs are characterized by a loss of the long arm of chromosome 22, which in turn results in a loss of the *hSNF5/INI-1* gene. The loss of INI1 expression is now regarded as a pathognomonic finding of an ATRT (**Table**).[8,12]

Conclusions

In this case report, radiotherapy used in spinal ATRT treatment in an adult patient was shown to improve the patient's symptoms.

More studies are needed for more accurate results. ■

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The study has no sponsor.

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RAPID REPORTER

ONCOLOGY Reviews Key Presentations From the
2023 Kidney Cancer Research Summit

Lenvatinib/Pembrolizumab Elicits Responses in Metastatic Renal Cell Carcinoma

Follow-up data from the phase 1/2 111/KEYNOTE-146 trial (NCT02501096) of lenvatinib (Lenvima) plus pembrolizumab (Keytruda) in patients with metastatic renal cell carcinoma, including a subset of patients who had received or were naïve to checkpoint inhibitors, demonstrated a clinical benefit.

Patients who were treatment-naïve (n = 22) achieved an objective response rate of 77.5% (95% CI, 54.6%-82.2%) compared with 52.9% (95% CI, 27.8%-77.0%) in previously treated, immune checkpoint inhibitor (ICI)–naïve patients (n = 17) and 58.7% (95% CI, 48.6%-60.2%) in ICI-pretreated patients (n = 104). The median duration of response (DOR) was 24.2 months (95% CI, 10.3-40.4), 9.0 months (95% CI, 3.5-not estimable), and 14.1 months (95% CI, 10.6-16.4), respectively.

When responders were evaluated by response duration, 58.8%, 33.3%, and 34.4% of treatment-naïve, previously treated ICI-naïve, and ICI-pretreated patients, respectively, had responses lasting at least 18 months. For 24 or more months, these rates were 47.1%, 22.2%, and 24.6% and for at least 30 months were 41.2%, 22.2%, and 8.2%.

Treatment-related adverse events (AEs) of grade 3 or higher were reported in 63.5% of patients who were ICI-pretreated and in 66.2% of patients overall. In all patients, these included diarrhea (6.9%), fatigue (5.5%), proteinuria (11.0%), hypertension (22.1%), nausea (1.4%), decreased appetite (1.4%), and arthralgia (2.8%).

Clinically significant AEs of grade 3 or higher (47.6%) in all patients included hypertension (25.5%), proteinuria (11.0%), hemorrhage (3.4%), renal events (4.1%), hepatotoxicity (4.8%), arterial thromboembolic events (3.4%), and cardiac dysfunction (2.1%). AEs of special interest (13.1%) were adrenal insufficiency (1.4%) and colitis (3.4%).

Reference
Lee CH, Shah AY, Rao A, et al. Final database lock results of the phase 2 cohort of lenvatinib + pembrolizumab for progressive disease after a PD-1/PD-L1-containing therapy in metastatic clear cell renal cell carcinoma. Presented at: 2023 Kidney Cancer Research Summit; July 13-14, 2023; Boston, MA. Poster 65.

→ **To view the full article and references, visit:** Cancernetwork.com/KCRS23_KN146

Olaparib Improves Efficacy in *BAP1*-Mutated Renal Cell Carcinoma

The interim analysis of the phase 2 ORCHID trial (NCT03786796) showed favorable antitumor responses when patients with renal cell carcinoma *BAP1* or other DNA repair gene mutations were treated with olaparib (Lynparza).

Treatment with the agent resulted in a disease control rate of 18% in this population (n = 11). The objective response rate with olaparib was 9%, and the stable disease (SD) rate was 18%. Moreover, 27% of patients experienced tumor reduction, including 2 patients with *BAP1*-mutated disease. One of those patients achieved a durable partial response to treatment, and the other experienced prolonged SD lasting 10 months.

Overall, olaparib monotherapy was found to be well tolerated, with limited grade 3 or higher adverse effects (AEs) observed. The most common treatment-related AEs reported in 2 or more of patients who received the agent included anemia (any grade, 69.2%; ≤ grade 3, 23.1%), diarrhea (30.8%; 0%), fatigue (30.8%; 0%), increased creatinine level (23.1%; 0%), musculoskeletal pain (23.1%; 7.7%), nausea (23.1%; 7.7%), hyperkalemia (15.4%; 7.7%), and peripheral edema (15.4%; 0%), respectively.

Reference
Ged Y, Elias R, Rifkind I, et al. Interim analysis of the ORCHID study (A phase II study of Olaparib in Metastatic Renal cell carcinoma patients HarborIng BAP1 or other DNA repair gene mutations). Presented at: 2023 Kidney Cancer Research Summit; July 13-14, 2023; Boston, MA. Abstract 32.

→ **To view the full article and references, visit:** Cancernetwork.com/KCRS23_ORCHID

Pembrolizumab Prolongs DFS Across Clear Cell RCC Disease Subgroups

Treatment with adjuvant pembrolizumab (Keytruda) improved disease-free survival vs placebo among patients with clear cell renal cell carcinoma (RCC) regardless of disease risk or disease stage, according to data from an exploratory analysis of the phase 3 KEYNOTE-564 study (NCT03142334).

The estimated median disease-free survival (DFS) for patients with The University of California Los Angeles Integrated Staging System (UISS) intermediate-risk disease was not reached (NR) in either the pembrolizumab arm or the placebo arm (HR, 0.65; 95% CI, 0.48-0.88). The 24-month DFS rates in each respective arm were 81.5% and 72.4%.

For those with UISS high-risk disease, the estimated median DFS was NR (95% CI, 25.8-NR) in the pembrolizumab arm vs 40.5 months (95% CI, 19.4-NR) in the placebo arm, with 24-month DFS rates of 65.0% and 55.9% in each respective arm (HR, 0.77; 95% CI, 0.49-1.20). The estimated median DFS among patients following nephrectomy and complete resection of metastasis was NR (95% CI, 25.7-NR) with pembrolizumab vs 11.6 months (95% CI, 5.6-NR) with placebo, and the respective 24-month DFS rates were 78.4% and 37.9% in each arm (HR, 0.28; 95% CI, 0.12-0.66).

The DFS and distant metastasis–free survival benefits observed with pembrolizumab in the intent-to-treat population extended across all subgroups based on UISS disease risk and American Joint Committee on Cancer primary tumor stage and lymph node involvement. The investigators advised interpreting these data with caution based on the small sample size of some patient subgroups and noted that they did not perform formal statistical testing for the post hoc analysis.

Reference
Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab for renal cell carcinoma across UCLA integrated staging system risk groups and disease stage: subgroup analyses from the KEYNOTE-564 study. Presented at the 2023 Kidney Cancer Research Summit; July 13-14, 2023; Boston, MA. Abstract 69.

→ **To view the full article and references, visit:** Cancernetwork.com/KCRS23_KEYNOTE-564

Lenvatinib/Pembrolizumab Improves Responses Vs Sunitinib in Advanced Renal Cell Carcinoma

Combining lenvatinib (Lenvima) with pembrolizumab (Keytruda) produced a higher objective response rate (ORR) vs sunitinib (Sutent) in the patients with advanced renal cell carcinoma, according to findings from the final overall survival (OS) analysis of the phase 3 CLEAR study (NCT02811861).

The ORR was 71.3% (95% CI, 66.6%-76.0%) among patients receiving lenvatinib plus pembrolizumab compared with 36.7% (95% CI, 31.7%-41.7%) among those receiving sunitinib. Of those with a response to lenvatinib plus pembrolizumab, 53.0% experienced a partial response (PR), 18.3% had a complete response (CR), and 18.9% had stable disease. Of those with a PR, 16.6% had a PR with at least a 75% reduction in tumor size, 23.7% had a PR with a reduction between 50% and less than 75%, and 12.7% had a PR with a reduction between 30% and less than 50%.

The median duration of response (DOR) was 26.7 months (95% CI, 22.8-34.6) among patients receiving lenvatinib plus pembrolizumab vs 14.7 months (95% CI, 9.4-18.2) among those receiving sunitinib.

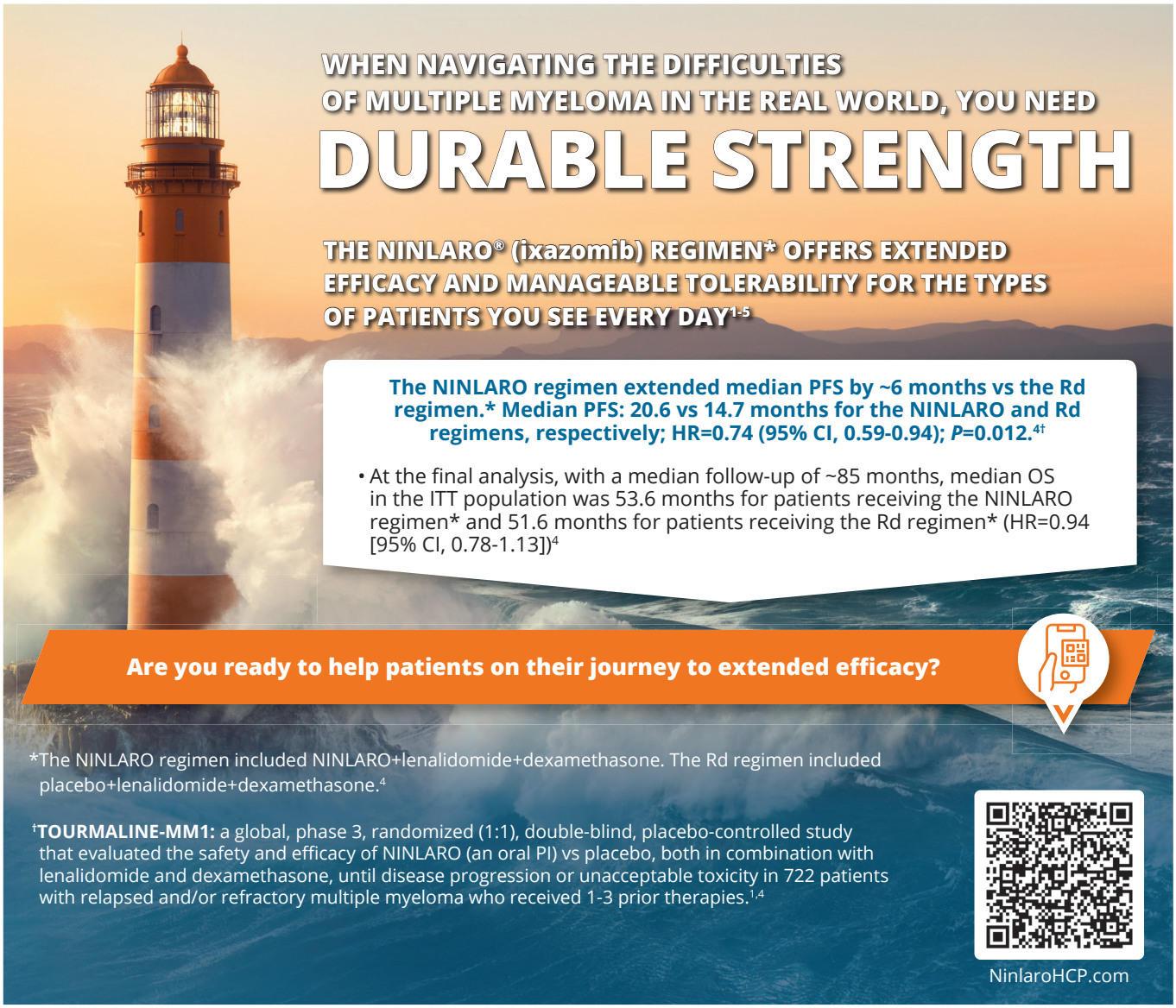
For patients receiving lenvatinib plus pembrolizumab, the median DOR was 43.7 months (95% CI, 39.2-not evaluable [NE]) among those with a CR and 20.4 months (95% CI, 17.0-25.7) among those with a PR. Additionally, the median DOR was 30.5 months (95% CI, 22.4-NE) for those with a PR and higher (≥ 75%) tumor reduction, 19.6 months (95% CI, 13.0-25.8) for those with a PR and intermediate reduction (between 50% and less than 75%), and 14.7 months (95% CI, 8.9-20.2) for those with a PR and lower reduction (between 30% and less than 50%).

Across all responders, 28.9% to 84.6% of patients experienced a response of least 18 months.

The median OS was not evaluable (95% CI, NE-NE) for those with a CR or near CR and 46.3 months (95% CI, 39.5-NE) for those with a PR and a maximum tumor reduction of at least 30% and less than 75%. The 24-month and 36-month OS rates in these responder groups were 100% vs 79.5% and 96.9% vs 61.7%, respectively.

Reference
Motzer RJ, Powles T, Hutson T, et al. Characterization of tumor response with lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma: final overall survival analysis of the CLEAR study (4-year median follow up). Presented at the 2023 Kidney Cancer Research Summit; July 13-14, 2023; Boston, MA. Abstract 66.

→ **To view the full article and references, visit:** Cancernetwork.com/KCRS23_CLEAR_Trial ■



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.

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

CONTINUING MEDICAL EDUCATION (CME)

Facing the Challenges of Implementing Palliative Care

FACULTY

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This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

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- Explain the role of the medical oncologist and the training received for such care
- Discuss the best practices associated with the implementation of palliative care

RELEASE DATE: September 1, 2023
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The World Health Organization's definition of palliative care is "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness. It prevents and relieves suffering through early identification, correct assessment, and treatment of pain and other problems, whether physical, psychosocial, or spiritual."[1] By improving patients' quality of life and reducing their pain, palliative care also provides substantial financial benefits to hospitals in terms of reducing readmittance and end-of-life hospitalizations.[2] In this article, Raymond Pastore, MD, MSc, evaluates the state of palliative care in the United States, highlighting advancements in access and education as well as remaining areas of unmet need. While good progress has been made, conscious efforts to improve clinician awareness of palliative care options and to destigmatize palliative care in the public perception are needed to bring access to these services to a greater percentage of patients with serious illnesses.

Q: What is the perception of palliative care among patients and the public?

PASTORE: We have seen a surge in palliative care services over the past 2 decades.[3] There is an established board of palliative medicine. Hospice medicine has become its own specialty whose membership continues to grow. In terms of patients with cancer and the public in general, one of the challenges relates to the stigma. Palliative care is often associated with hospice, and that's not necessarily the case.[4] Throughout the trajectory of illness, palliative care can be very helpful from diagnosis to treatment and recovery.[2] The palliative care team can support the patient and the oncology team in so many ways, which is why early involvement is important. Many patients worry that collaborating with palliative care is an acknowledgement that they've reached the end of their journey, which is not the case. Palliative care can lengthen and enhance that journey.

Q: Palliative care is not frequently offered to patients with severe illnesses. How does this impact the quality of care and outcomes?

PASTORE: A number of papers in oncology show that patients fare better when palliative care services are incorporated early on in their disease course for symptom management.[2] And these outcomes can be overall wellness, symptom burden, distress—not only patients' distress, but also caregiver distress—and quality of life.[5] These factors are important, because one's self-efficacy, or belief that one can overcome a challenge, or a medical circumstance can correlate with an improved outcome by enabling a patient to endure the rigors of therapy and stay on schedule. The palliative care team can certainly help with symptom management, whether it's expected symptoms, nausea, loss of appetite, shortness of breath, or pain.[2] And the collaboration between the primary team and the palliative care team is so important.

Q: How can we improve the knowledge among patients and relatives regarding palliative care?

PASTORE: We are all accustomed to the direct-to-consumer advertising in the pharmaceutical space. These attractive and motivating advertisements educate patients about important therapeutic advances. Patients will bring that knowledge to their clinical visit. It would be wonderful to use this strategy to increase the outreach about the benefits of palliative care so that patients could ask for it just the way they may ask for a particular monoclonal antibody or kinase inhibitor. On a smaller scale, oncologists should introduce palliative care to patients and their families early in the course of illness to familiarize them with the concept and the potential benefits. Patients will be more accepting later. This "grassroots approach" will allow the knowledge to spread.

Q: How can we overcome the current stigma associated with palliative care?

PASTORE: I think it's important to acknowledge that palliative care is not for the end of life but, rather, throughout the treatment journey.[4] It's meant not only to help patients manage troublesome symptoms but also to offer an extra layer of support, particularly as patients and their families are making important decisions with the expertise of the oncologist. This reframing of the roles played by palliative care is critical.

Q: How can we improve the visibility of the palliative care team within the hospital on the floors and hospital-wide events in general?

PASTORE: Palliative care teams exist in many hospitals, and they continue to grow, with a presence among many different services.[3] Patients can schedule outpatient palliative care appointments, which will happen in tandem with their medical oncology appointment. The palliative care visit may focus more on symptom management and coping strategies whereas the oncology visit would focus more on treatment of the cancer. Both go hand in hand.

At Weill Cornell [Medical Center], our palliative care clinics are embedded into our oncology clinics so that the patients can have a comprehensive visit with all aspects of their care and concerns addressed. These teams are multidisciplinary, including physicians and nurse practitioners who are trained

in palliative care, in addition to social workers, chaplains, and sometimes physical therapists. Lately, there has been a lot of cross-training with physicians and advanced practice providers in other other primary specialties, such as oncology, pulmonary, cardiology, and even emergency medicine, double boarding or double training in palliative care.[6] These dual-certified individuals are also infiltrating the teams and enhancing the level of care that can be offered.

Q: What is the state of palliative care training in medical school?

PASTORE: Some of the more progressive medical school curricula incorporate clinical work and clinical exposure from the beginning and have sessions about palliative care and hospice early, so students can appreciate their benefit.[7] Likewise, there are sessions on how to communicate with patients clearly, effectively, and with empathy to validate patient concerns. These sessions address how to deal with difficult circumstances and topics, so students are well-prepared for the clinical challenges they may face. I think what's difficult is that the curriculum is compartmentalized. These palliative care sessions are encapsulated lessons that punctuate the curriculum, but what we need is longitudinal exposure.

Q: What does palliative care training look like in the hematology/oncology health care workforce?

PASTORE: There has been a shift over the past several decades from a paternalistic approach, where we would minimize what we tell patients, to shared decision-making—partnering with patients and family to overcome not only the diagnosis but whatever limitations may arise.[8] We strive to create a health care workforce that is well-versed in primary palliative care. All oncologists should feel comfortable with the management of common symptoms and that is practiced in basic communication skills. The palliative care specialist might be reserved for more complex or challenging cases or complicated family dynamics. To embrace this mission of universal palliative care, there are training modules available. These continuing medical education efforts must be encouraged and promoted. We rely on our specialty societies to do that.[a]

Q: How can we improve patients' referral to palliative care?

PASTORE: There are some convenient and discreet pop-ups in the electronic medical record—basically, some best practice alerts—that may appear in the chart if a patient has certain triggers based on a statement of prognosis or even the diagnosis.[9] These electronic alerts can remind the provider to consider a palliative care referral.

Introducing the palliative care specialist and the palliative care team early on can provide support as significant decisions are being made.[2] As new symptoms develop during treatment, the primary team and the palliative care team can manage them together. At Weill Cornell, we have regular meetings and collaborations with the palliative care team to talk about difficult cases. Sometimes, the course of treatment does not go as planned, or the time is less than we might have imagined. That same palliative care team can provide support in making those end-of-life decisions. Patients are grateful to their oncology team, but, at the same time, they carry a burden of not wanting to let their oncologist down, not wanting to disappoint the team. It can be helpful just having that third party to provide assurance and advocacy.

Q: Access to opioid pain relief is not adequate right now; it fails to meet international convention on access to essential medicines. What could be done to overcome such limitations?

PASTORE: We have an opioid crisis, and so we must be responsible about our prescribing patterns to all patients and have a safe plan for the use and the storage of those medicines.[10] Spending the time with the patient outlining those safety approaches is important. There's also a stigma with opioid use in terms of the potential for dependency. But when we're treating cancer-associated pain, there's more of a physiologic need and less of an issue with dependency. There are some important adjunctive medicines that are not opioid based that can enhance pain relief.[11] We need to embrace those options as well, whether it's gabapentin to treat neuropathic pain, or the use of Reiki or other meditation methods, topical agents, judicious use of NSAIDs (nonsteroidal anti-inflammatory drugs), or nerve blocks.

There's a multimodal management of pain that can be embraced, but the opioids have a critical role.[10] In the cancer population, we need to continue to prescribe opioids to our patients, albeit responsibly. What's challenging is that opioids have become so monitored that many providers are reluctant to write those prescriptions, fearing they might be cited for their prescribing patterns.[12] We must make sure that we're still able to meet the palliative needs of our cancer population. The rationale for a particular pain management program should be documented in the medical record with mention of therapeutic alternatives and safe-prescribing practices.

Q: What trends do you see with insurance companies and current health policies in their support for palliative care among patients with serious illnesses?

PASTORE: Palliative services can be expensive.[13] It's the cost of the time needed to meet with patients, to understand their concerns and to offer

validation and support. A palliative care provider might not be able to visit many patients in a day. Quality palliative care does not allow the same high throughput that other specialties may have. Nonetheless, the work is important and, for many patients, essential. Insurance plans will vary in terms of what they will offer patients, particularly in terms of home services and other supportive treatments. It can be a barrier to care if one can't finance the care. Hospice is a Medicare-approved benefit, but not all our patients with cancer have Medicare as their insurance. Some commercial plans restrict which hospices patients might be able to consider, both in terms of inpatient hospice and home hospice.

But even before hospice, we would want to be able to offer patients certain supportive care services, whether it is home physical therapy, an attendant at home, or telehealth services for psychosocial support. We need more lobbying to promote the use of these services, because they allow patients to feel well, and they enhance their outcomes.[2]

Q: How can we identify the populations that can benefit the most from the palliative care service?

PASTORE: Individuals with chronic illnesses—certainly our patients with cancer in addition to those with heart failure or COPD [chronic obstructive pulmonary disease]—would certainly benefit.[2] Uncontrolled pain or shortness of breath or nausea could trigger a referral to palliative care.[9] We should all get comfortable identifying the potential need. Also, we should be mindful of advanced care planning and allow patients to have the opportunity to imagine how much support they might want if their condition were to change, and they might not be able to speak or articulate their own wishes.[14] Choosing a health care proxy is important, as is trying to give some guidance in terms of how aggressive the care might be, where the clinical circumstances change. The palliative care team can help with those discussions as well.

All of us should have a health care proxy and advanced directives, and there are established and prepared instruments that can help us achieve these goals.[15] If the advanced care planning has not happened before the diagnosis, it should occur as the patient becomes more accepting of the new medical challenge, or when there is a change in treatment course. These are useful opportunities to guide patients to articulate their wishes.[16] There is something called the "surprise question," namely, "Would I be surprised if the patient died in the next 12 months?"[17] If the answer is "Yes," there is an opportunity for palliative care to partner with the care team to focus on not only symptoms, but also to clarify goals.

Q: What is the role of palliative care in supporting psychiatric health in patients requiring it?

PASTORE: There is an emerging field of psycho-oncology with psychologists and psychiatrists specialized in the treatment of individuals confronting life-threatening illness. As patients confront the seriousness of their condition, they may revisit certain episodes of their life or past trauma as they contemplate their mortality.[18] Those psycho-oncologists are important members of the palliative care team, and can help patients in their journey as they make decisions and process the existential distress as they ponder their own mortality and the meaning of life, and what the future may have in store and what their legacy might be.

Psychological care is critical, and we need more of it.

Q: What is the role of diversity in palliative care access?

PASTORE: I think it is critical. We must acknowledge that we all have different backgrounds and different traditions related to our upbringing—our culture, our mores, ethnicity, and spirituality.[20] We have to understand where the patient is coming from, what their belief system is, what their wishes are, and how those coordinate with what the offered approach might be. Palliative care is sensitive to that diversity. It needs to be encouraged, because, otherwise, it becomes the elephant in the room where we fail to acknowledge who the patient is. It is part of their identity and must be understood so that we can best help them.

Q: Are there ongoing clinical trials in palliative care?

PASTORE: There are many different clinical trials with novel treatment modalities coupled with conventional pharmaceutical methods to palliate pain.[21] There is significant work in the supportive care arena which incorporates health services research. Communication techniques are evaluated to highlight the most effective methods and to identify those pitfalls that may deter discussion. The most efficacious and efficient ways of educating providers about these techniques is debated. Lastly, prognostication is an important area of research as we strive to develop tools to predict future clinical outcomes. Even the most seasoned clinicians can have difficulty predicting the time course of illness. ■

Key References

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