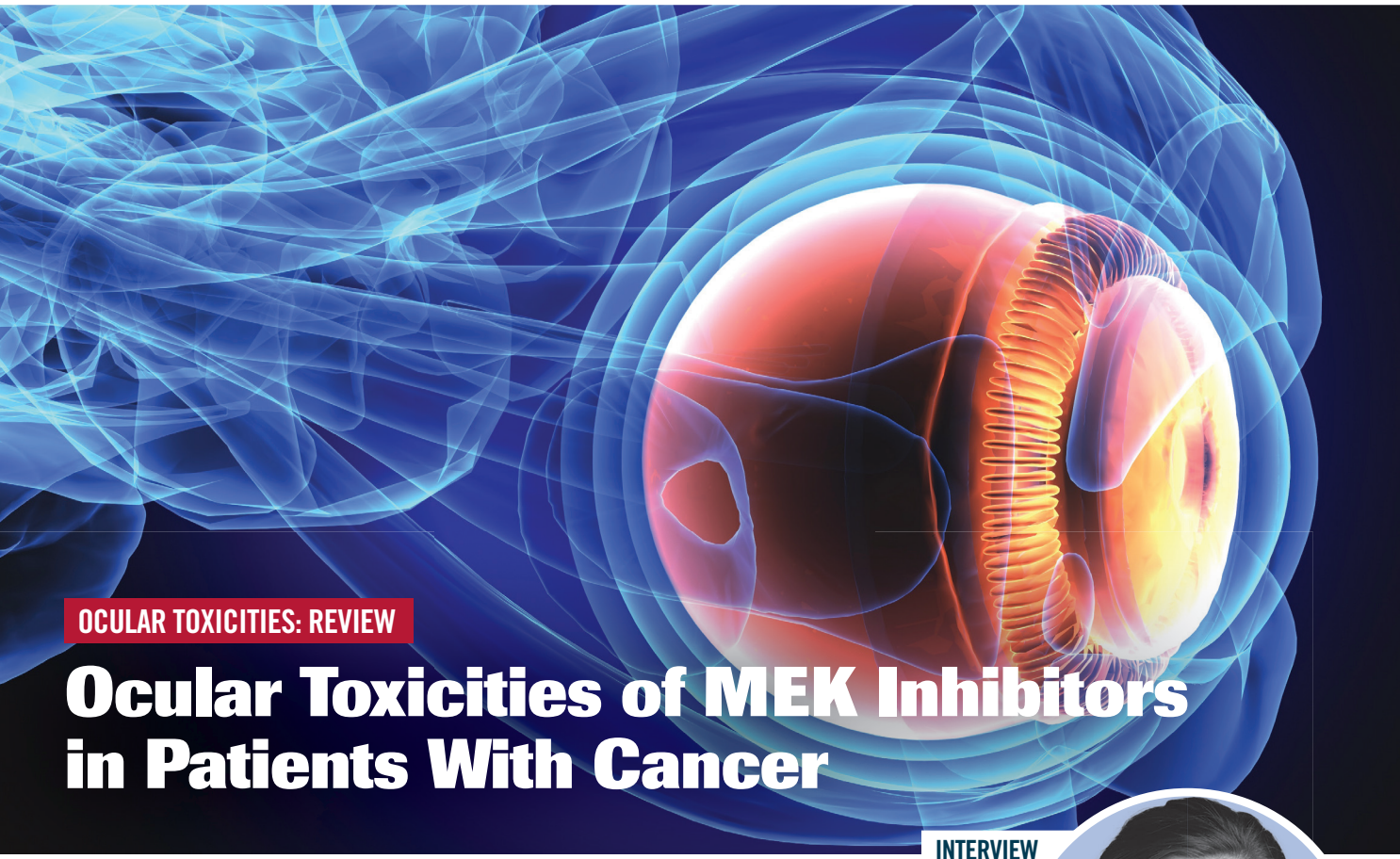
cancernetwork.com

gotoper.com

PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

MARCH 2023 | Vol 37 • No 3



OCULAR TOXICITIES: REVIEW

Ocular Toxicities of MEK Inhibitors in Patients With Cancer

INTERVIEW

Racial and Ethnic Disparities in Opioid Use Across the Cancer Continuum

ANDREA C. ENZINGER, MD

PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

EDITORIAL ADVISORY BOARD

MISSION STATEMENT

ONCOLOGY® and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of *ONCOLOGY®* and CancerNetwork.com's articles and features. Focused discussions capture key clinical take-aways for application in today's time-constrained practice environment.

EDITORS-IN-CHIEF

Julie M. Vose, MD, MBA
Omaha, NE

Howard S. Hochster, MD
New Brunswick, NJ

EDITORIAL BOARD

TUMOR CHAIRS

BREAST CANCER
Sara A. Hurvitz, MD, Los Angeles, CA

GENITOURINARY CANCER
Robert A. Figlin, MD, Los Angeles, CA

GASTROINTESTINAL CANCER
Tanios S. Bekaii-Saab, MD, Phoenix, AZ

HEAD AND NECK CANCER
Eric J. Sherman, MD, New York, NY

HEMATOLOGIC MALIGNANCIES
C. Ola Landgren, MD, PhD, Miami, FL

THORACIC MALIGNANCIES
Hossein Borghaei, DO, MS, Philadelphia, PA

BOARD MEMBERS

BREAST CANCER
William J. Gradishar, MD, FACP, Chicago, IL
Tari King, MD, Boston, MA
Stephen M. Schleicher, MD, MBA, Lebanon, TN
Vered Stearns, MD, Baltimore, MD
Melinda L. Telli, MD, Palo Alto, CA

CANCER SURVIVORSHIP
Matthew J. Matasar, MD, MS, New York, NY

CLINICAL QUANDARIES
María T. Bourlon, MD, MSc, Mexico City, MX

COLORECTAL/GASTROINTESTINAL CANCER
Edward Chu, MD, Pittsburgh, PA
Mehmet Sitki Copur, MD, FACP, Omaha, NE
Daniel Haller, MD, Philadelphia, PA
John L. Marshall, MD, Washington, DC
Shubham Pant, MD, Houston, TX
Matthew B. Yurgelun, MD, Boston, MA

GENITOURINARY CANCER
L. Michael Glodé, MD, FACP, Denver, CO
Paul Mathew, MD, Boston, MA
Elisabeth Heath, MD, FACP, Detroit, MI
Bobby Liaw, MD, New York, NY

GYNECOLOGIC ONCOLOGY
Mario M. Leitao Jr, MD, New York, NY
Ritu Salani, MD, Los Angeles, CA

HEAD AND NECK CANCER
Apar K. Ganti, MD, MS, FACP, Omaha, NE

HEALTH ECONOMICS
Nora Janjan, MD, MPSA, MBA, Dallas, TX

HEMATOLOGIC MALIGNANCIES
Danielle M. Brander, MD, Durham, NC
Christopher R. Flowers, MD, Houston, TX
Steven T. Rosen, MD, Duarte, CA
Naval G. Daver, MD, Houston, TX
Ehab L. Atallah, MD, Milwaukee, WI

INFECTIOUS DISEASE
Genovefa Papanicolaou, MD, New York, NY

INTEGRATIVE ONCOLOGY
Ting Bao, MD, New York, NY
Linda Carlson, PhD, RPsych, Calgary, Alberta, Canada

LUNG CANCER
David S. Ettinger, MD, Baltimore, MD
James L. Mulshine, MD, Chicago, IL
Edward S. Kim, MD, Duarte, CA
Jennifer W. Carlisle, MD, Atlanta, GA

MELANOMA
Richard D. Carvajal, MD, New York, NY
Jason Luke, MD, FACP, Pittsburgh, PA

NEURO-ONCOLOGY
David A. Reardon, MD, Boston, MA
Stuart A. Grossman, MD, Baltimore, MD
Nicole A. Shonka, MD, Omaha, NE

PEDIATRIC ONCOLOGY
David G. Poplack, MD, Houston, TX
Richard A. Drachtman, MD, New Brunswick, NJ

PROSTATE CANCER
Tomasz M. Beer, MD, Portland, OR
E. David Crawford, MD, Denver, CO
Judd W. Moul, MD, FACS, Durham, NC

PSYCHO-ONCOLOGY
Daniel C. McFarland, DO, New York, NY
Michelle Riba, MD, Ann Arbor, MI

RADIATION ONCOLOGY
Louis Potters, MD, FACR, Hempstead, NY
James B. Yu, MD, MHS, New Haven, CT

SARCOMA
Kenneth Cardona, MD, FACS, Atlanta, GA

SUPPORTIVE AND PALLIATIVE CARE
Thomas J. Smith, MD, FACP, Baltimore, MD
N. Simon Tchekmedyian, MD, Irvine, CA

SURGICAL ONCOLOGY
Burton L. Eisenberg, MD, Newport Beach, CA

INTERESTED IN SUBMITTING TO *ONCOLOGY®*?

Please contact CancerNetwork@mjhlifesciences.com for submission guidelines.

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]
TZ-FL-BR-22-0031
Rx Only

TAZVERIK®
(tazemetostat) tablets
200 mg

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

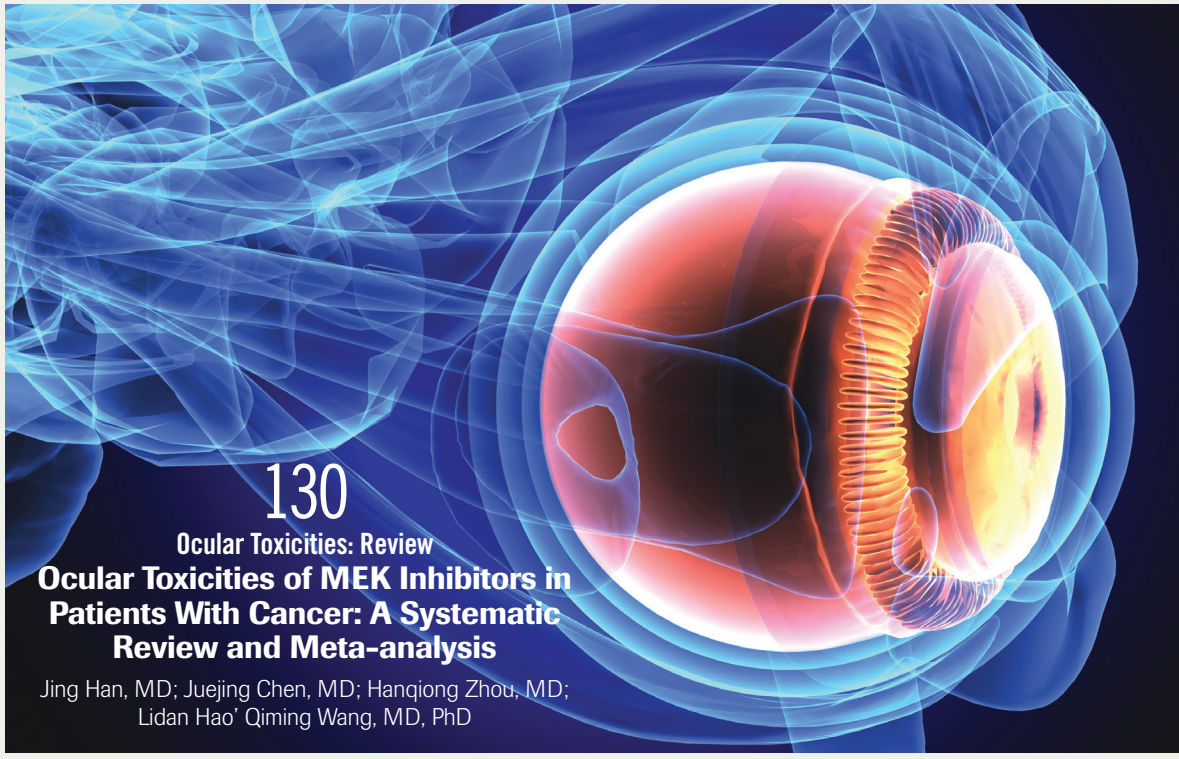
Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

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

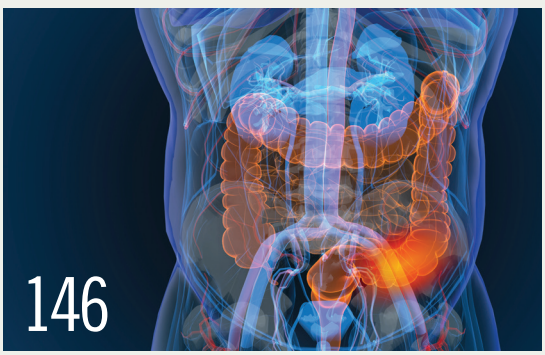
EZH2=enhancer of zeste homolog 2; MT=mutant type; WT=wild type.

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

Epizyme®
AN IPSEN COMPANY



IN THIS ISSUE



OUR KEY OPINION LEADERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT HAVE BEEN UP TO.

Breast Tumor Chair

Sara A. Hurvitz, MD

Hurvitz recently published updated data from the phase 3 DESTINY-Breast03 trial (NCT03529110) in *The Lancet Oncology*. The trial evaluated fam-trastuzumab deruxtecan-nxki (Enhertu) vs ado-trastuzumab emtansine (Kadcyla) in patients with HER2-positive unresectable or metastatic breast cancer who had received prior anti-HER2 therapy and saw an improvement in overall survival. The results helped lead to the approval in May 2022 for the treatment combination.

Gynecologic Oncology Editorial Board Member

Mario M. Leitao Jr, MD

In the March issue of *Annals of Surgery*, Leitao, principal investigator of the study, published the long-term results of the RECOURSE study. This study investigated the outcomes of the use of robotic assistance during surgery across various cancer types. The results showed that outcomes were the same between robotic vs laparoscopic/thoracoscopic surgery, with no safety signal requiring further research.

CALL FOR REVIEWERS AND PAPERS

ONCOLOGY® is seeking to expand its list of ad hoc reviewers to provide constructive feedback on manuscripts that have received initial editorial approval. Comments and criticisms are a necessary and invaluable part of the journal's process, and our need for more willing experts grows in step with the journal.

We are also seeking to expand coverage of original peer-reviewed research articles and are now encouraging authors to submit high-quality original manuscripts about clinical trials and investigations.

Please visit CancerNetwork.com/guidelines for more information or contact us at **CancerNetwork@mjhlifesciences.com**

EDITORS NOTE

In the January issue, we ran an article titled "Experts Discuss Treatment Methodologies in RCC", in which we incorrectly used lenalidomide in place of lenvatinib. The correction has been made and updated on our website which you can view here: **CancerNetwork.com/RCC_1.23**

In the February issue, we ran an article titled "Mayo and Moffitt Face-Off in Myeloma Data Presentation" in which talquetamab was incorrectly stated as being FDA approved. We have updated the article accordingly which you can view here: **CancerNetwork.com/Face-Off_2.23**

PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

MARCH 2023 ▪ VOL. 37 ▪ NO. 3

MJH Life Sciences, LLC | 2 Clarke Dr. Suite 100, Cranbury, NJ 08512 | (609) 716-7777

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

Updated Data and Groundbreaking Research Lead to an Exciting 2023 ASCO GI

The 2023 Gastrointestinal Cancer Symposium (GI) hosted by the American Society of Clinical Oncology (ASCO) had its 25th anniversary, and the conference now covers multidisciplinary GI cancers. A few important studies presented will affect our treatment standards and are worth highlighting.

Colon Cancer

The big phase 3 study in the colon cancer space was the SUNLIGHT study (NCT04737187) comparing trifluridine/tipiracil (Lonsurf) with or without bevacizumab (Avastin).[1] In total, 492 patients with metastatic colon cancer who had received 2 prior regimens, with all standard drugs, were randomly assigned 1:1 to trifluridine/tipiracil plus bevacizumab or trifluridine/tipiracil alone. The study was conducted mainly in Europe, with an enrollment rate of 64%, and only 3% were North American participants despite 10 centers being open for treatment. Additionally, 72% of participants had left-sided primary tumors, 70% had a *RAS* mutation, 72% had received prior bevacizumab, and 45% had an ECOG performance status of 0. The differences were quite substantial, with a major improvement in all efficacy parameters. The median overall survival (OS) was 10.8 months in the combination arm vs 7.5 months in the trifluridine/tipiracil arm (HR, 0.61; 95% CI, 0.49-0.77; $P < .001$), the median progression-free survival (PFS) was 5.6 months vs 2.4 months (HR, 0.44; 95% CI, 0.36-0.54; $P < .001$), the objective response rate was 6.3 months vs 0.9 months ($P = .004$), and the disease control rate was 77% vs 47% ($P < .001$), respectively.

Also, in colon cancer we saw interesting presentations on cell-free DNA (cfDNA) interference with circulating tumor DNA (ctDNA) detection based on more than 30,000 Natera tests, found the effects were minor and ctDNA can be drawn by week 2 postoperatively.[2] Continued data were reported on adjuvant therapy in a prospective trial for stage II colon cancer, with participants assigned to standard-of-care therapy or ctDNA-directed therapy.[3] The ctDNA panel consisted of 15 common gene mutations, and only patients who tested positive for one of these in the tumor were eligible. In this study (N = 450 patients), for the ctDNA-directed treatment arm, only 15% received adjuvant chemotherapy and 62% of these received oxaliplatin. This can be compared with the standard-of-care control arm where 28% of patients were treated with adjuvant chemotherapy, with 90% of these receiving single agent fluropyrimidine and only 10% FOLFOX or CapeOX . The 3-year relapse-free survival (RFS) was equivalent and noninferior in the ctDNA arm, showing that even a suboptimal ctDNA test can be used to direct therapy resulting in almost half as many patients receiving adjuvant chemotherapy. Additionally, ctDNA-positive patients treated with chemotherapy had an 86% RFS rate at 3 years, compared with about 20% RFS without treatment in recent no-treatment ctDNA prospective trials. It is important to verify this experience with the phase 2/3 COBRA trial (NCT04068103) using a broader, a more commercially available test and with the phase 2/3 CIRCULATE-US trial (NCT05174169) for the treatment of stage III disease.

Hepatocellular Carcinoma

The phase 3 NRG/RTOG 1112 study (NCT01730937) should set a new standard for management of hepatocellular carcinoma (HCC).[4] Patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C tumors and who are not eligible for local therapy were randomly assigned to sorafenib (Nexavar) with or without stereotactic body radiation therapy (SBRT) in 5 fractions. With 193 patients, this is the largest prospective randomized study of radiation in HCC. Patients had disease not amenable to resection or transarterial chemoembolization (TACE), fewer than 5 lesions, a sum of diameters less than 20 cm, and a Child-Pugh A score of 60,000 platelets or more. The median OS was improved with SBRT at 15.8 months in the sorafenib plus SBRT arm

vs 12.3 months in the sorafenib alone arm (HR, 0.77; 1-sided P = .0554), and the median PFS was 9.2 months vs 5.5 months (HR, 0.55; 95% CI, 0.40-0.75; 2-sided P = .0001) with no major toxicity issues. SBRT may be a potential treatment option for patients who are not eligible for TACE or radiofrequency ablation and who have vascular invasion.

Biliary Cancer

The phase 3 S1815 trial (NCT03768414) enrolled 441 patients with biliary cancer to gemcitabine-cisplatin with or without albumin-bound nab-paclitaxel based on results from the phase 2 study.[5] Patients were randomly assigned 2:1 to the combination regimen, and remarkably, patients were accrued in 2 years for this groundbreaking biliary cancer trial. Overall, the addition of nab-paclitaxel did not improve outcomes, but there was a substantial benefit in those with gallbladder cancer for both PFS and OS. Further hypotheses in this key study will carry the field forward.

Pancreatic Cancer

The phase 3 NAPOLI 3 trial (NCT04083235) was reported at the conference and again raised more questions than it answered.[6] This study for metastatic first-line therapy of pancreatic cancer used reduced doses of NALIRIFOX (5-fluorouracil/leucovorin, oxaliplatin, liposomal irinotecan) vs gemcitabine/nab-paclitaxel. Although the NALIRIFOX regimen was somewhat better than gemcitabine/nab-paclitaxel (HR, 0.83; P = .04), this is largely due to an "overpowered" study of 770 patients. Another issue is whether NALIRIFOX is a real benefit over free irinotecan. The sponsor has never compared these 2 directly in any randomized trial, and there is no clear indication that NALIRIFOX is more effective or less toxic than free irinotecan. This is not like liposomal doxorubicin, which completely changed the toxicity profile of doxorubicin. This should not be considered a new reference regimen as stated by the presenters of the study. More data are needed here.

The trials and the movement forward continue. Your contributions to clinical trials can help. ■

References

1. Tabernero J, Prager GW, Fakih M, et al. Trifluridine/tipiracil plus bevacizumab for third-line treatment of refractory metastatic colorectal cancer: the phase 3 randomized SUNLIGHT study. *J Clin Oncol.* 2023;41(suppl 4):4. doi:10.1200/JCO.2023.41.3_suppl.4

2. Cohen SA, Kasi PM, Aushev VN, et al. Kinetics of postoperative circulating cell-free DNA and impact on minimal residual disease detection rates in patients with resected stage I-III colorectal cancer. *J Clin Oncol.* 2023;41(suppl 3):5. doi:10.1200/JCO.2023.41.3_suppl.5

3. Tie J. Circulating tumor DNA: prime time or jumping too soon? Presented at: 2023 Gastrointestinal Cancer Conference; January 19-22, 2023; San Francisco, CA.

4. Dawson LA, Winter KA, Knox J, et al. NRG/RTOG 1112: randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC). *J Clin Oncol.* 2023;41(suppl 4):489. doi:10.1200/JCO.2023.41.4_suppl.489

5. Shroff RT, Guthrie KA, Scott AJ, et al. SWOG 1815: a phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. *J Clin Oncol.* 2023;41(suppl 4):LBA490. doi:10.1200/JCO.2023.41.3_suppl.LBA490

6. Wainberg ZA, Melisi D, Macarulla T, et al. NAPOLI-3: a randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). *J Clin Oncol.* 2023;41(suppl 4):LBA661. doi:10.1200/JCO.2023.41.4_suppl.LBA661

IN RELAPSED/ REFRACTORY CLL

LOW RATES OF ATRIAL FIBRILLATION, HYPERTENSION, AND MAJOR BLEEDING EVENTS[1,2]

ELEVATE-RR: The first Phase 3 head-to-head trial of CALQUENCE vs ibrutinib in R/R CLL[1]

ELEVATE-RR was a randomized, multicenter, open-label, Phase 3 trial of CALQUENCE vs ibrutinib in 533 patients with relapsed/refractory CLL with the presence of 17p deletion and/or 11q deletion. Patients were randomized 1:1 to receive 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]

Common adverse events[1]

- At 40.9-month median follow-up, the most common AEs of any grade (≥20%) in patients receiving CALQUENCE were infections (78%), bleeding (38%), diarrhea (35%), headache (35%), cough (29%), cardiac events (24%), pyrexia (23%), anemia (22%), neutropenia (21%), and fatigue (20%)[1]
- Median duration of exposure: 38.3 months (range: 0.3-55.9) in the CALQUENCE arm; 35.5 months (range: 0.2-57.7) in the ibrutinib arm[1]

Select events of clinical interest at 40.9-month median follow-up[1]

	CALQUENCE (n=266)		ibrutinib (n=263)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
CARDIOVASCULAR EVENTS				
Cardiac events	24	9	30	10
Atrial fibrillation†	9‡	4.9	16‡	3.8
Ventricular arrhythmias§	0	0	1.1	0.4
Bleeding events	38	3.8	51	4.6
Major bleeding events‖	4.5	3.8	5	4.6
Hypertension¶	9	4.1	23	9
OTHER				
Infections#	78	31‡	81	30‡
Interstitial lung disease/pneumonitis	2.6	0.4	7	0.8
Second primary malignancies, excluding non-melanoma skin cancers	9	6	8	5

- Any grade cardiac arrhythmias of unspecified origin were reported including tachycardia (2.6%), arrhythmia (0.8%), and extrasystoles (0.8%) for CALQUENCE; tachycardia (2.7%), arrhythmia (0.8%), and extrasystoles (0.4%) for ibrutinib[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]
†Defined as the preferred terms atrial fibrillation and atrial flutter.[1]
‡Select secondary endpoint.[1]
§Includes events with preferred terms: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation.[1]
‖Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).[1]
¶Defined as the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.[1]
#Most common Grade ≥3 infections were pneumonia (CALQUENCE, 10.5%; ibrutinib, 8.7%), sepsis (CALQUENCE, 1.5%; ibrutinib, 2.7%), and urinary tract infection (CALQUENCE, 1.1%; ibrutinib, 2.3%).[1]

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

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

ASCEND was a Phase 3, open-label, randomized, multicenter trial in 310 patients with relapsed/refractory CLL. Patients received either CALQUENCE monotherapy 100 mg orally 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.[2,3]

Common adverse events[2]

- **At 46.5-month median follow-up,** the most common adverse events (≥20%) of any grade in patients receiving CALQUENCE were infection (68%), hemorrhage (31%), neutropenia (24%), headache (23%), and diarrhea (21%)[2]
  - 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%)[3]
  - 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%)[3,4]
  - The median duration of CALQUENCE exposure was 15.7 months (range: 1.1-22.4)[3,4]

Events of clinical interest at 46.5-month median follow-up[2]

	CALQUENCE (n=154)		IdR (n=118)		BR (n=35)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
CARDIOVASCULAR EVENTS						
Atrial fibrillation	8	1.3	3.3	0.8	2.9	2.9
Hemorrhage	31	2.6	8	2.6	6	2.9
Major hemorrhage*	3.2	2.6	2.6	2.6	2.9	2.9
Hypertension	8	4.5	6	0.8	0	0
OTHER						
Infections	68	29	73	34	49	11
Second primary malignancy excluding non-melanoma skin carcinomas	7	6	1.7	0.8	2.9	2.9
Tumor lysis syndrome	0.6	0.6	0.8	0.8	0	0

*Major hemorrhage was defined as any serious or grade ≥3 hemorrhage or central nervous system hemorrhage of any grade.[2]

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

CALQUENCE tablets can be taken with any acid-reducing agent, including proton pump inhibitors, antacids, and H2-receptor antagonists[3]

To learn more about the tablet formulation visit calquencehcp.com/tablet

IMPORTANT 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.

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%). 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 jiroveci* 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.

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.

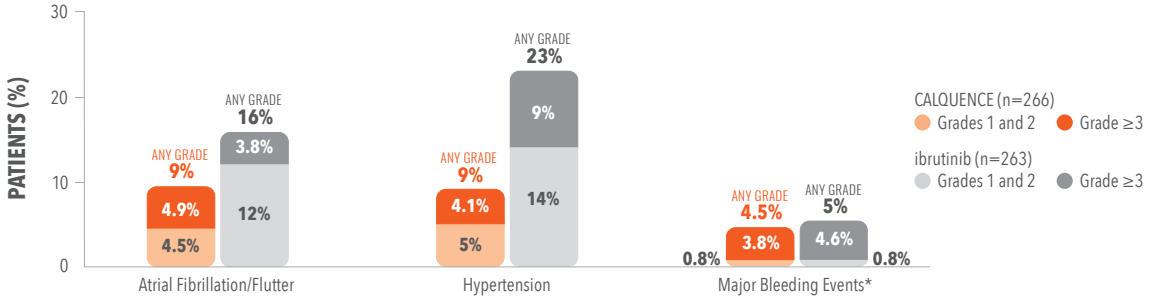
Atrial Fibrillation and Flutter

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.

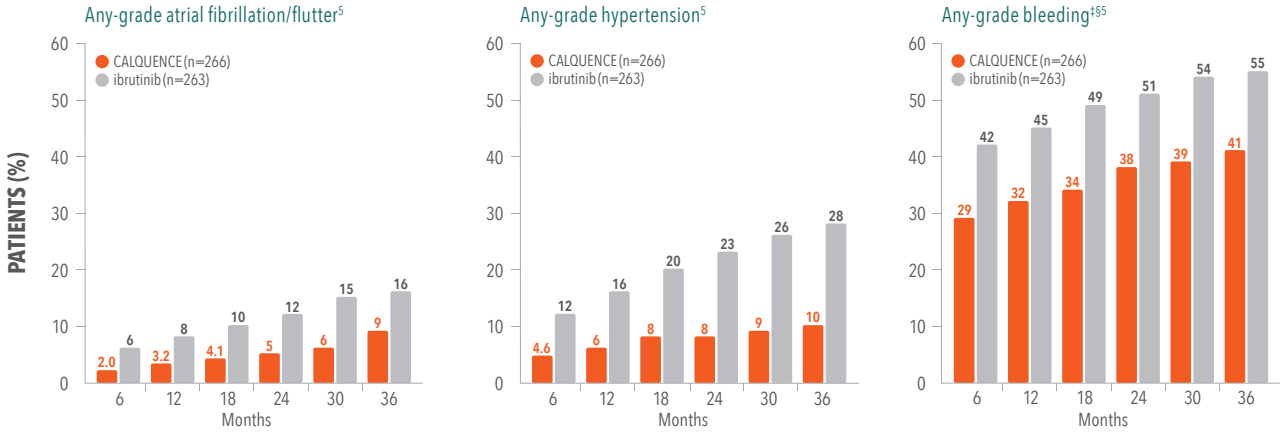
VIEW HEAD-TO-HEAD TRIAL RESULTS

CALQUENCE®
acalabrutinib 100 mg tablets

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



ELEVATE-RR: Post hoc analysis of cumulative incidence of select AEs of clinical interest†[5]



- Overall incidence rates of bleeding (any grade, Grade ≥3): CALQUENCE (38%, 3.8%), ibrutinib (51%, 4.6%)[1]

*Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or that was a central nervous system hemorrhage (any severity grade).[1]
†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.[1,5]
‡Includes multiple adverse event terms including major bleeding, which was defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or that was a central nervous system hemorrhage (any grade).[5]
§Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis.[5]

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

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

*Treatment-emergent decreases (all grades) of hemoglobin, platelets, and neutrophils were based on laboratory measurements and adverse reactions.

In patients with previously untreated CLL exposed to CALQUENCE, 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 plus obinutuzumab arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (7% and 2.8%, respectively).

Adverse reactions led to CALQUENCE dose reduction in 7% and 4% of patients in the CALQUENCE plus obinutuzumab arm (N=178) and CALQUENCE monotherapy arm (N=179), respectively. Adverse events led to discontinuation in 11% and 10% of patients, respectively. Increases in creatinine to 1.5 to 3 times the upper limit of normal (ULN) occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

In patients with relapsed/refractory CLL exposed to CALQUENCE, 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.

Adverse reactions led to CALQUENCE dose reduction in 3.9% of patients (N=154), dose interruptions in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and discontinuation in 10% of patients, most frequently due to second primary malignancies followed by infection. Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid co-administration of CALQUENCE with a strong CYP3A inhibitor. If these inhibitors will be used short-term, interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE.

Moderate CYP3A Inhibitors: Reduce the dosage of CALQUENCE to 100 mg once daily when co-administered with a moderate CYP3A inhibitor.

Strong CYP3A Inducers: Avoid co-administration of CALQUENCE with a strong CYP3A inducer. If co-administration is unavoidable, increase the dosage of CALQUENCE to 200 mg approximately every 12 hours.

SPECIFIC POPULATIONS

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. Advise pregnant women of the potential risk to a fetus.

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 1 week following the last dose of CALQUENCE.

It is not known if CALQUENCE is present in human milk. Advise lactating women not to breastfeed while taking CALQUENCE and for 2 weeks after the last dose.

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.

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

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, 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.** Jurczak W, Pluta A, Wach M, et al. Acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia: ASCEND results at ~4 years of follow-up. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022. Abs 7538. **3.** CALQUENCE® (acalabrutinib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022. **4.** 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. **5.** 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.

AstraZeneca

CALQUENCE®
acalabrutinib 100 mg tablets

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]*.

Distributed by:
AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

08/22 US-66174 8/22

MEET OUR EXPERT

Andrea C. Enzinger, MD, is the lead author on the study, assistant professor of medicine at Harvard Medical School, and a physician at Dana-Farber Cancer Institute.

Racial and Ethnic Disparities in Opioid Use Across the Cancer Continuum

"The proportion of patients who filled 1 or more opioid prescriptions in the last month of life, Black patients were about 4.3% less likely to fill any opioid prescription than White patients, and Hispanic patients had a similar difference."

A recent study, conducted between 2007 and 2019, aimed to determine the prevalence of racial and ethnic disparities in opioid access among Black, Hispanic, and White patients with cancer. The study found that there was a substantial gap in the ability to receive opioids, but socioeconomic factors did not play a role in this inequity.

CancerNetwork® spoke with **Andrea C. Enzinger, MD,** about the impact these results can have on care for older patients with cancer. Some of the biggest disparities that occurred were in the number of opioids received, whether they were long acting, and the size of each daily dose.

Enzinger discussed the results from this trial, the barriers still to be overcome, and where the research may be headed.

Q: Can you discuss the racial and ethnic disparities in opioid access in patients with cancer reported in the study?

ENZINGER: We found striking and pervasive inequities in access to prescription opioids among older, Medicare-insured patients who are dying from cancer. We looked at more than 300,000 Black, White, and Hispanic patients with poor prognoses who died between 2007 and 2019.

If you looked at, for example, the proportion of patients who filled 1 or more opioid prescriptions in the last month of life, Black patients were about 4.3% less likely to fill any opioid prescription than White patients, and Hispanic patients had a similar difference. That may sound like a small number, but you have to keep in mind that by 2019, only a little more than 30% of patients filled a prescription for an opioid. If you're looking at a 4.3% difference between Black and White patients with an overall cohort prevalence of about 30%, that's a meaningful difference.

We saw larger differences in access to long acting opioids, which are critical for palliating severe and persistent pain from advanced cancers. Black patients were about 3.2 percentage points less likely than White patients to fill a long-acting opioid in the last month of life. The differences are similar between Hispanic and White patients. To put that into context, by 2019, only about 9% of patients [dying of cancer] filled a long-acting opioid in the last month of life, so a difference of 3 or more percentage points is huge.

We also found that, when patients of color filled a prescription, the doses were lower. It's useful to examine the difference in the average total dose filled by patients of color vs White patients. As an example, Black patients received or filled about 200 mg less of morphine equivalents in the last month of life than White patients, which amounts to around twenty-eight 5-mg oxycodone tablets. [That's] about 1 less pill per day for the average Black patient compared with the average White patient. Again, we saw similar differences between Hispanic and White populations.

Q: Which findings were most surprising?

ENZINGER: Sadly, coming into this study, we did expect to see disparities in access because they've been shown across conditions and settings, including among pediatric populations and among patients with fractures [or]

postoperative pain. What's startling is that this is the population in whom you would hope to never see disparities, [not] among people who are dying. There are lots of downsides to prescription opioids, and one could argue that it's a good thing that we're not giving as many opioid pain medications in settings like [after] tooth extractions, where we know they can lead to substance abuse and addiction. [However], these are dying patients, so it's difficult to defend any disparity—especially [those of] the magnitude we observed.

Another surprising and disconcerting finding was that we saw huge variation if you drilled down beyond just race and ethnicity, and particularly if you look at the interaction between patients' gender and race. Black men were dramatically more affected by disparities and opioid access vs any other group. If you look, for example, at the difference between White men and Black men in access to prescription opioids, Black men were about 6 percentage points less likely to fill any opioid in the last month of life. They were more than 4% less likely to fill a long-acting opioid. If you look at the difference in total dose, they filled about 300 mg less of morphine equivalents than White men in the last month of life. All the disparities were magnified substantially when examining Black men.

Q: Are there any plans to continue this research?

ENZINGER: Our team is planning several follow-up studies; there are some important unanswered questions. This is the largest study to date to examine the magnitude and scope of opioid access disparities in populations with cancer. We've only just begun examining older populations with terminal cancer, and the degree of disparities seen with them is probably much larger if you examine younger populations or those with mixed insurance types. We're interested in examining disparities in younger populations and those who may have Medicaid or commercial insurance.

We're [also] interested in different phases of cancer care. For example, [we want to examine disparities] during definitive cancer treatment, or after surgery. It's important to know where the disparities are most extreme. The other thing our team is interested in looking at is the mechanisms: Why is this happening? We tried to examine a few possible mechanisms by running models that adjusted for the characteristics of patients and the communities in which they lived. How deprived [are] the communities? We [were] wondering if this was all due to structural factors. Adjusting for that, for poverty, and whether patients lived in urban or rural communities made no difference in the magnitude of the disparities that we saw.

Q: What strategies do you think could be implemented to help mitigate these disparities?

ENZINGER: We'll need to take a multipronged approach to tackle these disparities. We also need more information about what the key drivers are. There needs to be some element of bias training for providers.

We also need more logistical support around getting patients of color help in filling their prescriptions. [Patients] may face racial prejudices while trying to fill their prescriptions. They [also] may have difficulty getting to the pharmacy, or difficulty with co-pays.

We need institutional initiatives [toward] equity, and [the institutions need to] hold themselves accountable to those. Policy makers and insurers should take a hard look at all the added regulations and burdens that they've placed on opioid prescription with the goal of reducing misuse and addiction. [Inadvertently], they may also be placing an undue burden on patients with cancer who need these medications, [especially] racial and ethnic minority patients. ■

Reference

1. Enzinger AC, Ghosh K, Keating NL, et al. Racial and ethnic disparities in opioid access and urine drug screening among older patients with poor-prognosis cancer near the end of life. *J Clin Oncol*. Published online January 10, 2023. doi:10.1200/JCO.22.01413

TRODELVY® (sacituzumab govitecan-hziy) is indicated for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

NCCN **PREFERRED** for 2L and later mTNBC

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®): Sacituzumab govitecan-hziy (TRODELVY) is recommended as a preferred treatment option* for adult patients with unresectable locally advanced or mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease.[1,2]

SACITUZUMAB GOVITECAN-HZIY (TRODELVY) IS AN NCCN-PREFERRED TREATMENT OPTION,* AS EARLY AS 2L FOR mTNBC[1,2]

*Category 2A.
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.
2L=second line; NCCN=National Comprehensive Cancer Network.

EXPLORE MORE POSSIBILITIES. SCAN TO VISIT TRODELVYHCP.COM.

INDICATION

TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.**

CONTRAINDICATIONS

- Severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

Diarrhea: Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Pre-infusion medication is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

GILEAD

For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

PROVEN SURVIVAL BENEFIT IN 2L AND LATER mTNBC
IN THE PHASE 3 ASCENT TRIAL*

In brain-met negative population[3*] **3X LONGER MEDIAN PFS** *than single-agent chemotherapy*

5.6 months with TRODELVY (95% CI: 4.3–6.3) (n=235) vs **1.7 months** with single-agent chemotherapy (95% CI: 1.5–2.6) (n=233); HR: 0.41 (95% CI: 0.32-0.52) *P*<.001

In the full population[1*]

- Median PFS was 4.8 months for TRODELVY (95% CI: 4.1–5.8) (n=267) vs 1.7 months with single-agent chemotherapy (95% CI: 1.5–2.5) (n=262); HR: 0.43 (95% CI: 0.35-0.54) *P*<.0001

In brain-met negative population[3*] **1 YEAR MEDIAN OS**

12.1 months with TRODELVY (95% CI: 10.7–14.0) (n=235) vs **6.7 months** with single-agent chemotherapy (95% CI: 5.8–7.7) (n=233); HR: 0.48 (95% CI: 0.38-0.59) *P*<.001

In the full population[1*]

- Median OS was 11.8 months for TRODELVY (95% CI: 10.5–13.8) (n=267) vs 6.9 months with single-agent chemotherapy (95% CI: 5.9–7.6) (n=262); HR: 0.51 (95% CI: 0.41-0.62) *P*<.0001

***TRODELVY was studied in ASCENT, a phase 3, randomized, active-controlled, open-label trial. Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=267) or physician's choice of single-agent chemotherapy (n=262), which included eribulin, vinorelbine, gemcitabine, or capecitabine. Patients were treated until disease progression or unacceptable toxicity. The efficacy analysis included Progression-Free Survival (PFS) in brain metastases-negative patients (primary endpoint) by BICR based on RECIST 1.1 criteria, PFS for the full population (all patients with and without brain metastases), and Overall Survival (OS) vs single-agent chemotherapy.[3]**

- **88% of the full population were brain-met negative.[1] Results in these patients were similar to those seen in the full population (all randomized patients).[3] See exploratory findings for brain-met positive population at TRODELVYHCP.com**
- **13% of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy). Efficacy results for this subgroup of patients were consistent with those who had received at least 2 prior lines in the metastatic setting[1]**

BICR=blinded, independent, central review; brain-met=brain metastases; CI=confidence interval; HR=hazard ratio; OS=Overall Survival; PFS=Progression-Free Survival; RECIST=Response Evaluation Criteria in Solid Tumors.

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

Nausea and Vomiting: Nausea occurred in 66% of all patients treated with TRODELVY and Grade 3 nausea occurred in 4% of these patients. Vomiting occurred in 39% of patients and Grade 3-4 vomiting occurred in 3% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV). Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to Grade ≤1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of Grade 3-4 neutropenia was 67% in patients homozygous for the UGT1A1*28, 46% in patients heterozygous for the UGT1A1*28 allele and 46% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 function.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

ADVERSE REACTIONS

In the ASCENT study (IMMU-132-05), the most common adverse reactions (incidence ≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.

References: 1. TRODELVY [package insert]. Foster City, CA: Gilead Sciences, Inc.; October 2021. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer v.8 2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 13, 2021. To view the most recent and complete version of the guidelines, go online to NCCN.org. **3.** Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384(16):1529-1541. doi: 10.1056 /NEJMoa2028485.

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.

TRODELVY® (sacituzumab govitecan-hziy) for injection, for intravenous use
Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.**

[See Warnings and Precautions and Dosage and Administration]

INDICATIONS AND USAGE

*Also see **Clinical Studies***

TRODELVY (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

*Also see **Warnings and Precautions***

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38.

The recommended dose of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg. Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

- First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions.
- Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.
- Premedication: Prior to each dose of TRODELVY, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended. Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist, as well as other drugs as indicated).

Dose Modifications for Infusion-related Reactions: Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions.

Dose Modifications for Adverse Reactions: Withhold or discontinue TRODELVY to manage adverse reactions as described below. Do not re-escalate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Severe Neutropenia, defined as Grade 4 neutropenia ≥7 days, OR Grade 3 febrile neutropenia (absolute neutrophil count or ANC <1000/mm^3 and fever ≥38.5°C), OR at time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1:

- At first occurrence, 25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF). At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY.
- At time of scheduled treatment, if Grade 3-4 neutropenia occurs which delays dosing beyond 3 weeks for recovery to ≤Grade 1, discontinue TRODELVY at first occurrence.

Severe Non-Neutropenic Toxicity, defined as Grade 4 non-hematologic toxicity of any duration, OR any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents, OR other Grade 3-4 non-hematologic toxicity persisting >48 hours despite optimal medical management, OR at time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤Grade 1:

- At first occurrence, 25% dose reduction. At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY.
- In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤Grade 1 within 3 weeks, discontinue TRODELVY at first occurrence.

CONTRAINDICATIONS

*Also see **Warnings and Precautions***

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS

*Also see **BOXED WARNING, Dosage and Administration, Contraindications, Clinical Pharmacology, Nonclinical Toxicology,** and **Use in Specific Populations***

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur in patients treated with TRODELVY. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7% of patients. Withhold TRODELVY for ANC below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Diarrhea: TRODELVY can cause severe diarrhea. Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of all patients treated with TRODELVY. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of patients. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1. At the onset of diarrhea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY treatment. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Premedication for infusion reactions in patients receiving TRODELVY is recommended. Have medications and emergency equipment to treat infusion-related reactions, including anaphylaxis, available for immediate use when administering TRODELVY. Closely monitor patients for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

Nausea and Vomiting: TRODELVY is emetogenic. Nausea occurred in 66% of all patients treated with TRODELVY. Grade 3 nausea occurred in 4% of patients. Vomiting occurred in 39% of patients. Grade 3-4 vomiting occurred in 3% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of CINV. Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to ≤Grade1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of neutropenia and anemia was analyzed in 701 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 3-4 neutropenia was 67% in patients homozygous for the UGT1A1*28 (n=87), 46% in patients heterozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=313). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

ADVERSE REACTIONS

*Also see **BOXED WARNING, Warnings and Precautions,** and **Clinical Studies***

The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in 795 patients from three studies, IMMU-132-01, IMMU-132-05 and IMMU-132-06 which included 366 patients with mTNBC who had received prior systemic chemotherapy for advanced disease and 180 patients with mUC. Among the 795 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 59 months). The most common (≥ 25%) adverse reactions were nausea (66%), diarrhea (65%), fatigue (62%), neutropenia (61%), alopecia (45%), anemia (42%), vomiting (39%), constipation (37%), decreased appetite (34%), rash (32%) and abdominal pain (28%).

Metastatic Triple-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label trial (ASCENT, IMMU-132-05) in patients with mTNBC who had previously received a taxane and at least two prior therapies. Patients were randomized (1:1) to receive either TRODELVY (n=258) or single agent chemotherapy (n=224) and were treated until disease progression or unacceptable toxicity. For patients treated with TRODELVY, the median duration of treatment was 4.4 months (range: 0 to 23 months). Serious adverse reactions occurred in 27% of patients, and those in > 1% included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients, including respiratory failure (0.8%) and pneumonia (0.4%). TRODELVY was permanently discontinued for adverse reactions in 5% of patients. These adverse reactions (≥1%) were pneumonia (1%) and fatigue (1%). The most frequent (≥5%) adverse reactions leading to a treatment interruption in 63% of patients were neutropenia (47%), diarrhea (5%), respiratory infection (5%), and leukopenia (5%). The most frequent (>4%) adverse reactions leading to a dose reduction in 22% of patients were neutropenia (11%) and diarrhea (5%). G-CSF was used in 44% of patients who received TRODELVY. The most common adverse reactions (≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most common Grade 3-4 lab abnormalities (≥25%) were decreased neutrophils (49%), decreased leukocytes (41%), and decreased lymphocytes (31%).

Locally Advanced or Metastatic Urothelial Cancer

The safety of TRODELVY was evaluated in a single-arm, open-label study (TROPHY, IMMU-132-06) in patients (n=113) with mUC who had received previous platinum-based and anti-PD-1/PD-L1 therapy. Serious adverse reactions occurred in 44% of patients, and those in >1% included infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), sepsis or bacteremia (5%), diarrhea (4%), anemia, venous thromboembolism, and small intestinal obstruction (3% each), pneumonia, abdominal pain, pyrexia, and thrombocytopenia (2% each). Fatal adverse reactions occurred in 3.6% of patients, including sepsis, respiratory failure, epistaxis, and completed suicide. TRODELVY was permanently discontinued for adverse reactions in 10% of patients. The most frequent of these adverse reactions was neutropenia (4%, including febrile neutropenia in 2%). The most common adverse reactions leading to dose interruption in 52% of patients were neutropenia (27%, including febrile neutropenia in 2%), infection (12%), and acute kidney injury (8%). The most common (>4%) adverse reactions leading to a dose reduction in 42% of patients were neutropenia (13%, including febrile neutropenia in 3%), diarrhea (11%), fatigue (8%), and infection (4%). G-CSF was used in 47% of patients who received TRODELVY. The most common adverse reactions (incidence ≥25%) were diarrhea, fatigue, neutropenia, nausea, any infection, alopecia, anemia, decreased appetite, constipation, vomiting, rash, and abdominal pain. The most common Grade 3-4 lab abnormalities (≥25%) were decreased neutrophils (43%), decreased leukocytes (38%), and decreased lymphocytes (35%). Other clinically significant adverse reactions (≤15%) include: peripheral neuropathy (12%), sepsis or bacteremia (9%), and pneumonia (4%).

DRUG INTERACTIONS

*Also see **Warnings and Precautions** and **Clinical Pharmacology***

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.

USE IN SPECIFIC POPULATIONS:

*Also see **Warnings and Precautions, Clinical Pharmacology,** and **Nonclinical Toxicology***

Pregnancy: TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Lactation: There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Females and Males of Reproductive Potential: Verify the pregnancy status of females of reproductive potential prior to initiation. TRODELVY can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Infertility: Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential.

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

Geriatric Use: Of the patients who received TRODELVY, 264/795 (33%) of all patients were ≥ 65 years old, and 11% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

Hepatic Impairment: No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin ≤ 1.5 ULN and AST/ALT < 3 ULN). The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established, and no recommendations can be made for the starting dose in these patients.

See PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

GILEAD

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

Signaling Pathways in the Relapse of Glioblastoma

Javier Orozco-Mera, MD, FACS, MSc[1*]; Fernando Peralta-Pizza, MD[2]; Oscar Escobar-Vidarte, MD[3]; Brenda Coll-Tello, MSc[4]; Aurelio Ariza, MD[5]

ABSTRACT

Background: Glioblastoma is the most common primary neoplasm of the central nervous system. Standard treatment includes surgery with maximum safe resection and radiotherapy plus concomitant and adjuvant chemotherapy; however, almost invariably, tumor relapse occurs. We aimed to describe signaling pathways and molecular mechanisms present in tumor relapse of glioblastoma.

Methods: This systematic review followed the PRISMA guidelines. We searched the PubMed, EMBASE and Web of Science databases. We included studies that enrolled patients 15 years or older with a diagnosis of glioblastoma according to Louis criteria and focused on signaling pathways and molecular mechanisms present in tumor relapse of glioblastoma. The outcome of interest was progression-free survival.

Results: We identified 1470 articles; 31 met the inclusion criteria. From each publication, we obtained the associated markers O-6-methylguanine-DNA methyltransferase, isocitrate dehydrogenase, mRNA, epidermal growth factor receptor (EGFR), p53, and others. All publications were evaluated with the Q-Genie checklist tool for quality assessment.

Conclusions: We identified a wide variety of signaling pathways and molecular processes that are involved in glioblastoma relapse. This diversity would explain intra- and intertumor heterogeneity, treatment evasion, and relapse. However, only a few molecular processes have robust evidence for clinical utility.

INTRODUCTION

Glioblastoma (GB) is the most common primary neoplasm of the central nervous system, with an overall incidence of 0.59 to 3.69 per 100,000.[1] It has a very poor prognosis, with a mean survival of 12 to 15 months from its diagnosis; only 3% to 5% of patients survive after 3 years. Standard treatment, based on the Stupp protocol,[2] includes surgery with maximum safe resection and radiotherapy plus concomitant and adjuvant chemotherapy. Despite this, almost invariably, tumor relapse occurs. In GB, unlike in other types of cancer, mortality is not associated with the appearance of metastasis but rather with tumor relapse, given the tumor's ability to evade treatment and the limitation in many cases for optimal resection of the neoplasm by the eloquence of the affected areas. Understanding the mechanisms used by the tumor to evade treatment is fundamental to finding new therapeutic targets. Our objective was to describe the signaling pathways and molecular mechanisms present in tumor relapse of GB considering the evolutionary processes of cancer described by Hanahan and Weinberg.[3]

METHODS

The search followed the declaration of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.[4]

Inclusion and exclusion criteria

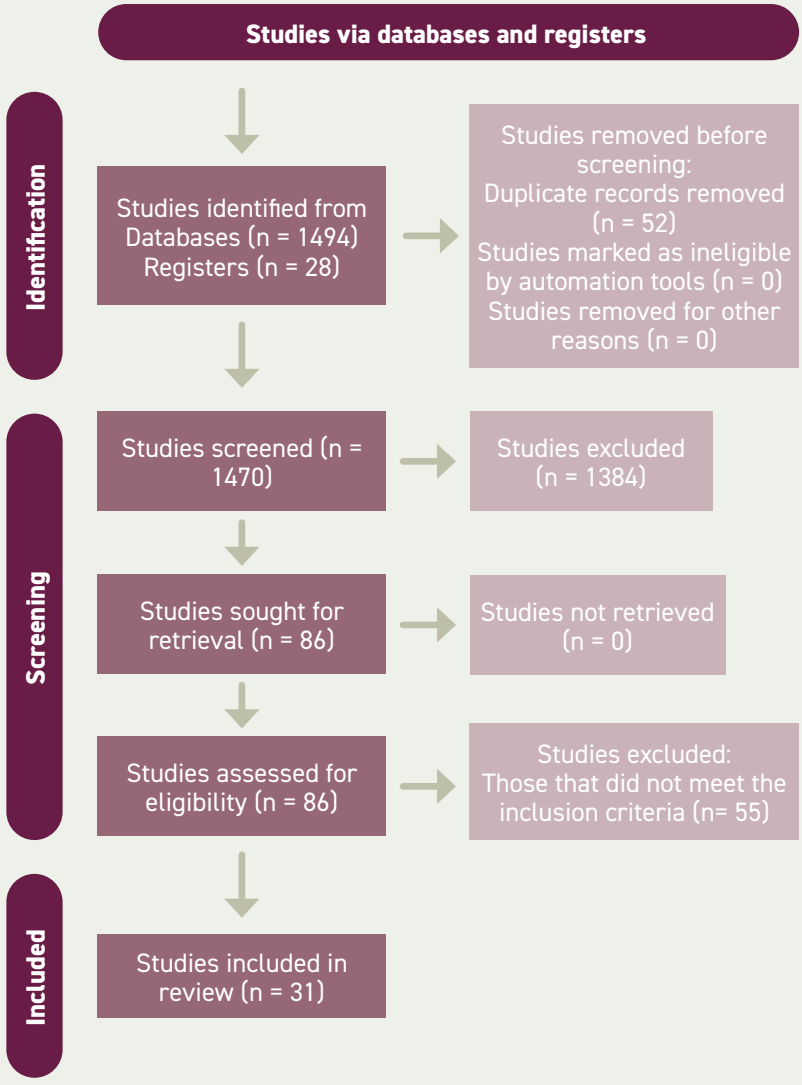
We included observational, case-control, and retrospective or prospective cohort studies that enrolled patients aged 15 years or older with a GB diagnosis according to the Louis criteria of 2007 updated in 2016; the patients must have received frontline treatment with surgery, followed by chemotherapy (Stupp protocol or otherwise, as indicated by the author) and/or radiotherapy, and must subsequently have experienced tumor relapse. The type of intervention analyzed in each article corresponded to which signaling pathways and molecular mechanisms could have been involved in disease progression according to the cancer hallmarks identified by Hanahan and Weinberg.[3] Exclusion criteria included those studies that, at the time of evaluation, did not have information on progression-free survival (PFS). The expected outcome was

TABLE 1. **Q-Genie Quality Assessment Scores for the Included Studies**

Studies	Items											Total
	1	2	3	4	5	6	7	8	9	10	11	
Cheng et al (2015)	4	5	3	2	5	3	3	7	3	4	4	43
Yin et al (2018)	4	5	3	4	3	3	3	7	4	4	6	46
Marziali et al (2017)	6	4	5	5	3	3	2	3	5	4	2	42
Adam et al (2012)	2	4	3	5	3	3	2	5	3	4	7	41
Weller et al (2014)	3	5	3	4	3	3	3	5	2	4	6	41
Dréan et al (2018)	6	4	5	5	4	3	3	3	6	4	4	47
Ohba et al (2019)	6	3	5	4	5	3	2	5	5	4	6	48
Swellam et al (2019)	6	3	4	5	4	3	3	4	5	4	5	46
Lalezari et al (2013)	6	5	3	4	3	3	3	3	3	4	6	43
De Carlo et al (2018)	6	5	3	5	3	3	2	3	5	4	6	45
Tini et al (2018)	3	5	3	4	3	3	3	6	4	4	3	41
Meng et al (2014)	4	6	5	3	5	3	3	5	5	4	7	50
Toraih et al (2019)	6	5	4	5	4	3	2	5	2	4	7	47
Zhang et al (2016)	3	4	4	5	4	3	3	4	4	4	6	44
Li et al (2008)	6	3	4	5	4	3	3	3	4	4	3	42
Kim et al (2017)	6	5	4	3	4	3	3	5	4	4	5	46
Dong et al (2017)	3	4	4	5	4	3	2	4	3	4	3	39
Wang et al (2017)	5	5	4	4	4	3	3	5	4	4	5	46
Pinel et al (2017)	6	4	4	4	3	3	3	5	3	4	5	44
Eoli et al (2017)	6	5	3	4	3	3	2	4	3	4	4	41
Kim et al (2012)	3	5	4	3	4	3	3	4	4	4	4	41
Kim et al (2017)	6	5	4	4	4	3	3	5	4	4	5	47
Shastry et al (2016)	5	6	3	3	4	3	2	5	5	4	6	46
Fan et al (2013)	5	4	3	3	4	3	3	5	4	4	6	44
Griguer et al (2013)	5	6	3	4	4	3	2	4	3	4	6	44
Limam et al (2019)	3	6	4	5	3	3	3	4	3	4	5	43
Lee et al (2013)	3	6	3	3	4	3	2	4	5	4	4	41
Wang et al (2014)	6	6	3	4	3	3	3	5	5	4	3	45
Tabouret et al (2015)	6	4	3	6	3	3	2	4	3	4	6	44
Sana et al (2014)	3	5	4	4	4	3	3	4	3	4	6	43
Olmez et al (2014)	6	3	3	3	3	3	3	3	3	3	3	36

Items: (1) justification of the study, (2) selection and definition of the outcome of interest, (3) selection and comparability of comparison groups, (4) technical classification of the exposition, (5) no technical classification of the exposition, (6) other sources of bias, (7) sample size and power, (8) classification of a priori analysis, (9) statistical methods and confusion control, (10) test of assumptions and interferences for genetic analysis, (11) suitability of the inferences drawn from the results.
Score: 1 to 7 (1 poor, 7 excellent).

FIGURE. **2020 PRISMA Flow Diagram**



relapse, defined as the reappearance of tumor lesions documented by images and confirmed by histology. PFS was sought as a criterion for this outcome.

Search strategy

On March 3, 2020, a systematic search was performed in the PubMed, EMBASE, and Web of Science databases, from January 2004 through December 2019; the late end date ensured the inclusion of the most relevant literature at the time. Search terms were selected based on the population/exposure/outcome (PEO) framework and combined using Boolean operators ("AND", "OR"). Filters were used to limit the results to those using human subjects, written in English, and published within the desired time frame. These terms were used in the search strategy: glioblastoma, methyltransferase, tumor suppressor gene, phosphatidylinositol, cell senescence proto-oncogene, neurofibromin, sustaining proliferative signaling, avoiding growth suppression, avoiding immune destruction, tumors promoting inflammation, dysregulation of cellular energy, DNA repair enzymes, regulatory genes of gene expression, tumor suppressor, signal transduction, genomic instability, cell reprogramming, phosphatidylinositol 3-kinases, *ERB-1* genes.

Study selection and data extraction

After removing duplicates, titles and abstracts were screened for their relevance to the scope of this review. Two authors, J.O. and F.P., independently assessed the eligibility of retrieved articles. To determine suitability for inclusion in this review, the full text of each potentially relevant article was analyzed for overall content and compliance with the eligibility criteria. The following data were extracted from each eligible article: authors, year of publication, study design, population studied, molecular process, diagnostic method, and main findings. The outcome of interest was PFS or time to progression (TTP). Disagreements were resolved by consensus.

Quality and risk of bias assessment

The quality and risk of bias of the studies were assessed through the Q-Genie tool, developed by the Quality of Genetic Association Studies.[5] Q-Genie consists of 11 items. Each item was rated using a 7-point Likert scale (1 = poor; 2-3 = good; 4-5 = very good; 6-7 = excellent). The overall quality of the articles was classified by comparing the scores for each topic. Studies were classified as good, moderate, or poor quality if their scores were greater than 40, between 32 and 40, and less than 32, respectively.

Synthesis methods

HRs were extracted, along with their 95% CIs and *P* values. For continuous

TABLE 2. **Characteristics of the Included Studies**

Reference	Country	N	Age range (yrs)	Mean age (yrs)	Factor	
Cheng et al (2015)	China	19	ND	ND	miR-222, -145, -20a, -132, -129	
Yin et al (2018)	France (RAUH) Neurosurgery Departments of Rennes and Angers University Hospitals	79	36-75	58.9	Epigenetic silencing (TRIM58, ADRA2C); restatement (TRIM38, MS4A7);	
Yin et al (2018)	Canada/Germany (GSE36278-Gen expression omnibus series)	57	18-57	42.2	Epigenetic silencing (TRIM58, ADRA2C); restatement (TRIM38, MS4A7);	
Marziali et al (2017)	Italy	35	30-80	59.5	miR-23a, miR-27a, miR-9 expression	
					MGMT methylation	
					EGFR vIII overexpression	
					PTEN little expression	
					VEGF overexpression	
Adam et al (2012)	Germany	60	33-86	61	ALDH1A1 expression	
					MGMT methylation	
Weller et al (2014)	Germany	179	24-84	60.6	EGFR vIII overexpression	
Dréan et al (2018)	France	51	ND	ND	ABCA13 overexpression	
					MGMT methylation	
Ohba et al (2019)	Japan	59	17-86	54.5	cMET overexpression	
Swellam et al (2019)	Egypt	20	>18	60	miR-221 overexpression	
					miR-222 overexpression	
Lalezari et al (2013)	USA	355	22.3- 90.0	57.6	MGMT ≥30 vs <30%	
					IDH1 not mutated	
					MGMT methylation	
					IDH1 not mutated	
					MGMT BISEQ ≥3 vs <3	
					IDH1 not mutated	

Abbreviations: ADN, methyltransferases; CcO, cytochrome oxidase; cMET, hepatocyte growth factor receptor; CXCL12, CXC motif chemokine ligand 12; CXCR, chemokine receptor family; DGKI, diacylglycerol kinase iota; DNA-PKcs, DNA-dependent protein kinase; DNMT, DNA methyltransferases; GLI1, glioma-associated oncogene homologue 1; HIF1a, inducible factor for hypoxia; HMT, histone methyl transferase; IDH, isocitrate dehydrogenase; IFIT1, interferon-induced protein with tetratricopeptide repeats 1; LAPTM4B-35, lysosomal protein transmembrane 4 beta; lncRNA, long noncoding RNA; MDM2, murine double minute 2; MGMT, O-6-methylguanine DNA methyltransferase; miR, microRNA; MS_P, statistical significance log rank test;

	Method	MSpos (mo)	MSneg (mo)	MSdif (mo)	MSDIF CI	MS_P	HR	HR, 95% CI
	Chinese Glioma Genome Atlas; high vs low risk mirVana miRNA Isolation 27 Kit	4.3	22.1	17.8	ND	0.0113	3.39	1.44-12.91
	Infinium Human Methylation 450k platform (Illumina Inc)	10.3	13.9	3.6	ND	0.008	ND	ND
	Infinium Human Methylation 450k platform (Illumina Inc)	8.3	48	39.7	ND	0.0001	ND	ND
	qPCR	5	4	1	ND	0.4921	ND	ND
	MSP	14	8	6	ND	0.0167	ND	ND
	IHQ	8	10.5	2.5	ND	0.5389	ND	ND
	IHQ	9	8	1	ND	0.0284	ND	ND
	IHQ	9	3	6	ND	0.1459	ND	ND
	IHQ	8	6	2	ND	0.267	0.826	0.48-1.41
	MSP	11	6	5	ND	0.016	0.516	0.29-0.92
	MLPA, IHQ, RTPCR	7.4	6.6	0.8	ND	0.803	ND	ND
	Accutase StemPro RT qPCR, IHQ	ND	ND	ND	ND	0.0064	1.12	ND
	MSP	ND	ND	ND	ND	ND	3.13	ND
	IHQ	5.3	8.3	3	ND	0.045	ND	ND
	miRNeasy Mini kit qPCR	7.3	10.4	3.1	ND	0.001	ND	ND
	miRNeasy Mini kit qPCR	7.6	10.4	2.8	ND	0.0001	ND	ND
	IHQ	7.8	10.9	3.1	ND	0.0001	1.49	1.18-1.89
	ND	ND	ND	ND	ND	0.0436	0.54	
	MSP	13.3	7.8	5.5	ND	0.0001	0.53	0.42-0.67
	ND	ND	ND	ND	ND	0.081	0.62	0.36-1.06
	BiSEQ	11.5	7.9	3.6	ND	0.0001	0.64	0.49-0.82
	ND	ND	ND	ND	ND	0.1162	0.54	0.29-0.99

Abbreviations Continued: MS4A7, membrane spanning 4-domains A7; MSdif, median survival difference; MSneg, mean survival in negative (unexposed); MSpos, mean survival in positive (exposed); N, number of patients; ND, no data; P53, protein 53; PTCH, patched; PP1A, nuclear protein phosphatase 1; PTEN, phosphatase and tensin homologue; SLC7A7, solute carrier family 7 member 7; TCTN1, tectonic family member 1; TRIM38, tripartite motif containing 38.

To view the full Table 2, visit **cancernetwork.com/Glioblastoma_3.23**

results, we extracted data from means, standard deviations, and the number of participants in each group. For continuous asymmetric data, data from medians, ranges, and *P* values were extracted from nonparametric tests. All results are presented in tables.

RESULTS

Study selection

We identified 1470 articles. After the addition of filters, duplication removal, eligibility screening, and final selection, 31 studies were included (**Figure**).

Quality assessment

A detailed quality rating for each of the 31 articles is shown in **Table 1.** Two were classified as moderate quality and 29 were classified as good quality; all scored between 36 and 50 on the Q-Genie checklist. In the itemized analysis, we found that most publications have "very good" and "excellent" scores in the following: selection of the working hypothesis, selection and definition of the outcome of interest, a priori planning of the analysis, and ideal inference extracted from the results. The items "statistical methods" and "selection of groups" were generally scored as "good" on the Likert scale (Table 1).

Study and subject characteristics

The study types included were cross-sectional, cohort, and observational follow-up. **Table 2** shows all characteristics of included studies. **Table 3** presents a detailed description of the signaling pathways and molecular processes that are involved in the relapse of GB. A total of 3585 subjects participated in the 31 studies, with a mean age of 56.05 years (range, 15-90) at the time of GB relapse.

Molecular pathology

The publications describe the processes of deparaffinization, DNA recovery and RNA recovery with different kits, immunohistochemical (IHC) techniques, quantitative polymerase chain reaction (qPCR) with TaqMan and SYBR green probes, multiplex-ligation dependent probe amplification, and high-resolution melting, among other laboratory techniques. The methylation status of O-6-methylguanine DNA methyltransferase (MGMT) was performed in most cases by methylation-specific PCR (MSP) and in others by pyrosequencing (PyroMark Q96 ID). CpG island methylation was measured with Infinium Human Methylation 450k platform (Illumina Inc) and VeraCode GoldenGate Methylation technology (Illumina Inc), among others. The expression of micro-RNA was obtained by mirVana miRNA Isolation 27 Kit and miRNeasy Mini kit; pyrosequencing is the most widely used sequencing technique.

Outcomes

The PFS or TTP was defined by each article as the time between the first surgery and the appearance of a new lesion in imaging studies using McDonald criteria.[5] In some previous studies, PFS was measured but not defined, and the outcomes were described as median survival times, which were compared using the log rank test. Some included studies estimated HRs through Cox regression. Quantitative analysis is shown in Table 2.

O-6-methylguanine DNA methyltransferase (MGMT)

MGMT was reviewed in 21 publications. When the method used to identify MGMT methylation status was immunohistochemistry (IHC), Lalezari et al.[6], Zhang et al,[7] and Wang et al[8] reported statistically significant differences ($P \leq .05$) in the overall survival of patients with MGMT methylation present, with HRs between 1.49 and 2.162. Limam et al[9] did not find statistical significance through this method.

Marziali et al,[10] Adam et al,[11] Dréan et al,[12] Lalezari et al,[6] Tini et al,[13] Kim et al,[14] Eoli et al,[15] Kim et al,[16] Wang et al,[17] Lee et al,[18] Limam et al,[9] Kim et al,[19] and Sana et al.[20] measured MGMT status by MSP and reported statistically significant differences ($P \leq .05$). When the exposure factor was MGMT methylation, they obtained HRs between 0.45 and 0.59; when the exposure factor was unmethylated MGMT, they reported HRs between 1.6 and 2.505.

Limam,[9] who did not obtain statistical significance when using IHC, acquired statistically significant differences (HR, 0.096; 95% CI, 0.02-0.46; $P = .0001$) with MSP. Toraih et al,[21] Sadones et al,[22] and Pinel et al.[23] did not find significant differences.

Isocitrate dehydrogenase

Lalezari et al,[6] De Carlo et al,[24] Etcheverry et al,[25] Wang et al,[17] studied the effect of isocitrate dehydrogenase (*IDH*) with pyrosequencing, finding statistically significant differences for the mutated state, with HRs of 0.12, 0.42, and 0.62, and for the nonmutated state, with an HR of 4.1. Kim[19] found no differences using IHC.

Micro-RNA

Cheng et al,[26] Swellam et al,[27] and Sana et al,[20] investigated micro-RNA (miR) signatures, finding statistically significant differences. Cheng et al[26] used the mirVana miRNA Isolation 27 Kit, finding overexpression of miR-222, -132, and -129 in the CGGA (Chinese Glioma Genome Atlas), with an HR of 3.39. Swellam et al[27] evaluated miR-221 and -222 by qPCR. Sana[20] observed that miR-224, miR-432, miR-454, and miR-672 were overexpressed, while miR-31 and miR-885-5p were under expressed (TaqMan Array Human MicroRNA A + B Cards Set v3.0), with an HR of 1.98.

Epidermal growth factor receptor

Tini et al[13] measured epidermal growth factor receptor (EGFR) expression by

TABLE 3. **Summary of Molecular Processes With Statistical Significance That Interfere in Each of the Capacities Acquired and Necessary for Tumor Growth and Progression, Stratified According to Cancer Hallmarks**

Molecular process	Acquired capacities										Strategy
	1	2	3	4	5	6	7	8	9	10	
MGMT			X				X				The silencing of this repair mechanism allows the accumulation of chemotherapy-induced damage, which generates cell death as long as the cell death mechanisms are intact, or instability if they are not.
miR-222	X					X	X				Overexpression, associated with silencing of MGMT, but also with greater invasion
miR-145						X					Lower expression associated with adducin 3 (ADD3) in the cytoskeleton and SOX9 involved in initiation and progression in solid tumors, and resistance to prostate cancer therapy
miR-132					X				X		Overexpression, promoter of angiogenesis and inflammation
miR-129	X					X					Lower expression, considered tumor suppressor
miR-20a	X										Overexpression in glioblastoma stem cells
miR-23a	X					X					Overexpression, modulate PTEN MAX-interacting protein 1, suppressor of cMyc
miR-27a	X		X								Overexpression, regulates progression in the cell cycle
miR-9						X					Decreased expression, participates in mesenchymal differentiation by JAK/STAT suppression
miR- 21 miR- 22	X					X					Overexpression, silencing PTEN, PUMA (pro-apoptotic), TIMP3 (metalloprotein inhibitor), activation of AKT
miR-485-3p	X		X			X					Decreased expression, tumor suppressor, associated with resistance to therapy due to its relationship with NFYB (beta subunit of nuclear transcription factor Y), NTRK3 (tropomyosin tyrosine kinase family)
miR-31	X					X					Low expression
miR-224	X					X					Overexpression, involved in the activity of CXCR4, metalloproteinase 1
miR-885-5p						X					Low expression
IFIT1	X		X				X				It is a gene induced by interferon α/β, which participates in the inhibition of MGMT, binds to the ribosomal protein L5 to inhibit tumor growth, and forms complexes with IFIT2/3 to induce apoptosis. IFIT overexpression would confer increased response to treatment.
DGKI	X										Diacylglycerol (DAG) activates Ras guanyl nucleotide-releasing proteins by activating the Ras signal. DAG kinase (DGKi) promotes the conversion of DAG to phosphatidic acid. DGKi methylation, in the context of methylated MGMT, would explain the poor response, having the Ras pathway activated.
CpG TRIM38									X	X	Negative regulator of innate immunity and inflammatory response
CpG TRIM58										X	Regulator of innate immune response
CpG MS4A7										X	Cell maturation in monocytes
IDH								X			Cycle of tricarboxylic acids; they catalyze the decarboxylation of isocitrate to alpha ketoglutarate. Their mutation generates depletion of NADPH, deoxynucleotides, and antioxidants, making these models more sensitive to radiotherapy.
SLC7A7	X							X			Amino acid transporter in the plasma membrane. It is overexpressed at the mRNA and protein levels and would confer proliferative capacity to the tumor cell.

Table 3 continues on next page

(CONT.) TABLE 3. **Summary of Molecular Processes With Statistical Significance That Interfere in Each of the Capacities Acquired and Necessary for Tumor Growth and Progression, Stratified According to Cancer Hallmarks**

Molecular process	Acquired capacities										Strategy
	1	2	3	4	5	6	7	8	9	10	
GLI1	X				X	X					Unlike in other types of cancer, here nGLI1 and PATCH at high levels correlated with better PFS.
PTCH	X				X	X					Unlike in other types of cancer, here nGLI1 and PATCH at high levels correlated with better PFS.
CMET	X		X		X	X					Involved with activation by synergistic network Ras, PI3K/Akt, SRC (proto-oncogene)
TCTN1	X				X	X					It would be a regulator of the Hedgehog downstream Gli-Smo pathway. Despite finding high levels of TCTN1 in glioblastoma, its role in the Hedgehog pathway is not clear.
PTEN			X								Loss of function of PTEN; releases survival signals of AKT
CD44	X					X					A cell surface antigen involved in cell migration and adhesion; stem cell marker
PP1A			X								It seems to be associated with p53 since it is overexpressed only in glioblastomas with mutated *TP53*.
P53			X								Genotoxic stress resulting from ionizing radiation or chemotherapeutics increases p53 levels, which induces the expression of proteins such as p21 or pro-proteins such as BAX and PUMA
CXCR4					X						A switch between the primary tumor and recurrence was observed, passing from VEFGR2-HIF1a to CXCL12-CXCR4 at both the mRNA and protein levels. This could imply a transition from angiogenesis to vasculogenesis.
HIF1A					X						The recruitment of myeloid precursors necessary for vasculogenesis would be mediated by CXCL12 and would be independent of HIF1a.
VEGFR2					X						Decrease in its expression with respect to the initial tumor, a product of the switch to vasculogenesis
LAPTM4B	X				X	X					Increase in angiogenesis. Activates the PI3K/Akt signal. It favors chemoresistance by increasing the release of chemotherapeutic drugs such as doxorubicin, paclitaxel, and cisplatin due to its relationship with the *MDR1* gene (multidrug resistance).
DNAPKS							X				The cytotoxicity of radiation therapy depends on its ability to generate double-stranded DNA damage. Nonhomologous recombination is the main mechanism to repair this damage and depends largely on the expression of DNA PKcs.
Cytochrome c oxidase			X					X			The increase in cytochrome oxidase increases the capacity for electron flow, more efficient mitochondrial coupling, and a decrease in the production of reactive ROS oxygen species, protecting the tumor cell.
Tetraspanin CD151	X				X	X					Activation of CDC42 and Rac: Rho family, motility. Activation of HGF/c-Met, PI3K/Akt/GSK-3b/Snail

CXCL12, CXC motif chemokine ligand 12; CXCR, chemokine receptor family; DGKI, diacylglycerol kinase iota; DNA-PKcs, DNA-dependent protein kinase; GLI1, glioma-associated oncogene homologue 1; HIF1a, hypoxia-inducible factor 1 subunit alpha; IDH, isocitrate dehydrogenase; IFIT1, interferon-induced protein with tetratricopeptide repeats 1; LAPTM4B-35, lysosomal protein transmembrane 4 beta; MGMT, O-6-methylguanine DNA methyltransferase; miR, microRNA; MS4A7, membrane-spanning 4-domains subfamily A member 7; NADPH, nicotinamide adenine dinucleotide phosphate; P53, protein 53; PFS, progression-free survival; PP1A, nuclear protein phosphatase 1 alpha; PTEN, phosphatase and tensin homologue; PTCH, patched; ROS, reactive oxygen species; SLC7A7, solute carrier family 7 member 7; TCTN1, tectonic family member 1; *TP53*, tumor protein 53; TRIM38, tripartite motif containing 38.

Acquired capacities and tumor progression stratified according to cancer hallmarks: (1) sustained proliferation signal, (2) evasion of suppressors, (3) evasion of apoptosis, (4) immortality, (5) angiogenesis, (6) invasion and metastasis, (7) genomic instability, (8) metabolism, (9) inflammation, (10) evasion of the immune system.

IHC, associating it with statistically significant differences in median survival: $P = .003$ (HR, 1.79; 95% CI, 1.15-2.8). Eoli et al[15] and Limam et al[9] did not find statistical significance by the same method. Marziali et al[10] and Weller et al[28] measured EGFRvIII without finding significant differences.

P53

Li et al[29] and Wang et al[17] used IHC to evaluate p53 expression or mutations in *TP53*, finding a significant difference (HR, 0.149) in median survival favoring patients with *TP53* mutation. Eoli et al[15] and Limam et al[9] did not find significant differences. Additionally, Limam et al[9] studied MDM2 measured by IHC without finding significant differences.

DISCUSSION

Although the clinical course of each patient with GB is unique and is influenced by the location of the tumor and their age, comorbidities, and Karnofsky Performance Status grade, among other factors, all patients receive the same treatment because no personalized treatment is yet available. Maximum safe resection is performed, in which the tumor is removed macroscopically. The patient subsequently undergoes radiotherapy and concomitant chemotherapy, if their comorbidities allow it, then receives only adjuvant chemotherapy for a generally short time, until the disease appears to be under control. However, relapse occurs in virtually 100% of patients because of the limited treatment options, few of which offer any evidence of increased survival. Cells resistant to multiple therapies persist in the brain parenchyma around the postoperative and postirradiated cavity. Genomic analysis pre- and post-treatment has shown that the recurrent tumor activates pathways associated with clonal and subclonal evolution; these are the origin of treatment failure, development of resistance, and, finally, tumor relapse.

Many molecular pathways and processes are activated during tumor relapse in GB, associated with its evolutionary process. These include: sustained proliferation signals, in which we identified the role of EGFR, miR, IFIT1, DGKI, SLC7A7, GLI1, and PTCH, among others; evasion of apoptosis, with different alterations in *TP53*, *PTEN*, *PP1A*, and *MGMT*; angiogenesis, associated with the differentiated expression of CXCR4, CXCL12, HIF1α, and VEGFR2; invasion processes, related to miR, tetraspanin CD151, LAPTM4B, and CD44 clusters; genomic instability, associated with alteration in repair mechanisms such as MGMT and DNA PKs (DNA-dependent protein kinase); energy dysregulation or metabolic changes associated with IDH; tumor-promoted inflammation in relation to miR and TRIM38 expression; and, finally, immune system evasion associated with TRIM58 or MS4A7 (Table 3). These processes, already described by Hanahan and Weinberg,[3] are not a series of steps accomplished one after another, but rather are launched at different times and in different ways in each tumor, reflecting their intratumoral and intertumoral heterogeneity.

The present review aimed to assess the clinical relevance of the markers identified in each of these different molecular processes or signaling pathways. Some markers have good evidence and clinical applicability, such as MGMT and IDH. Others have substantial theoretical evidence but discrepancies in clinical studies. Some markers that are good candidates emerge rapidly, such as miR and others; these constitute the vast majority of the evidence found, but they require more study in glioblastoma, although they have been described in other types of cancer. Notably, we also found biomarkers with good evidence of their involvement in tumor relapse expressed in terms of PFS, such as MGMT and IDH.

The *MGMT* gene is located on chromosome 10q26 and encodes a DNA repair protein that removes alkyl groups from the O6-position of guanine. Epigenetic silencing mediated by MGMT promoter methylation generates decreased DNA repair, causing greater chemosensitivity. Moreover, the absence of methylation means that each time an alkylating agent injures the guanine in the O6 position, it is repaired by MGMT, causing chemoresistance.[30] This methylation status appears in the multivariate analysis of 21 publications. Whenever a factor associated with recurrence is postulated, it must be verified that it is independent of the possible effect of the methylation status of MGMT. To our knowledge, MGMT methylation confers more chemosensitivity, but it remains uncertain why some tumors with methylation do not respond to initial therapy. Zhang et al[11] analyzed IFIT1 and found that MGMT inhibition is associated with its overexpression. Cohen et al,[31] when evaluating tumors with MGMT methylation without clinical response, found differential expression in DGKI, a RAS modulator.

IDHs are a group of enzymes fundamental in the tricarboxylic acid cycle. They catalyze the decarboxylation of isocitrate to α-ketoglutarate. IDH1 acts at the level of cytosol and peroxisome, while IDH2/3 acts at the mitochondrial level. IDH1/2 has important functions associated with glucose consumption, lipogenesis, glutathione catabolism, and defense against reactive oxygen species and radiation.[32] The *IDH1* mutation identified by De Carlo et al[24] and Wang et al[17] is found more frequently in secondary glioblastomas and generates depletion of NADPH, deoxynucleotides, and antioxidants, making these models more sensitive to radiotherapy and more likely to be associated with a higher PFS. Tumors with nonmutated *IDH1*, according to Lalezari et al[6] and Etcheverry et al,[25] are

more frequently primary glioblastomas and associated with a lower PFS.

Under normal conditions, in response to genotoxic stress, p53 protein induces cycle stop, mainly in the G1 phase to repair the DNA damage; ultimately, this leads to apoptotic cell death or senescence, thus preventing cell replication with DNA damage. Genotoxic stress secondary to ionizing radiation or chemotherapeutics increases p53 levels, which induces the expression of regulatory cell cycle proteins, such as p21, or pro-apoptotic proteins, such as BAX and PUMA.[29] *TP53* mutation, studied by Li et al,[29] Wang et al,[21] Eoli et al,[19] and Limam et al,[9] is associated with chemosensitivity and higher PFS, while functional p53 is associated with a lower PFS.

Some of the most attractive markers currently under research are miRs: small noncoding RNA molecules, highly conserved, and composed of between 18 and 25 nucleotides. They are responsible for the posttranscriptional negative regulation of gene expression. Bioinformatics tools estimate that miRNAs regulate up to 60% of human genes, including genes associated with chemo- and radioresistance. miRNAs generally act in clusters and adopt the role of oncogenes or tumor suppressor genes, depending on their target. In this way, they can inactivate suppressor genes or activate oncogenes.[20]

Wang et al,[8] when comparing the miRNA profile of glioblastomas with that of healthy subjects in peripheral blood, has found a decrease in the expression of miR-485-3p, suggesting its role as tumor suppressor. Its participation in chemoresistance has also been described. This decrease in expression was associated with lower disease-free survival. Cheng et al[26] studied miR 222, which is widely recognized as an oncogene. The miRNAs showed differential expression between tumors with and without *MGMT* methylation. Therefore, the signature constituted by miR-222, miR-145, miR-20a, miR-132, and miR-129 was postulated by Cheng et al[26] as associated with a decrease in PFS even in the presence of promoter methylation.

From our perspective, there is ever-increasing knowledge of gliomagenesis and why successful treatment has been so elusive. We have synthesized a great deal of evidence and framed it in the landmarks of cancer proposed by Hanahan and Weinberg. However, the new therapies have only slightly increased PFS, with no benefit to OS, which shows that we still have "lost pieces." As such, it is necessary to standardize laboratory tests as well as the exhaustive application of current criteria for the follow-up of patients at the time of evaluating a tumor recurrence. The new therapies have expanded our vocabulary with terms like pseudoprogression and pseudoresponse. We believe that the best way to evaluate these "escape routes" is by analyzing recurrence in terms of the central precepts of molecular biology, and what occurs at many levels: DNA, RNA expression, transcriptional, protein and posttranscriptional, and epigenomic. We have ever-more alternatives framed in immunotherapy, vaccines, target therapies, and bioprospecting studies. Multidisciplinary research is clearly necessary—including basic, clinical, and bioengineering research—which at some point must achieve longer life expectancies for our patients.

Limitations

A limitation of the review is the large amount of isolated data presented, which is useful for research but not as relevant in the clinical field if no other studies exist to support them. Moreover, many studies lack information on PFS, and for this reason 21 studies initially considered were excluded. Information about disease-free survival was requested from all authors via email, but few data were obtained. Finally, the categorization of molecular processes according to the evolutionary processes described is difficult to achieve due to the great integration of the pathways. Occasionally it becomes a somewhat subjective task, although it is very useful to visualize tumor escape pathways.

Another limitation is the lack of standardization in the tests; results may vary according to the proposed analysis. With MGMT, for instance, results differ depending on the technique used. Likewise, there is a lack of standardization for the use of radiological criteria of relapse; some studies still use the McDonald criteria, while others use the RANO or the iRANO criteria.

CONCLUSIONS

It is possible to identify a wide variety of signaling pathways and molecular processes implied in the relapse of GB, as well as in the evolution of many types of cancer. This diversity would explain intra- and intertumor heterogeneity, treatment evasion, and, finally, relapse. However, there are few molecular processes for which robust evidence is available that have resulted in clinical utility. Therefore, it is necessary to subject the candidate processes to additional clinical trials, to build a larger body of evidence that allows personalization of GB therapy. In this context, knowledge of the signaling pathways activated in each case will determine the type of treatment and the temporal pattern of its administration. ■

AUTHOR AFFILIATIONS: [1]Department of Neurosurgery, Hospital Universitario del Valle "Evaristo García," University of Valle; Cali, Colombia; javier.orozco@correounivalle.edu.co
[2]Department of Neurosurgery, Hospital Universitario del Valle "Evaristo García," University of Valle; Cali, Colombia; fperaltap@unal.edu.co
[3]Department of Neurosurgery, Hospital

Universitario del Valle "Evaristo García," University of Valle; Cali, Colombia; oscar.escobar@correounivalle.edu.co
[4]Research and Innovation Unit, Hospital Universitario del Valle "Evaristo García," University of Valle; Cali, Colombia; brenda.coll@correounivalle.edu.co
[5]Service of Anatomic Pathology, Hospital Germans Trias I Pujol, Autonomous University of Barcelona; Barcelona, Spain; aurelio.ariza@uab.cat

CORRESPONDING AUTHOR: *Javier Orozco-Mera, MD, FACS, MSc
Neurosurgeon
Department of Neurosurgery
Hospital Universitario del Valle "Evaristo García"
University of Valle
Street 5 # 36-08, Valle del Cauca
Cali, Colombia
Phone (+57) 6206000 ext. 1804 / (+57) 5195082
ORCID: 0000-0002-4293-4659
Email: javier.orozco@correounivalle.edu.co

COMPETING INTERESTS: The authors declare they have no conflicts of interest.

FUNDING: This research did not receive external funding.

ACKNOWLEDGMENTS: To Rey Juan Carlos University and Hospital Universitario del Valle "Evaristo García" for the academic space to accomplish this investigation.

ACKNOWLEDGMENTS AND DISCLOSURES: No conflicts of interest are reported by authors. Each author met each of the authorship requirements as stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, namely the conception, design, acquisition, analysis, interpretation of the data, writing the draft, and final approval.

REFERENCES

1. Nguyen HS, Shabani S, Awad AJ, Kausha M, Doan N. Molecular markers of therapy-resistant glioblastoma and potential strategy to combat resistance. *Int J Mol Sci.* 2018;19(6):1765. doi:10.3390/ijms19061765

2. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996. doi:10.1056/NEJMoa043330

3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646-674. doi:10.1016/j.cell.2011.02.013

4. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi:10.1136/bmj.n71

5. Chinot OL, Macdonald DR, Abrey LE, Zahlmann G, Kerloëguen Y, Cloughesy TF. Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of antiangiogenic therapy. *Curr Neurol Neurosci Rep*. 2013;13(5):347. doi:10.1007/s11910-013-0347-2

6. Lalezari S, Chou AP, Tran A, et al. Combined analysis of O6-methylguanine-DNA methyltransferase protein expression and promoter methylation provides optimized prognostication of glioblastoma outcome. *Neuro Oncol*. 2013;15(3):370-381. doi:10.1093/neuonc/nos308

7. Zhang J-F, Chen Y, Lin G-S, et al. High IFIT1 expression predicts improved clinical outcome, and IFIT1 along with MGMT more accurately predicts prognosis in newly diagnosed glioblastoma. *Hum Pathol*. 2016;52:136-144. doi:10.1016/j.humpath.2016.01.013

8. Wang ZQ, Zhang MY, Deng ML, Weng NQ, Wang HY, Wu SX. Low serum level of miR-485-3p predicts poor survival in patients with glioblastoma. *PLoS One*. 2017;12(9):e0184969. doi:10.1371/journal.pone.0184969

9. Limam S, Missaoui N, Abdessayed N, et al. Prognostic significance of MGMT methylation and expression of MGMT, P53, EGFR, MDM2 and PTEN in glioblastoma multiforme. *Ann Biol Clin (Paris)*. 2019;77(3):307-317. doi:10.1684/abc.2019.1448

10. Marziali G, Buccarelli M, Giuliani A, et al. A three-microRNA signature identifies two subtypes of glioblastoma patients with different clinical outcomes. *Mol Oncol*. 2017;11(9):1115-1129. doi:10.1002/1878-0261.12047

11. Adam SA, Schnell O, Pöschl J, et al. ALDH1A1 is a marker of astrocytic differentiation during brain development and correlates with better survival in glioblastoma patients. *Brain Pathol.* 2012;22(6):788-797. doi:10.1111/j.1750-3639.2012.00592.x

12. Dréan A, Rosenberg S, Lejeune F-X, et al. ATP binding cassette (ABC) transporters: expression and clinical value in glioblastoma. *J Neurooncol.* 2018;138(3):479-486. doi:10.1007/s11060-018-2819-3. Published correction appears in *J Neurooncol.* 2018;138(3):487.

13. Tini P, Nardone V, Pastina P, et al. Epidermal growth factor receptor expression predicts time and patterns of recurrence in patients with glioblastoma after radiotherapy and temozolomide. *World Neurosurg.* 2018;109:e662-e668. doi:10.1016/j.wneu.2017.10.052

14. Kim J, Lee S-H, Jang JH, Kim M-S, Lee EH, Kim YZ. Increased expression of the histone H3 lysine 4 methyltransferase MLL4 and the histone H3 lysine 27 demethylase UTX prolonging the overall survival of patients with glioblastoma and a methylated MGMT promoter. *J Neurosurg.* 2017;126(5):1461-1471. doi:10.3171/2016.4.JNS1652

15. Eoli M, Menghi F, Bruzzone MG, et al. Methylation of O6-methylguanine DNA methyltransferase and loss of heterozygosity on 19q and/or 17p are overlapping features of secondary glioblastomas with prolonged survival. *Clin Cancer Res.* 2007;13(9):2606-2613. doi:10.1158/1078-0432.CCR-06-2184

16. Kim YS, Kim SH, Cho J, et al. MGMT gene promoter methylation as a potent prognostic factor in glioblastoma treated with temozolomide-based chemoradiotherapy: a single-institution study. *Int J Radiat Oncol Biol Phys.* 2012;84(3):661-667. doi:10.1016/j.ijrobp.2011.12.086

17. Wang K, Wang Y-Y, Ma J, et al. Prognostic value of MGMT promoter methylation and TP53 mutation in glioblastomas depends on IDH1 mutation. *Asian Pac J Cancer Prev.* 2014;15(24):10893-10898. doi:10.7314/APJCP.2014.15.24.10893

18. Lee D, Suh Y-L, Park T-I, et al. Prognostic significance of tetraspanin CD151 in newly diagnosed glioblastomas. *J Surg Oncol.* 2013;107(6):646-652. doi:10.1002/jso.23249

19. Kim Y, Do I-G, Hong M, Suh Y-L. Negative prognostic effect of low nuclear GLI1 expression in glioblastomas. *J Neurooncol.* 2017;133(1):69-76. doi:10.1007/s11060-017-2426-8

20. Sana J, Radova L, Lakomy R, et al. Risk score based on microRNA expression signature is independent prognostic classifier of glioblastoma patients. *Carcinogenesis.* 2014;35(12):2756-2762. doi:10.1093/carcin/bgu212

21. Toraih EA, El-Wazir A, Hussein MH, et al. Expression of long intergenic non-coding RNA, regulator of reprogramming, and its prognostic value in patients with glioblastoma. *Int J Biol Markers.* 2019;34(1):69-79. doi:10.1177/1724600818814459

22. Sadones J, Michotte A, Veld P, et al. MGMT promoter hypermethylation correlates with a survival benefit from temozolomide in patients with recurrent anaplastic astrocytoma but not glioblastoma. *Eur J Cancer.* 2009;45(1):146-153. doi:10.1016/j.ejca.2008.09.002

23. Pinel B, Duchesne M, Godet J, et al. Mesenchymal subtype of glioblastomas with high DNA-PKcs expression is associated with better response to radiotherapy and temozolomide. *J Neurooncol. 2017*;132(2):287-294. doi:10.1007/s11060-016-2367-7

24. De Carlo E, Gerratana L, De Maglio G, et al. Defining a prognostic score based on O6-methylguanine-DNA methyltransferase cut-off methylation level determined by pyrosequencing in patients with glioblastoma multiforme. *J Neurooncol.* 2018;140(3):559-568. doi:10.1007/s11060-018-2981-7

25. Etcheverry A, Aubry M, Idbaih A, et al. DGKI methylation status modulates the prognostic value of MGMT in glioblastoma patients treated with combined radio-chemotherapy with temozolomide. *PLoS One.* 2014;9(9):e104455. doi:10.1371/journal.pone.0104455

26. Cheng W, Ren X, Cai J, et al. A five-miRNA signature with prognostic and predictive value for MGMT promoter-methylated glioblastoma patients. *Oncotarget.* 2015;6(30): 29285-29295. doi:10.18632/oncotarget.4978

27. Swellam M, Ezz El Arab L, Al-Posttany AS, Said SB. Clinical impact of circulating oncogenic MiRNA-221 and MiRNA-222 in glioblastoma multiform. *J Neurooncol.* 2019;144(3):545-551. doi:10.1007/s11060-019-03256-2

28. Weller M, Kaulich K, Hentschel B, et al; German Glioma Network. Assessment and prognostic significance of the epidermal growth factor receptor vIII mutation in glioblastoma patients treated with concurrent and adjuvant temozolomide radiochemotherapy. *Int J Cancer.* 2014;134(10):2437-2447. doi:10.1002/ijc.28576

29. Li S, Jiang T, Li G, Wang Z. Impact of p53 status to response of temozolomide in low MGMT expression glioblastomas: preliminary results. *Neurol Res.* 2008;30(6):567-570. doi:10.1179/174313208X297913

30. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997-1003. doi:10.1056/NEJMoa043331

31. Olmez OF, Cubukcu E, Evrensel T, et al. The immunohistochemical expression of c-Met is an independent predictor of survival in patients with glioblastoma multiforme. *Clin Transl Oncol.* 2014;16(2):173-177. doi:10.1007/s12094-013-1059-4

32. Cohen A, Holmen S, Colman H. IDH1 and IDH2 mutations in gliomas. *Curr Neurol Neurosci Rep.* 2013;13(5):345. doi:10.1007/s11910-013-0345-4

KISQALI—it's not just

Indications

KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

IMPORTANT SAFETY INFORMATION

Interstitial lung disease/pneumonitis. Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

Across clinical trials in patients with advanced or metastatic breast cancer treated with KISQALI in combination with an aromatase inhibitor or fulvestrant ("KISQALI treatment groups"), 1.6% of patients treated with KISQALI had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

living longer. It's living well.

MONALEESA-2, statistically significant overall survival and preserved quality of life in 1L postmenopausal patients: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. At a median follow-up of 26 months, median TTD ≥10% was 27.7 months vs 27.6 months; HR=0.944 (95% CI: 0.720-1.237). PFS was the primary end point.

1L=first line; HR=hazard ratio; NR=not reached; OS=overall survival; PFS=progression-free survival; TTD=time to deterioration.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

KISQALI®
ribociclib 200 mg tablets

NCCN RECOMMENDED

National Comprehensive Cancer Network® (NCCN®) now recognizes ribociclib (KISQALI®) + ET, a Category 1 preferred treatment option, for showing an **OS BENEFIT IN 1L PATIENTS** with HR+/HER2- mBC[1]

MONALEESA-2 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + letrozole (n=334) vs placebo + letrozole (n=334) in postmenopausal patients with HR+/HER2- mBC who received no prior therapy for advanced disease. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. Quality of life was a secondary end point: at a median follow-up of 26 months, median TTD ≥10% was 27.7 months vs 27.6 months; HR=0.944 (95% CI: 0.720-1.237).[2-6]

MONALEESA-7 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + ET (NSAI or tamoxifen) + goserelin vs placebo + ET (NSAI or tamoxifen) + goserelin (ITT) in premenopausal patients with HR+/HER2- mBC who received no prior ET for advanced disease. **KISQALI is not indicated for concomitant use with tamoxifen.** Efficacy results are from a prespecified subgroup analysis of 495 patients who received KISQALI (n=248) or placebo (n=247) with an NSAI + goserelin and were not powered to show statistical significance. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 54 months (exploratory analysis), median OS was 58.7 months with KISQALI + NSAI + goserelin (95% CI: 48.5-NR) vs 47.7 months with NSAI + goserelin (95% CI: 41.2-55.4); HR=0.798 (95% CI: 0.615-1.035). At a median follow-up of 35 months, statistical significance was established for overall survival in the ITT population; HR=0.71 (95% CI: 0.54-0.95); *P*=0.00973. Quality of life was a secondary end point: at a median follow-up of 35 months, median TTD ≥10% was 34.2 months vs 23.3 months; HR=0.69 (95% CI: 0.52-0.91).[2,7-10]

MONALEESA-3 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + fulvestrant (n=484) vs placebo + fulvestrant (n=242) for the treatment of postmenopausal patients with HR+/HER2- mBC who have received no or only 1 line of prior ET for advanced disease. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 71 months (exploratory analysis), in a 1L subgroup analysis, median OS was 67.6 months (95% CI: 59.6-NR) with KISQALI + fulvestrant vs 51.8 months with placebo + fulvestrant (95% CI: 40.4-61.2); HR=0.673 (95% CI: 0.504-0.899). At a median follow-up of 39 months, statistical significance was established for overall survival in the ITT population; HR=0.724 (95% CI: 0.568-0.924); *P*=0.00455. Quality of life was a secondary end point: at a median follow-up of 39 months, median TTD ≥10% was 35.9 months vs 33.1 months; HR=0.81 (95% CI: 0.62-1.06).[2,11-14]

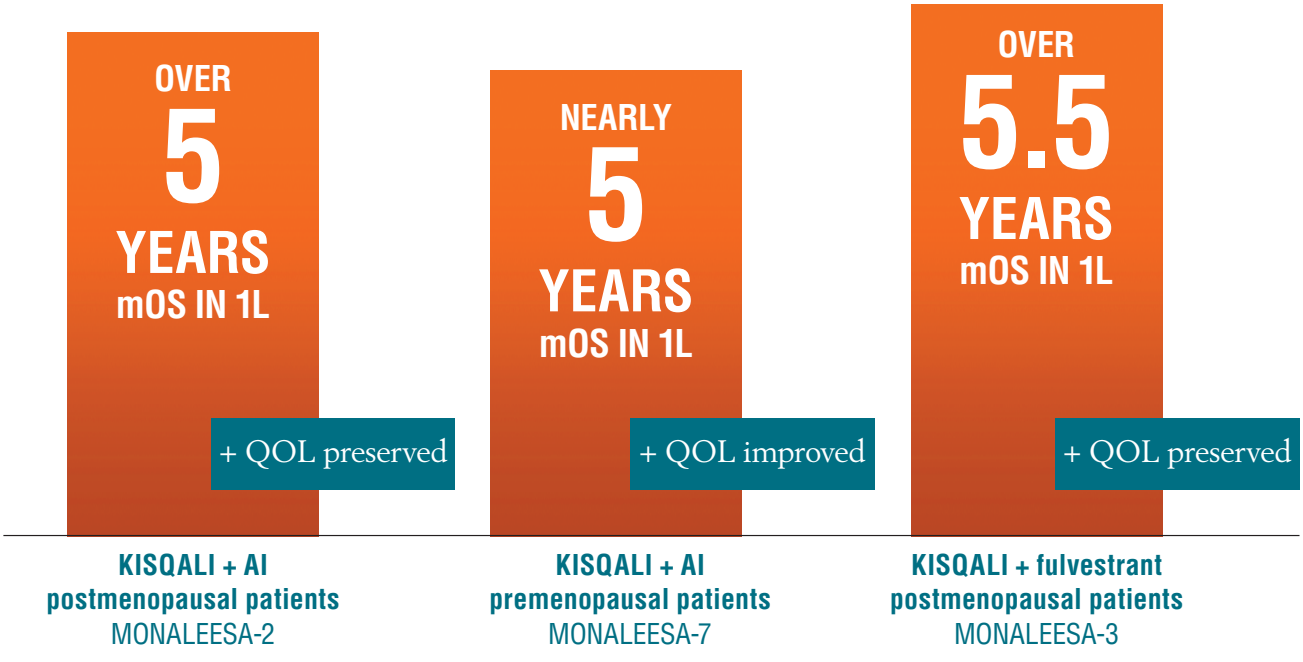
Quality of life was assessed using the EORTC QLQ-C30 questionnaire, a validated tool used worldwide to assess quality of life in patients with cancer. Quality of life was a secondary end point measured by patient-reported outcomes and was assessed at baseline and throughout treatment. Time to deterioration was defined as a decline of at least 10% of the global health status/QOL scale score. There was no prespecified statistical procedure controlling for type 1 error. The EORTC QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QOL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and perceived financial impact of the disease.[10,14-16]

AI=aromatase inhibitor; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ET=endocrine therapy; ITT=intent to treat; mBC=metastatic breast cancer; mOS=median overall survival; NSAI=nonsteroidal aromatase inhibitor; QOL=quality of life.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

Living longer, living well

Only KISQALI—a proven first-line overall survival benefit, with preserved quality of life, across all 3 phase III trials



1L refers to patients with mBC.

"Overall survival is the hardest end point to achieve in clinical trials. And in many respects, perhaps the most important…we're trying to improve the survival of a patient; not just the progression-free survival or the time where the tumor is controlled, but **how long they live…**"

Dennis Slamon, MD, PhD
University of California, Los Angeles

IMPORTANT SAFETY INFORMATION (continued)

Interstitial lung disease/pneumonitis (continued). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis.

KISQALI®
ribociclib 200 mg tablets

Isn't it time to start your next first-line patient on KISQALI?

"**[MONALEESA-2] demonstrates that patients with advanced hormone receptor-positive breast cancer can now expect on average to exceed a life expectancy of five years.** And for many of them, much longer than five years. And this is an important development."

Gabriel Hortobagyi, MD

"**Having independence means the world to me—** being able to do things on my own, go places when I feel like going. That's part of quality for life for me, being independent and doing my own thing."

Rose, KISQALI patient

See how KISQALI could help your next first-line patient

MONALEESA-2: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. At a median follow-up of 26 months, median TTD ≥10% was 27.7 months vs 27.6 months; HR=0.944 (95% CI: 0.720-1.237). PFS was the primary end point.[2-6]

IMPORTANT SAFETY INFORMATION (continued)

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI.

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

Important Safety Information (continued)

Severe cutaneous adverse reactions (continued). If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These electrocardiogram (ECG) changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the non-steroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Hepatobiliary toxicity. Across KISQALI treatment groups, increases in transaminases were observed. Across all trials, grade 3/4 increases in alanine aminotransferase (ALT) (11% vs 2.1%) and aspartate aminotransferase (AST) (8% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days and median time to resolution to grade ≤2 was 21 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the upper limit of normal (ULN) and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

KISQALI® ribociclib 200 mg tablets

IMPORTANT SAFETY INFORMATION (continued)

Neutropenia. Across KISQALI treatment groups neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 17 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1.7% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 1%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. Most common (incidence ≥20%) adverse reactions include infections, nausea, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, and back pain.

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased**.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Published June 21, 2022. Accessed October 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. **2.** Kisqali [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **3.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med.* 2022;386(10):942-950. doi:10.1056/NEJMoa2114663 **4.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748. doi:10.1056/NEJMoa1609709 **5.** Data on file. Novartis Pharmaceuticals Corp; 2021. **6.** Data on file. Novartis Pharmaceuticals Corp; 2017. **7.** Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915. doi:10.1016/S1470-2045(18)30292-4 **8.** Data on file. Novartis Pharmaceuticals Corp; 2020. **9.** Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307-316. doi:10.1056/NEJMoa1903765 **10.** Harbeck N, Franke F, Villanueva-Vazquez R, et al. Health-related quality of life in premenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer treated with ribociclib plus endocrine therapy: results from a phase III randomized clinical trial (MONALEESA-7). *Ther Adv Med Oncol.* 2020;12:1758835920943065. doi:10.1177/1758835920943065 **11.** Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472. doi:10.1200/JCO.2018.78.9909 **12.** Data on file. Novartis Pharmaceuticals Corp; 2022. **13.** Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524. doi:10.1056/NEJMoa1911149 **14.** Fasching PA, Beck JT, Chan A, et al. Ribociclib plus fulvestrant for advanced breast cancer: health-related quality-of-life analyses from the MONALEESA-3 study. *Breast.* 2020;54:148-154. doi:10.1016/j.breast.2020.09.008 **15.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748;(protocol). doi:10.1056/NEJMoa1609709 **16.** Fayers PM, Aaronson NK, Bjordal K, et al. EORTC QLQ-C30 Scoring Manual (3rd edition). 2001.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

NOVARTIS

KISQALI® ribociclib 200 mg tablets

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 1/23 245502

KISQALI® (ribociclib) tablets, for oral use
Initial U.S. Approval: 2017

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

Across clinical trials (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.1% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.3% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported *[see Adverse Reactions (6.2)]*.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis *[see Dosage and Administration (2.2) in the full prescribing information]*.

5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI *[see Adverse Reactions (6.2)]*.

If signs or symptoms of severe cutaneous reactions occur, interrupt KISQALI until the etiology of the reaction has been determined *[see Dosage and Administration (2.2) in the full prescribing information]*. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life threatening cutaneous reactions during KISQALI treatment.

5.3 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner *[see Clinical Pharmacology (12.2) in the full prescribing information]*. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.4)]*.

Across MONALEESA-2, MONALEESA-7, and MONALEESA-3 in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (1%) had a > 500 ms post-baseline QTcF value, and 59 out of 1054 patients (6%) had a > 60 ms increase from baseline in QTcF intervals.

These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, on the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 *[see Adverse Reactions (6)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy *[see Dosage and Administration (2.2) in the full prescribing information]*.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

5.4 Increased QT Prolongation With Concomitant Use of Tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was > 10 ms higher in the tamoxifen plus placebo subgroup compared with the non-steroidal aromatase inhibitors (NSAIs) plus placebo subgroup. In the placebo arm, an increase of > 60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of > 60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

5.5 Hepatobiliary Toxicity

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, Grade 3 or 4 increases in alanine aminotransferase (ALT) (10% vs. 2%) and aspartate aminotransferase (AST) (7% vs. 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 85 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≤ 2 was 22 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated *[see Dosage and Administration (2.2) in the full prescribing information]*.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobiliary Toxicity) *[see Dosage and Administration (2.2) in the full prescribing information]*. Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

5.6 Neutropenia

In MONALEESA-2, MONALEESA-7, and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (74%), and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in 1% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 0.8%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6 *[see Dosage and Administration (2.2) in the full prescribing information]*.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Population (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

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

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.2)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.3, 5.4)]*
- Hepatobiliary Toxicity *[see Warnings and Precautions (5.5)]*
- Neutropenia *[see Warnings and Precautions (5.6)]*

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.

MONALEESA-2: KISQALI in Combination with Letrozole

Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

The safety data reported below are based on MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Among patients receiving KISQALI plus letrozole, 7% were reported to have permanently discontinued both KISQALI and letrozole and 7% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus letrozole, 2% were reported to have permanently discontinued both and 0.9% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), vomiting (2%). Antiemetics and antidiarrheal medications were used to manage symptoms as clinically indicated.

On-treatment deaths, regardless of causality, were reported in three cases (0.9%) of KISQALI plus letrozole treated patients vs. one case (0.3%) of placebo plus letrozole treated patients. Causes of death on KISQALI plus letrozole included one case each of the following: progressive disease, death (cause unknown), and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation).

The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain.

The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, abnormal liver function tests, and lymphopenia.

In MONALEESA-2, syncope occurred in 9 patients (3%) in the KISQALI plus letrozole arm vs. 3 (1%) in placebo plus letrozole arm.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-2 are listed in Table 8 and Table 9, respectively.

Table 8: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-2 (All Grades)

	KISQALI + letrozole N = 334			Placebo + letrozole N = 330		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse Drug Reactions	%	%	%	%	%	%
Infections and Infestations						
Urinary tract infection	11	1	0	8	0	0
Blood and Lymphatic System Disorders						
Neutropenia	75	50	10	5	1	0
Leukopenia	33	20	1	1	< 1	0
Anemia	18	1	< 1	5	1	0
Lymphopenia	11	6	1	2	1	0
Metabolism and Nutrition Disorders						
Decreased appetite	19	2	0	15	< 1	0
Nervous System Disorders						
Headache	22	< 1	0	19	< 1	0
Insomnia	12	< 1	0	9	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea	12	1	0	9	1	0
Musculoskeletal and Connective Tissue Disorders						
Back pain	20	2	0	18	< 1	0
Gastrointestinal Disorders						
Nausea	52	2	0	29	1	0
Diarrhea	35	1	0	22	1	0
Vomiting	29	4	0	16	1	0
Constipation	25	1	0	19	0	0
Stomatitis	12	< 1	0	7	0	0
Abdominal pain	11	1	0	8	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	33	0	0	16	0	0
Rash	17	1	0	8	0	0
Pruritus	14	1	0	6	0	0
General Disorders and Administration-site Conditions						
Fatigue	37	2	< 1	30	1	0
Pyrexia	13	< 1	0	6	0	0
Edema peripheral	12	0	0	10	0	0
Investigations						
Abnormal liver function tests[1]	18	8	2	6	2	0

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.
[1]Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

Additional adverse reactions in MONALEESA-2 for patients receiving KISQALI plus letrozole included interstitial lung disease (0.3%), lung infiltration (0.3%), pneumonitis (0.3%), and pulmonary fibrosis (0.6%).

Table 9: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-2

	KISQALI + letrozole N = 334			Placebo + letrozole N = 330		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory Parameters	%	%	%	%	%	%
HEMATOLOGY						
Leukocyte count decreased	93	31	3	29	1	< 1
Neutrophil count decreased	93	49	11	24	1	< 1
Hemoglobin decreased	57	2	0	26	1	0
Lymphocyte count decreased	51	12	2	22	3	1
Platelet count decreased	29	1	< 1	6	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	46	8	2	36	1	0
Aspartate aminotransferase increased	44	6	1	32	2	0
Creatinine increased	20	1	0	6	0	0
Phosphorous decreased	13	5	1	4	1	0
Potassium decreased	11	1	1	7	1	0

MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor

Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a NSAI or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. The median duration of exposure on the KISQALI arm was 15.2 months with 66% of patients exposed for ≥ 12 months. The safety data reported below are based on 495 pre/perimenopausal patients receiving KISQALI plus NSAI plus goserelin or placebo plus NSAI plus goserelin.

Dose reductions due to ARs occurred in 33% of patients receiving KISQALI plus NSAI plus goserelin, and in 4% of patients receiving placebo plus NSAI plus goserelin. Among patients receiving KISQALI plus NSAI, 3% were reported to have permanently discontinued both KISQALI and NSAI and 3% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus NSAI, 2% were reported to have permanently discontinued both and 0.8% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation on KISQALI in patients receiving KISQALI plus NSAI (as compared to the placebo arm) were ALT increased (2% vs. 0.8%), AST increased (2% vs. 0.8%), drug-induced liver injury (1% vs. 0.4%). One patient (0.4%) died while on treatment with KISQALI plus NSAI plus goserelin due to the underlying malignancy.

The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) were neutropenia, infections, leukopenia, arthralgia, nausea, and alopecia. The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, and abnormal liver function tests. See Table 10 below.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-7 are listed in Table 10 and Table 11, respectively.

Table 10: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse Drug Reactions	%	%	%	%	%	%
Infections and Infestations						
Infections[1]	35	2	0	24	< 1	0
Blood and Lymphatic System Disorders						
Neutropenia	78	55	10	7	2	< 1
Leukopenia	29	13	< 1	3	< 1	0
Anemia	19	3	0	8	1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	15	0	0	10	0	0
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	33	< 1	0	29	1	0
Gastrointestinal Disorders						
Nausea	31	0	0	20	0	0
Constipation	16	0	0	12	0	0
Stomatitis	10	0	0	8	< 1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	21	0	0	13	0	0
Rash	17	< 1	0	9	0	0
Pruritus	10	0	0	4	0	0
General disorders and Administration-site Conditions						
Pyrexia	17	< 1	0	6	0	0
Pain in extremity	10	0	0	8	1	0
Investigations						
Alanine aminotransferase increased	13	5	0	9	1	0
Aspartate aminotransferase increased	13	4	0	10	1	0

Abbreviation: NSAI, non-steroidal aromatase inhibitor.
Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.
[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%).

Additional adverse reactions in MONALEESA-7 for patients receiving KISQALI plus NSAI included asthenia (12%), thrombocytopenia (9%), dry skin (8%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia, (2%), blood bilirubin increased (1%), syncope (0.4%), and pneumonitis (0.4%).

Table 11: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-7

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory Parameters	%	%	%	%	%	%
HEMATOLOGY						
Leukocyte count decreased	93	34	2	30	< 1	< 1
Neutrophil count decreased	92	54	9	27	2	0
Hemoglobin decreased	84	2	0	51	< 1	0
Lymphocyte count decreased	55	12	2	18	2	< 1
Platelet count decreased	26	< 1	0	9	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	33	6	0	31	1	< 1
Aspartate aminotransferase increased	37	5	0	35	1	< 1
Creatinine increased	21	2	< 1	20	< 1	< 1
Phosphorous decreased	14	2	0	11	< 1	< 1
Potassium decreased	11	< 1	< 1	14	< 1	< 1
Gamma-glutamyl transferase increased	42	5	2	42	8	1
Glucose serum decreased	10	< 1	0	10	< 1	0

MONALEESA-3: KISQALI in Combination with Fulvestrant

Postmenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy or After Disease Progression on Endocrine Therapy

The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months.

Dose reductions due to ARs occurred in 32% of patients receiving KISQALI plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Among patients receiving KISQALI plus fulvestrant, 8% were reported to have permanently discontinued both KISQALI and fulvestrant and 9% were reported to have discontinued KISQALI alone due to ARs. Among patients receiving placebo plus fulvestrant, 4% were reported to have permanently discontinued both and 2% were reported to have discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus fulvestrant (as compared to the placebo arm) were ALT increased (5% vs. 0%), AST increased (3% vs. 0.6%), and vomiting (1% vs. 0%).

On-treatment deaths, regardless of causality, were reported in seven patients (1.4%) due to the underlying malignancy and six patients (1.2%) due to other causes while on treatment with KISQALI plus fulvestrant. Causes of death included one pulmonary embolism, one acute respiratory distress syndrome, one cardiac failure, one pneumonia, one hemorrhagic shock, and one ventricular arrhythmia. Seven patients (2.9%) died due to the underlying malignancy and 1 patient (0.4%) died due to pulmonary embolism while on placebo plus fulvestrant.

The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, infections, and abnormal liver function tests. See Table 12.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 12 and Table 13, respectively.

Table 12: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-3 (All Grades)

	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
Adverse Drug Reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Infections[1]	42	5	0	30	2	0
Blood and Lymphatic System Disorders						
Neutropenia	69	46	7	2	0	0
Leukopenia	27	12	< 1	< 1	0	0
Anemia	17	3	0	5	2	0
Metabolism and Nutrition Disorders						
Decreased appetite	16	< 1	0	13	0	0
Nervous System Disorders						
Dizziness	13	< 1	0	8	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	22	0	0	15	0	0
Dyspnea	15	1	< 1	12	2	0
Gastrointestinal Disorders						
Nausea	45	1	0	28	< 1	0
Diarrhea	29	< 1	0	20	< 1	0
Vomiting	27	1	0	13	0	0
Constipation	25	< 1	0	12	0	0
Abdominal pain	17	1	0	13	< 1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	19	0	0	5	0	0
Pruritus	20	< 1	0	7	0	0
Rash	23	< 1	0	7	0	0
General Disorders and Administration-site Conditions						
Edema peripheral	15	0	0	7	0	0
Pyrexia	11	< 1	0	7	0	0
Investigations						
Alanine aminotransferase increased	15	7	2	5	< 1	0
Aspartate aminotransferase increased	13	5	1	5	< 1	0

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.
[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%).

Additional adverse reactions in MONALEESA-3 for patients receiving KISQALI plus fulvestrant included asthenia (14%), dyspepsia (10%), thrombocytopenia (9%) dry skin (8%), dysgeusia (7%), dry mouth (5%), vertigo (5%), dry eye (5%), lacrimation increased (4%), erythema (4%), hypocalcemia (4%), blood bilirubin increased (1%), syncope (1%), interstitial lung disease (0.4%), pneumonitis (0.4%), hypersensitivity pneumonitis (0.2%), and acute respiratory distress syndrome (0.2%).

Table 13: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-3

	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
Laboratory Parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	95	25	< 1	26	< 1	0
Neutrophil count decreased	92	46	7	21	< 1	0
Hemoglobin decreased	60	4	0	35	3	0
Lymphocyte count decreased	69	14	1	35	4	< 1
Platelet count decreased	33	< 1	1	11	0	0

(continued)

Table 13: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-3

	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
Laboratory Parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
CHEMISTRY						
Creatinine increased	65	< 1	< 1	33	< 1	0
Gamma-glutamyl transferase increased	52	6	1	49	8	2
Aspartate aminotransferase increased	49	5	2	43	3	0
Alanine aminotransferase increased	44	8	3	37	2	0
Glucose serum decreased	23	0	0	18	0	0
Phosphorous decreased	18	5	0	8	< 1	0
Albumin decreased	12	0	0	8	0	0

COMPLEEMENT-1: KISQALI in Combination with Letrozole and Goserelin or Leuprolide

Men with HR-positive, HER2-negative Advanced Breast Cancer for Initial Endocrine-Based Therapy

The safety of KISQALI in combination with letrozole was evaluated in men (n=39) in an open-label, multicenter clinical study for the treatment of adult patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEEMENT-1) *[see Clinical Studies (14) in the full prescribing information]*.

The median duration of exposure to KISQALI was 20.8 months (range: 0.5 to 30.6 months).

Other adverse reactions occurring in men treated with KISQALI plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with KISQALI plus endocrine therapy.

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of KISQALI. Because these events 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.

Respiratory disorders: Interstitial lung disease/pneumonitis

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug-induced hypersensitivity syndrome (DiHS)/Drug reaction with eosinophilia and systemic symptoms (DRESS)

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily *[see Dosage and Administration (2.2) in the full prescribing information]*.

Instruct patients to avoid grapefruit or grapefruit juice, which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib *[see Patient Counseling Information (17) in the full prescribing information]*.

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations
CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A (e.g., phenytoin, rifampin, carbamazepine, and St John's wort (Hypericum perforatum)).

7.3 Effect of KISQALI on Other Drugs
CYP3A Substrates with Narrow Therapeutic Index

Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone *[see Clinical Pharmacology (12.3) in the full prescribing information]*. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

7.4 Drugs That Prolong the QT Interval
Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT, such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, and ondansetron) *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information]*.

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of post implantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development, including increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13th ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

8.2 Lactation
Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential
Based on animal studies and mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to starting treatment with KISQALI.

Contraception
Females

Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility
Males

Based on animal studies, KISQALI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use
The safety and efficacy of KISQALI in pediatric patients has not been established.

8.5 Geriatric Use
Of 334 patients who received KISQALI in MONALEESA-2, 150 patients (45%) were ≥ 65 years of age and 35 patients (11%) were ≥ 75 years of age. Of 484 patients who received KISQALI in MONALEESA-3, 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.2) in the full prescribing information]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2) or moderate (30 mL/min/1.73 m^2 ≤ eGFR < 60 mL/min/1.73 m^2) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]*.

10 OVERDOSAGE

There is limited experience with reported cases of overdose with KISQALI in humans. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2022-03

Ocular Toxicities of MEK Inhibitors in Patients With Cancer: A Systematic Review and Meta-analysis

Jing Han, MD[1]; Juejing Chen, MD[2]; Hanqiong Zhou, MD[1]; Lidan Hao,[1]; Qiming Wang, MD, PhD[1]

ABSTRACT

Background: Mitogen-activated protein kinase (MEK) inhibitors, which integrate the important signaling chain of the RAS-RAF-MEK-ERK1/2 pathway, regulate cell functions such as division and proliferation for patients with solid tumors. However, various ocular adverse effects (AEs) affect patients during clinical treatment. This systematic review aimed to assess the occurrence of AEs during treatment with MEK inhibitors plus targeted therapy or chemotherapy.

Methods: A scientific literature search was conducted in PubMed, the Cochrane Library, Embase, and several Chinese databases to identify randomized controlled trials. Overall, ocular AEs were assessed as the primary end point; blurred vision, chorioretinopathy, and retinal detachment were assessed as secondary end points.

Results: Seventeen randomized controlled trials were included. Overall, the use of MEK inhibitors combined with other targeted inhibitors or chemotherapy was significantly associated with a nearly 7.3% increased risk of overall ocular toxicities vs therapy without MEK inhibitors (risk ratio [RR], 2.88; 95% CI, 1.42-5.85, $P < .05$). An increased risk of blurred vision (RR, 4.10; 95% CI, 2.55-6.58; $P < .05$), chorioretinopathy (RR, 8.36; 95% CI, 3.42-20.47; $P < .05$), and retinal detachment (RR, 8.98; 95% CI, 3.92-20.57; $P < .05$) was demonstrated.

Conclusions: Treatment with MEK inhibitors combined with targeted drugs or chemotherapy seems to increase overall ocular AEs. A more practical algorithm for the screening of ocular AEs was suggested to be conducted whenever new or worsening ocular toxicities occur.

PERSPECTIVE

David L. DeRemer, PharmD, BCOP, and Bently P. Doonan, MD, MS, share a perspective on treatment options for ocular toxicities on page 138.

MEK proteins are mitogen-activated protein kinase, an important downstream part of the RAS–mitogen-activated protein kinase (MAPK), also known as the RAS-RAF-MEK-ERK1/2 pathway, highly regulating and playing an important role in cell proliferation, differentiation, apoptosis, and stress responses.[1] Deregulation of the MAPK pathway occurs in more than 30% of various human cancers.[2] Many ongoing clinical trials or preclinical studies of corresponding drugs focus on targeting RAS, RAF, MEK, or ERK. For example, dabrafenib and vemurafenib significantly improved response rates, progression-free survival, and overall survival compared with chemotherapy in metastatic melanoma; however, resistance to treatment developed quickly in most patients. Hitherto, 4 MEK inhibitors have been developed and approved: 3 combined with v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) inhibitors to treat several *BRAF* V600 mutant solid tumors, and 1 for neurofibromatosis type.[3-6] Of note, apart from binimetinib, which is used only for melanoma,

trametinib has been indicated in combination with dabrafenib for melanoma, non–small cell lung cancer (NSCLC), anaplastic thyroid cancer, and other unresectable or metastatic solid tumors with *BRAF* V600E mutation in adult patients and pediatric patients 6 years and older.[4] Recently, cobimetinib has been newly indicated as a single agent for the treatment of adult patients with histiocytic neoplasms.[6]

Preclinical studies showed that MEK plays a critical role in maintaining the integrity of the retinal pigment epithelium (RPE) by protecting against various stresses, including oxidative stress, light-induced damage, and inflammation. The RPE is an epithelial barrier formed of RPE cells that maintains the outer blood-retinal barrier and is crucial for maintaining neural retinal function.[7] MEK inhibitors lead to acute RPE toxicity, which results in RPE hyperpermeability and breakdown of the retinal-blood barrier. Ocular toxicities are commonly associated with MEK inhibitors, aside from rash, diarrhea, fatigue, and elevated creatinine phosphokinase levels. Thus, this systematic review aimed to provide updated evidence of ocular toxicities related to MEK inhibitors combined with targeted therapy or chemotherapy and briefly discuss their management.

Materials and Methods

Search strategy

We performed a literature search of PubMed, the Cochrane Library, Embase, the Chinese National Knowledge Infrastructure, Wanfang Data, and Chinese Biomedical Literature from inception to November 11, 2020, with the last review performed on January 1, 2022. Keywords included *trametinib, binimetinib, selumetinib, cobimetinib, ocular,* and *eye*. A prospective protocol was created in advance and uploaded to the International Prospective Register of Systematic Reviews (PROSPERO) online platform (registration No. CRD42021235589).

Selection criteria and quality assessment

Two reviewers read titles, abstracts, or full texts to identify potential articles that met the inclusion criteria. Studies included in this meta-analysis were required to have (1) a randomized controlled trial (RCT) design, (2) patients with cancer undergoing MEK inhibitor therapy, and (3) eye-related adverse effects (AEs) reported in the outcomes.

Cochrane Collaborations' tool for assessing the risk of bias was used to assess the quality of included studies by 2 independent researchers. The items included in this tool were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

Data extraction and outcome measures

Two investigators (JH and HZ) independently extracted data from included studies. Disagreements were resolved by consensus or by involving a third review author (JC). Data extracted from studies included study characteristics, patient characteristics, details regarding MEK inhibitor and placebo groups, and outcome measures. The primary end points were clinical events (overall eye-related AEs). The secondary end points incorporated specific ocular AEs (retinal detachment, chorioretinopathy, and blurred vision).

Statistical analysis

This meta-analysis was performed using a statistical software program (Stata version 15.0; StataCorp LP). Outcome data were extracted as risk ratios (RRs) and 95% CIs. Random-effects models were used for all outcomes because of differences in study participants and length of follow-up. The Cochran *Q* test and the I^2 test were performed to assess the heterogeneity of the summary effects. If the *P* value of the Cochran *Q* test was less than .01 and I^2 was greater than 50%, heterogeneity was considered to exist.

Assessment of risk of bias in included studies

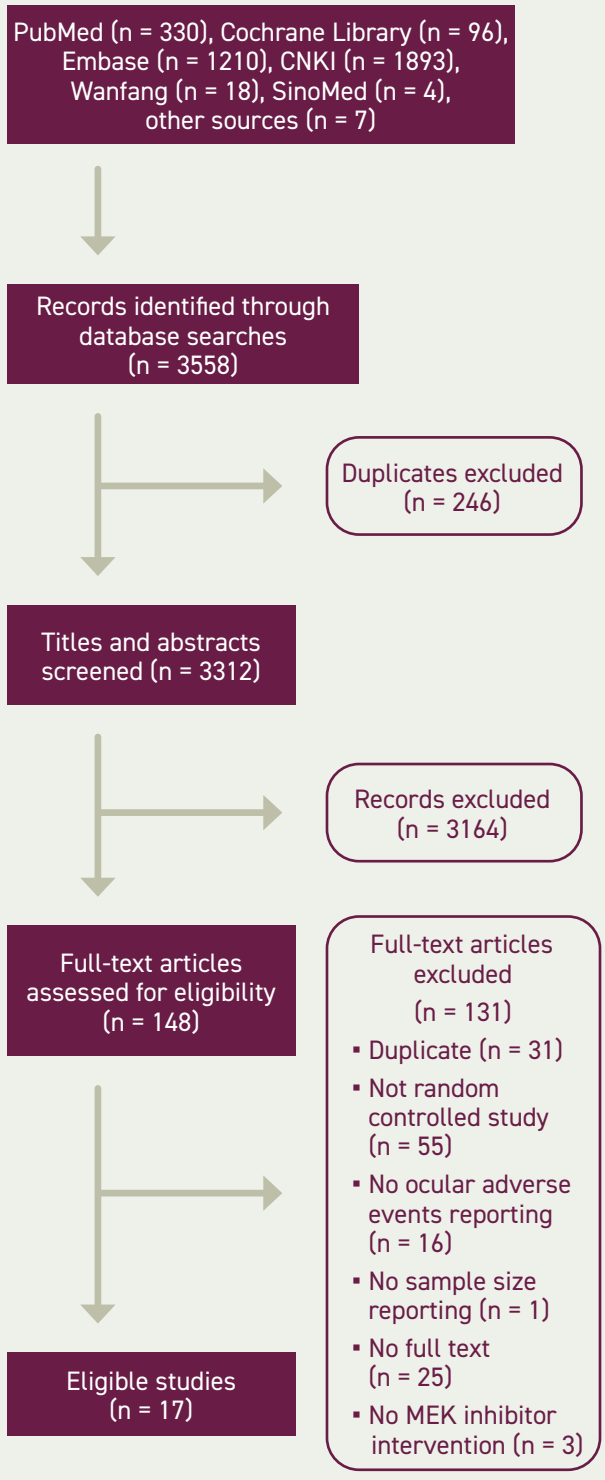
Two review authors (JH and HZ) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. We resolved disagreements by discussion or by involving a third review author (JC). We assessed the risk of bias according to the following domains: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. We graded each potential source of bias as high, low, or unclear risk and provided a quote from the study report together with a justification for our judgment in the risk of bias table. Publication bias was evaluated using a funnel plot of the effect sizes and standard errors of the studies. The Egger regression test was used to examine funnel plot asymmetry. Publication bias was considered to be present if the funnel plot was asymmetrical or the *P* value from the Egger test was less than .10.

Results

Systematic review and selection

The electronic searches identified 3558 records by searching databases and hand-searching relevant bibliographies. Relevant studies were identified according to the flow diagram in **Figure 1**. We excluded 246 duplicate records and screened 3312 records, of which 148 were identified as potentially eligible and obtained as full-text manuscripts. After a full-text screening, we considered

FIGURE 1. **Literature Research**



CNKI, Chinese National Knowledge Infrastructure.

17 studies eligible for inclusion in this review.

Study characteristics

After reading all the text, 17 studies (9 with double-blinded design, 6 with open-label design, 1 with single-blinded design, and 1 with design not mentioned) were included in the final analysis according to the selection criteria, which contained 16 RCTs (**Table 1**) and the coBRIM clinical trial, which reported secondary end points in 2 studies. Among these studies, 8 were phase 3 and 9 were phase 2, and all included treatment with MEK inhibitors: 3 with a single MEK inhibitor, 9 with a combination of MEK and other targeted inhibitors (such as BRAF inhibitors or epidermal growth factor receptor [EGFR], tyrosine kinase inhibitors, and estrogen antagonists), and 5 with a combination of MEK inhibitors and chemotherapy (such as dacarbazine, gemcitabine, or docetaxel). The MEK inhibitors covered in this study included trametinib, selumetinib, cobimetinib, binimetinib, and pimasertib. In all trials, the pathologic conditions included were colorectal cancer, bladder cancer, melanoma, pancreatic adenocarcinoma, NSCLC, or breast cancer. The criteria used for ocular AE classification was the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3 or 4.

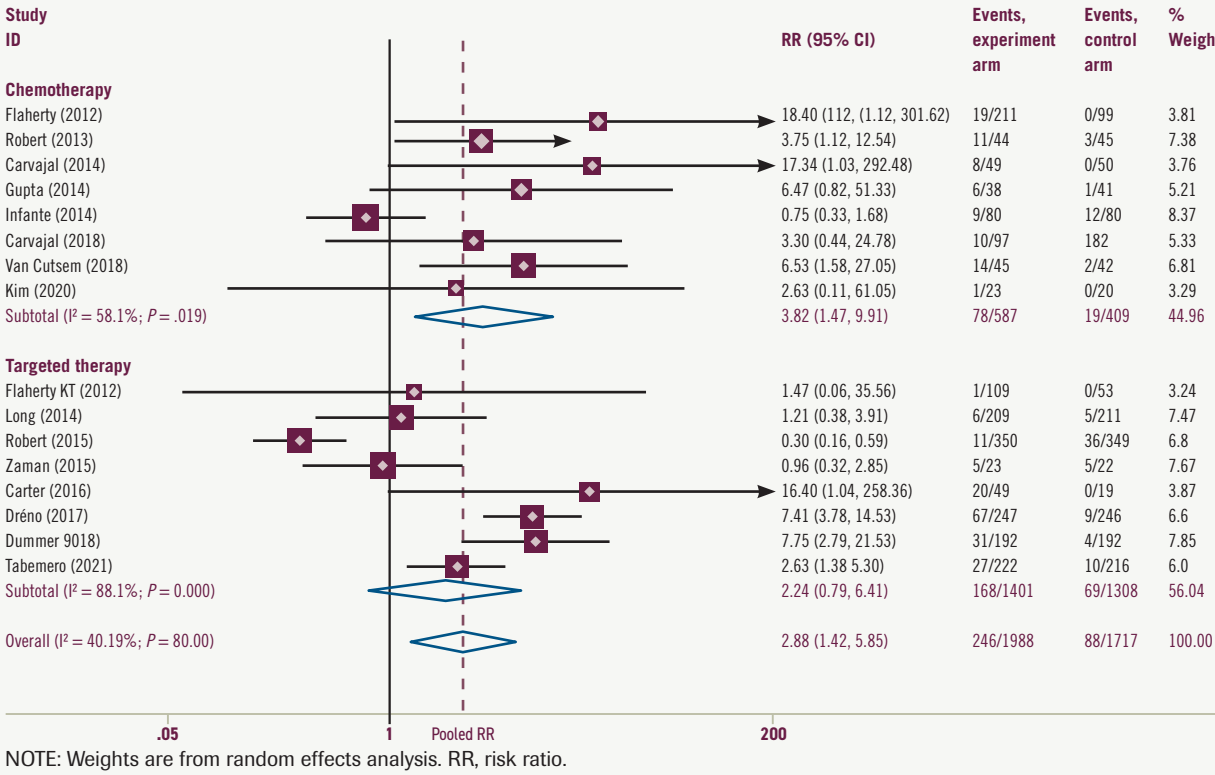
Overall ocular AEs

We performed data analyses for the following comparisons and subgroup analyses. Where applicable, we performed prespecified sensitivity analyses as noted in the Sensitivity Analysis and Risk of Bias section. The use of MEK inhibitors with or without other targeted inhibitors or chemotherapy (vs targeted therapy or chemotherapy without MEK inhibitors) was significantly associated with a nearly 7.3% increased risk of the overall ocular toxicities in a random-effects model meta-analysis of 16 RCTs (RR, 2.88; 95% CI, 1.42-5.85; $P < .05$) (**Figure 2**). The risks of all grades of ocular toxicities were 12.4% and 5.1% in the experimental and control arms, respectively.

Subgroup analyses showed that MEK inhibitor monotherapy or therapy with MEK inhibitors plus chemotherapy (vs chemotherapy with or without placebo) was significantly associated with an 8.7% increased risk of ocular AEs in 8 RCTs (RR, 3.82; 95% CI, 1.47-9.91; $P < .05$) (Figure 2). The risks of all grades of ocular toxicities in this chemotherapy subgroup were 13.3% and 4.6% in the experimental and control arms, respectively.

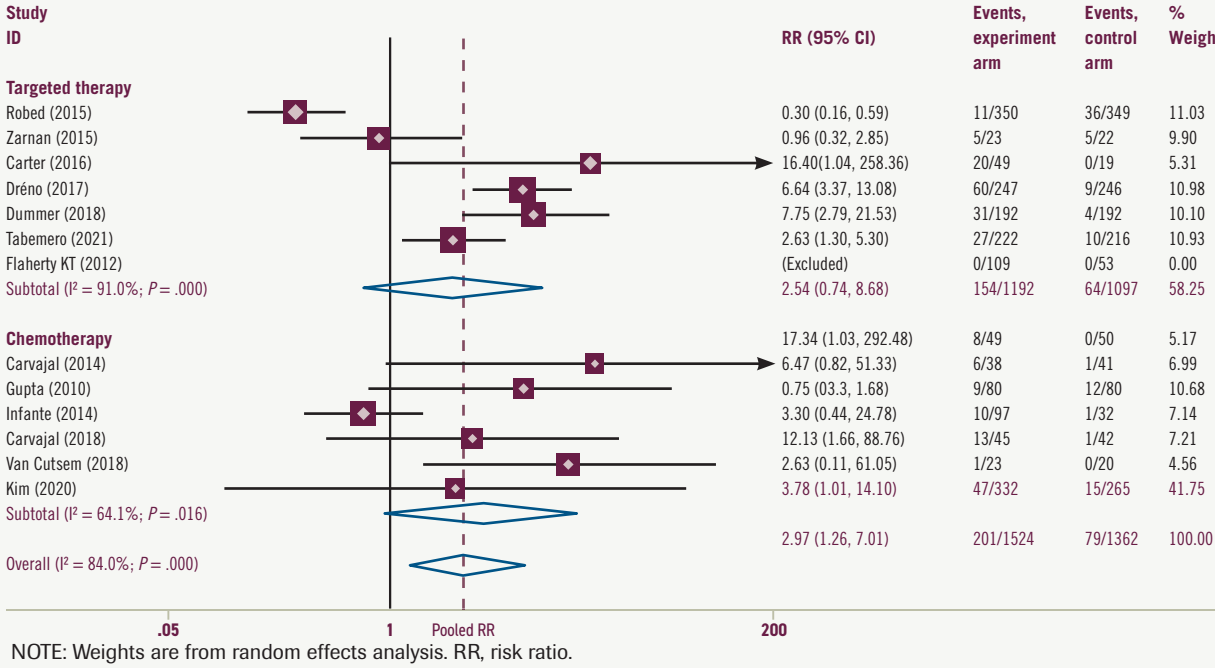
The results trend for all grades was similar in the targeted therapy subgroup, with 12.0% and 5.3% in the experimental and control arms, respectively. The

FIGURE 2. **Total Ocular Adverse Effect and Subgroup Analysis**



NOTE: Weights are from random effects analysis. RR, risk ratio.

FIGURE 3. **Total Ocular Grade 1/2 Adverse Effect and Subgroup Analysis**



NOTE: Weights are from random effects analysis. RR, risk ratio.

TABLE 1. **Characteristics of the Included Studies**

Source	Region	NCT No.	Phase	Cancer	
Tabernero et al,[8] 2021	Worldwide	02928224	3	*BRAF* V600E–mutated metastatic colorectal cancer	
Kim et al,[9] 2020	USA	02042443	2	Unresectable, locally advanced, or metastatic intra- or extrahepatic biliary system or gall bladder cancer	
Carvajal et al,[10] 2018	Worldwide	01974752	3	Metastatic uveal melanoma	
Dummer et al,[11] 2018	Worldwide	01909453	3	Locally advanced, unresectable, or metastatic cutaneous melanoma or unknown primary melanoma classified as stage IIIB, IIIC, or IV	
Van Cutsem et al,[12] 2018	Europe	01016483	2	Metastatic pancreatic adenocarcinoma	
de la Cruz-Merino et al,[13] 2017	Worldwide	01689519	3	*BRAF* V600 mutation–positive unresectable stage IIIC or IV melanoma	
Dréno et al,[14] 2017	Worldwide	01689519	3	*BRAF* V600 mutation–positive unresectable stage IIIC or IV melanoma	
Carter et al,[15] 2016	USA	_	2	KRAS wild-type advanced NSCLC	
Zaman et al,[16] 2015	Switzerland, Belgium	–	2	Advanced-stage endocrine-sensitive (estrogen (ER) and/or progesterone receptors (PgR)≥10%) breast cancer	
Robert et al,[17] 2015	Worldwide	01597908	3	Unresectable stage IIIC or IV melanoma with *BRAF* V600E or V600K mutations	
Carvajal et al,[18] 2014	USA	01143402	2	Metastatic uveal melanoma	
Long et al,[19] 2014	Worldwide	01584648	3	Unresectable stage IIIC or IV melanoma with a *BRAF* V600E or V600K mutation	
Gupta et al,[20] 2014	UK	01256359	2	Unresectable stage 3 or 4 *BRAF* wild-type melanoma	
Infante et al,[21] 2014	Worldwide	01231581	2	Previous untreated metastatic pancreatic adenocarcinoma	
Robert et al,[22] 2013	Worldwide	00936221	2	Stage III and IV, *BRAF*-mutant, cutaneous, or unknown primary melanoma	
Flaherty et al,[23] 2012	Worldwide	01245062	3	Metastatic melanoma with a *BRAF* V600E or V600K mutation	
Flaherty et al,[24] 2012	USA and Australia	01072175	2	Metastatic melanoma with either *BRAF* V600E or V600K mutations	

CTCAE, Common Terminology Criteria for Adverse Events; NCT, National Clinical Trial; NSCLC, non–small cell lung cancer; 5-FU/LV, 5-fluorouracil/leucovorin.

experimental arms of MEK inhibitors combined with BRAF inhibitors, EGFR inhibitors, or estrogen antagonists (vs BRAF inhibitors, EGFR inhibitors, or estrogen antagonist monotherapy with or without placebo) were associated with a 6.7% increased risk in 8 RCTs (RR, 2.24; 95% CI, 0.79-6.41; P > .05) (Figure 2).

In a random-effects model meta-analysis, MEK inhibitors with or without other targeted inhibitors or chemotherapy (vs targeted therapy or chemotherapy without MEK inhibitors) was significantly associated with a nearly 7.4% increased risk of grade 1/2 ocular toxicities (RR, 2.97; 95% CI, 1.26-7.01; $P < .05$) (**Figure 3**). As for chemotherapy subgroups, the pooled results showed that MEK inhibitor monotherapy or MEK inhibitors plus chemotherapy (vs chemotherapy with or without placebo) increased the risk of the grade 1/2 ocular toxicities by approximately 8.5% (RR, 3.78; 95% CI, 1.01-14.10; $P < .05$) (Figure 3). In the targeted therapy group, therapy

	Intervention	Comparator	Intervention group sample, No.	Control group sample, No.	CTCAE criterion
	Encorafenib + binimetinib + cetuximab	Encorafenib + cetuximab	222	216	4.03
	Trametinib	5-FU/LV or capecitabine	23	20	4.0
	Selumetinib + dacarbazine	Dacarbazine + placebo	97	32	4.0
	Encorafenib + binimetinib	Encorafenib	192	192	4.03
	Gemcitabine + pimasertib	Gemcitabine + placebo	45	42	4.0
	Cobimetinib + vemurafenib	Placebo + vemurafenib	247	246	4.0
	Cobimetinib + vemurafenib	Placebo + vemurafenib	247	246	4.0
	Erlotinib + selumetinib	Erlotinib	49	19	4.0
	Fulvestrant + selumetinib	Fulvestrant + placebo	23	22	4.0
	Dabrafenib + trametinib	Vemurafenib	350	349	4.0
	Selumetinib	Temozolomide or dacarbazine	49	50	4.0
	Dabrafenib + trametinib	Dabrafenib + placebo	209	211	4.0
	Docetaxel + selumetinib	Docetaxel + placebo	38	41	4.03
	Gemcitabine + trametinib	Gemcitabine + placebo	80	80	4.0
	Selumetinib + dacarbazine	Dacarbazine + placebo	44	45	3.0
	Trametinib	Dacarbazine or paclitaxel	211	99	4.0
	Dabrafenib + trametinib	Dabrafenib	109	53	4.0

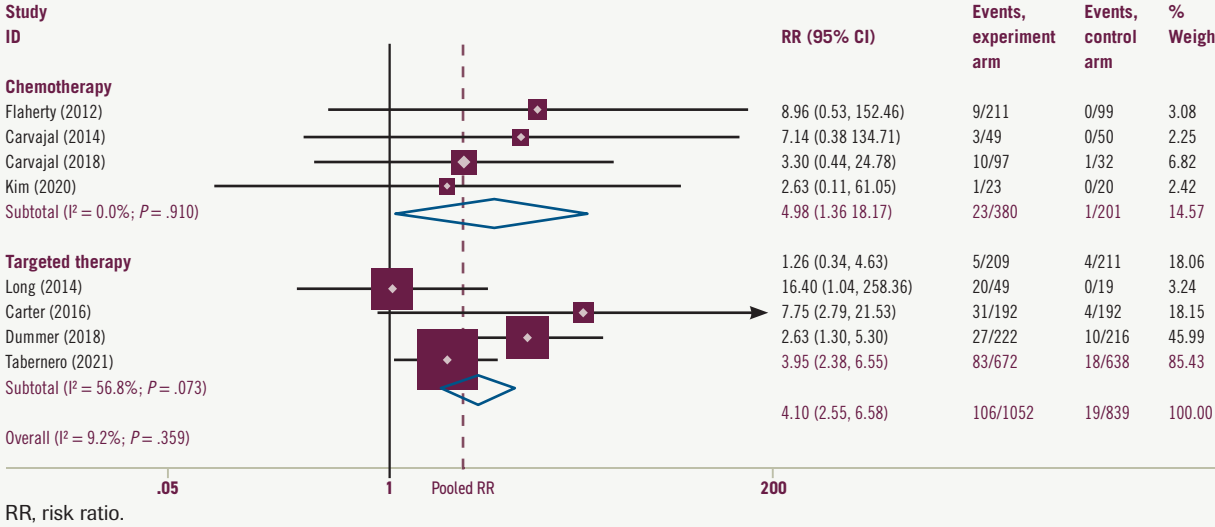
with MEK inhibitors tended to increase the occurrence of grade 1/2 ocular AEs, but this increase was not significant (RR, 2.54; 95% CI, 0.74-8.68; P > .05) (Figure 3).

The results for grade 3/4 ocular toxicities were similar when pooling in the targeted therapy subgroup (RR, 7.23; 95% CI, 1.04-50.28; $P < .05$) (Supplement S1). However, the risk-of-chemotherapy subgroup was presented in 1 article and thus could not be pooled effectively.

Secondary end points

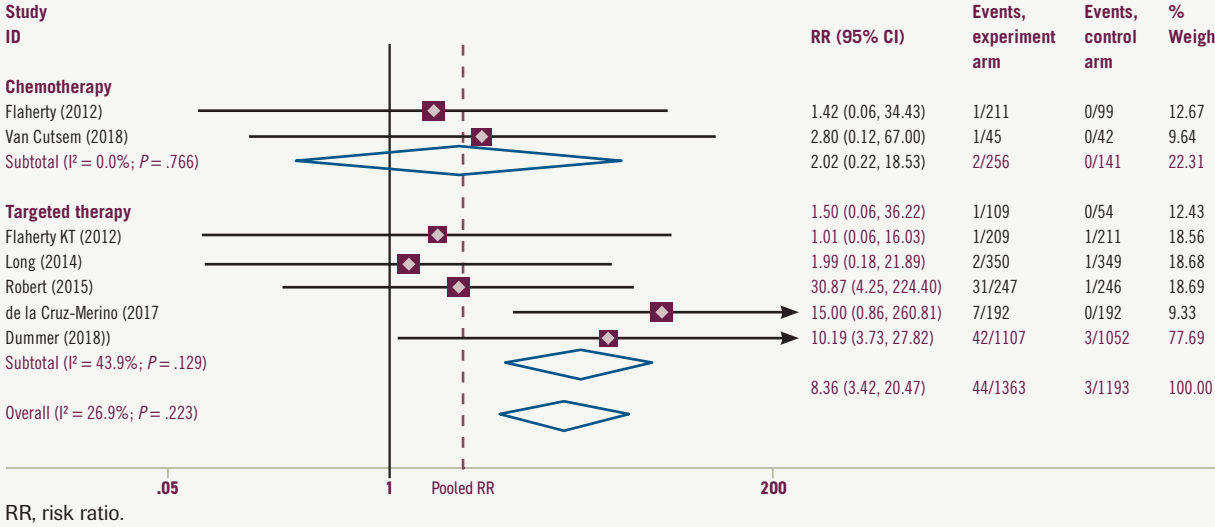
Data on blurred vision were extracted from 8 studies. The experimental group of MEK inhibitors was harmful in these studies (RR, 4.10; 95% CI, 2.55-6.58; $P < .05$) and the same in the chemotherapy group (RR, 4.98; 95% CI, 1.36-18.17; $P < .05$) and the targeted therapy group (RR, 3.95; 95% CI, 2.38-6.55; $P < .05$) (**Figure 4**). The risk of grade

FIGURE 4. **Blurred Vision Total Adverse Effect and Subgroup Analysis**



RR, risk ratio.

FIGURE 5. **Chorioretinopathy Total Adverse Effect and Subgroup Analysis**



RR, risk ratio.

1/2 AEs was 8.9% higher in the MEK inhibitors experimental group and was 9.6% and 7.3% higher (Supplement S2) in targeted therapy and chemotherapy groups, respectively. No risk of grade 3/4 blurred vision was reported in the included studies.

Data on chorioretinopathy was available in 7 studies. MEK inhibitors combined with BRAF inhibitors significantly increased the risk by 3.5% (95% CI, 3.73%-27.82%; $P < .05$) vs BRAFinhibitormonotherapy(**Figure5**). The results for grade 1/2 chorioretinopathy were similar, and MEK plus BRAF inhibitors tended to increase risk (RR, 3.14; 95% CI, 0.83%-13.92%; $P > .05$), but not significantly (Supplement S3). The risk of grade 3/4 chorioretinopathy was present in 2 articles in the targeted group, an increasing risk tendency but not significant (Supplement S4). In the chemotherapy group, MEK inhibitors with

or without chemotherapy (vs chemotherapy alone) did not significantly increase the risk of chorioretinopathy.

Data for retinal detachment were extracted from 3 studies: 2 compared MEK inhibitors plus BRAF inhibitors vs BRAF inhibitors alone, and 1 compared pimasertib plus gemcitabine vs gemcitabine plus placebo. The pooled meta-analysis of these 3 studies showed that the MEK inhibitors group increased the retinal detachment risk by 10.1% (RR, 8.98; 95% CI, 3.92-20.57; P <.05) (Supplement S5) compared with the no MEK inhibitors group.

Sensitivity analysis and risk of bias

To further explore the potential heterogeneity from any single study, sensitivity analysis was performed and showed that the present results were significantly affected by removing 1 study, and the pooled analysis showed increasing ocular toxicities risk in the MEK inhibitors group (Supplement S6). We summarize the risk of bias assessments for the primary outcome of this review in Supplements S7 and S8. We ran a comprehensive search and considered the risk of having missed published reports to be low. The funnel plot of data from the 16 studies included in the meta-analysis was symmetrical (Supplement S9). The P value for the Egger test was .199; there was no publication bias in the meta-analysis (Supplement S10).

Discussion

Clinical manifestations of the MEK-associated ocular adverse effect

During the past decade, newer targeted agents have been developed to exploit tumor-specific genetic alterations in signal transduction pathways, which have taken anticancer therapy into a new era. MEK inhibitors, a crucial part to break the MAPK pathway and a great partner for BRAF inhibitors, especially trametinib, have been developed and approved for use in combination with dabrafenib for early melanoma, specifically for unresectable or metastatic solid tumors with *BRAF* V600E mutations.[25] As the indications expand, the clinical safety of MEK inhibitors should be carefully examined.

Ever since the first MEK inhibitor, CI-1040, was clinically evaluated, ocular toxicities have been regularly reported for this class of drugs.[26] Common ocular toxicities included blurred vision and visual disturbances, and these tended to arise quickly after dosing in the first studies with the MEK inhibitors CI-1040, PD0325901, and selumetinib.[27,28] Thus, researchers of the phase 1 trials of trametinib suspected these toxicities to be related to the peak concentration. However, because these toxicities are very similar to those reported in newly developing MEK inhibitors, there seems to be a class effect.

In general, most patients with ocular toxicities identified various clinical manifestations, including reduced visual acuity, blurred vision, dyschromatopsia, chorioretinopathy, retinal detachment, and photophobia.[17,29] Herein, blurred vision, chorioretinopathy, and retinal detachment were pooled according to the included studies as secondary outcomes, for they were commonly described as such in the clinical trials. In fact, other types of ocular toxicities, such as cataracts, photosensitivity reactions, macular edemas, and macular fibroses, were also mentioned in 1 clinical trial, but they could not be pooled effectively. In contrast, the secondary end points we chose in this systematic review are consistent with the United States Common Terminology Criteria for Adverse Events evaluation standard (**Table 2**). Blurred vision represents a disorder characterized by visual perception of unclear or fuzzy images. Chorioretinopathy describes a disorder involving the choroid and retina. Retinal detachment was characterized by the separation of the inner retina layers from the underlying pigment epithelium. Of note, although these 3 toxicities have been classified as grades 1 to 5, most patients experienced grade 1/2 toxicities more often, according to the present results. What's more, MEK inhibitor–related retinopathy usually begins acutely within 1 week of taking the first dose. Clinical examination in patients with mild disease usually shows multifocal and bilateral small subretinal detachments, possibly with subretinal fluid accumulation. Moderate cases may have only multiple subretinal detachments. More severe cases may develop intraretinal fluid or cysts, as well as disorders of the outer retina. Clinical presentation is usually bilateral, although there are exceptions, and usually symmetrical. Symptoms vary widely; many patients are asymptomatic.

Retinal vein occlusion (RVO) is an uncommon but potentially serious AE reported in initial clinical trials of several MEK inhibitors, including cobimetinib and trametinib. Across all clinical trials, trametinib resulted in an RVO rate of 0.2%.[30,31] Predisposing factors included glaucoma, uncontrolled high blood pressure, and diabetes. In at least 1 patient, switching from continuous to intermittent dosing reduced the incidence of RVO.[32] At least 1 study has shown that MEK inhibitor–related RVO is associated with hyperhomocysteinemia, an inherited metabolic disease that predisposes to venous thromboembolism. These sparse data suggest that screening for hyperhomocysteinemia before initiation of MEK inhibitor therapy may be beneficial, but more data are needed.[33]

PERSPECTIVE BY

David L. DeRemer, PharmD, BCOP,[1,2]; and Bently P. Doonan, MD, MS[2,3]

Evaluating Treatment Options and the Multidisciplinary Care of Ocular Toxicities of MEK Inhibitors

Ocular toxicities associated with conventional cytotoxic chemotherapy and novel targeted therapies utilized in cancer care continue to evolve.

The authors of "Ocular Toxicities of MEK Inhibitors in Patients With Cancer: A Systemic Review and Meta-Analysis" provide a comprehensive analysis of 17 randomized clinical trials. Because the RAS-MAPK activation pathway is a common mutation in multiple malignancies, MEK inhibitor use continues to expand in treatment recommendations. Recent advancements include the BRAF/MEK inhibitor combination of dabrafenib (Tafinlar) plus trametinib (Mekinist) receiving FDA approval for a tissue-agnostic indication in solid tumors harboring a *BRAF* V600E mutation.[1] Other examples of expanding use of MEK inhibitors beyond *BRAF* V600E mutations include binimetinib (Mektovi) for *NRAS*-mutated melanoma and neurofibromatosis type 1–associated tumors, particularly progressive low-grade gliomas and plexiform neurofibromas.[2,3]

With this increasing clinical presence, clinicians need to be cognizant of these unique risks of therapy and appropriate monitoring strategies to mitigate toxicities.

Results from this meta-analysis report an increased risk of ocular adverse effects (AEs), specifically blurred vision, chorioretinopathy, and retinal detachment when MEK inhibitors are combined with additional targeted or traditional chemotherapy. Most of these ocular AEs are National Cancer Institute Common Terminology Criteria for Adverse Events grade 1 or 2 in severity. Grading of ocular AEs—given the diversity of toxicities—can be challenging; notably, improvements have been made in the classification of retinal vascular disorders, MEK inhibitor–associated retinopathy, and blurred vision with Common Terminology Criteria for Adverse Events version 5.0.

Many patients are asymptomatic or present with mild symptoms depending on the ocular AEs, which can create challenges for clinicians in early clinical intervention. In the setting of suspected MEK inhibitor–associated retinopathy, MEK inhibitors can cause transient, dose, and time-dependent retinopathy. Elimination half-lives of MEK inhibitors vary (approximately 3.5 hours for binimetinib, 44 hours for cobimetinib [Cotellic], and 4.8 days for trametinib), so the timing of ocular AEs may differ. Interestingly, some patients experience these events immediately following the initiation of therapy, and the duration of therapy does not influence the development of ocular sequelae.[4] Adherence to product recommendations for dose reductions or discontinuations (temporary/permanent) based on toxicity is advised.

In many cases, MEK inhibitors can be safely resumed following the resolution of symptoms at a reduced dose without provoking repeat ocular AEs. These descriptive findings on ocular toxicity imply that there is a threshold for provocation in a dose-dependent manner and that alternative dosing strategies may be beneficial in patients with high baseline risks of ocular complications. The traditional paradigm in clinical trial design and drug development is to utilize anticancer drugs at maximum tolerated doses, so rarely do phase 3 trials incorporate multiple dosing strategies when seeking new indications of use.

However, there appears to be renewed interest in shifting to seeking minimum effective doses, particularly

Differentiating metastasis from drug toxicity

MEK inhibitors as a class of anticancer agents are commonly used in melanoma, NSCLC, and other solid tumor treatments. However, clinicians should distinguish visual disturbances caused by other medical etiologies (such as diabetic complications, hypertension complications, or concomitant medication) from ocular toxicities caused by MEK inhibitors. If the patient has a history of diabetes, hypertension, other diseases, or a special medication history, an ophthalmologic evaluation should be

in targeted therapies.[5] A recent example of this strategy is with sotorasib (Lumakras), which received FDA accelerated approval for *KRAS* G12C non–small cell lung cancer.[6] The FDA issued a postmarketing requirement to evaluate 960 mg vs 240 mg daily dosing to assess objective response rates with less toxicity (CodeBreaK201; NCT04933695). Because KRAS and MEK share the common pathway target of MAPK, further clinical investigation and use of MEK inhibitors would benefit from learning this lesson and exploring optimized dosing strategies to minimize common toxicities like those outlined in this manuscript.

In 2006, van Heeckeren et al wrote a brilliantly titled editorial, "Promise of New Vascular-Disrupting Agents Balanced With Cardiac Toxicity: Is It Time for Oncologists to Get to Know Their Cardiologists?" following the emergence of VEGF targeted therapies.[7] With the expanding use of MEK inhibitors and recent FDA approvals that include belantamab mafodotin-blmf (Blenrep), tisotumab vedotin-tftv (Tivdak), and mirvetuximab soravtansine-gynx (Elahere), we have reached the era where oncologists should "get to know" their ophthalmologists.

We would advocate for the development of collaborative practice partnerships due to the challenges of fragmented cancer care. With some novel agents requiring ophthalmic exams, including visual acuity and slit lamp exams at baseline and prior to each dose and the coordination of multiple eye drops (lubrication, corticosteroids, vasoconstrictor), these proposed partnerships to manage ocular AEs should be multidisciplinary. The establishment of integrated communication would foster improved coordination of patient care. For example, if a patient were to experience loss of vision or other visual disturbance while receiving a MEK inhibitor, it can be challenging to receive an ophthalmological evaluation within 24 hours as recommended. These proposed partnerships between oncology and ophthalmology could expedite consultations.

Clearly, all health care professionals need to be vigilant in their patient education sessions regarding the risk of ocular AEs and management strategies. ■

DISCLOSURES: DeRemer has nothing to disclose; Doonan receives research funding from Curis, Inc.

AFFILIATIONS: [1]Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics and Precision Medicine, College of Pharmacy, University of Florida, Gainesville
[2]University of Florida Health Cancer Center, Gainesville
[3]Division of Hematology and Oncology, Department of Medicine, University of Florida, Gainesville; University of Florida Health Cancer Center, Gainesville

CORRESPONDING AUTHOR(S):
David L. DeRemer, PharmD, BCOP, FCCP, FHOPA
Clinical Professor
Assistant Director, Experimental Therapeutics Group
University of Florida College of Pharmacy
University of Florida Health Cancer Center
Office: 352-294-8891
Email: dderemer@cop.ufl.edu
ORCID: 0000-0002-2207-9552

Bently P. Doonan, MD, MS
Assistant Professor
University of Florida College of Medicine
Division of Hematology and Oncology
University of Florida Health Cancer Center
Email: Bently.Doonan@medicine.ufl.edu
ORCID: 0000-0001-5401-2910

References

1. FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation. FDA. June 23, 2022. Accessed February 9, 2023. https://bit.ly/3HYXkhe

2. Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(4):435-445. doi:10.1016/S1470-2045(17)30180-8

3. Klesse LJ, Jordan JT, Radtke HB, et al. The use of MEK inhibitors in neurofibromatosis type 1-associated tumors and management of toxicities. *Oncologist*. 2020;25(7):e1109-e1116. doi:10.1634/theoncologist.2020-0069

4. Arora S, Surakiatchanukul T, Arora T, et al. Retinal toxicities of systemic anticancer drugs. *Surv Ophthalmol*. 2022;67(1):97-148. doi:10.1016/j.survophthal.2021.05.007

5. Piccart MJ, Hilbers FS, Bliss JM, et al. Road map to safe and well-designed de-escalation trials of systemic adjuvant therapy for solid tumors. *J Clin Oncol*. 2020;38(34):4120-4129. doi:10.1200/JCO.20.01382

6. FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC. FDA. May 28, 2021. Accessed February 13. 2023. https://bit.ly/3YEj1Kk

7. van Heeckeren WJ, Bhakta S, Ortiz J et al. Promise of new vascular-disrupting agents balanced with cardiac toxicity: is it time for oncologists to get to know their cardiologists? *J Clin Oncol*. 2006;24(10):1485-1488. doi:10.1200/JCO.2005.04.8801

performed before antitumor treatment. The exact etiology can be quickly distinguished when eye symptoms worsen. Of note, apart from these etiologies, tumor eye metastasis may be uncommon but can still happen in clinical practice and should be noted in patients with cancer. Oncologists and ophthalmologists should learn about the common intraocular metastatic lesions, often involving the uvea, which consists of the iris and ciliary body anteriorly

TABLE 2. **CTCAE Grading for Eye Disorders**

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best-corrected visual acuity 20/40 and better or ≤ 3 lines of decreased vision from known baseline); limiting instrumental ADLs	Symptomatic with marked decrease in visual acuity (best-corrected visual acuity worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADLs	Best-corrected visual acuity of 20/200 or worse in the affected eye	—
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic; moderate decrease in visual acuity (best-corrected visual acuity 20/40 and better or ≤ 3 lines of decreased vision from known baseline); limiting instrumental ADLs	Symptomatic with marked decrease in visual acuity (best-corrected visual acuity worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADLs	Best-corrected visual acuity of 20/200 or worse in the affected eye	—
Retinal detachment	—	—	Macular-sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment	—

ADL, activity of daily living; CTCAE, Common Terminology Criteria for Adverse Events (version 5.0; November 27, 2017).
A single dash (—) indicates a grade is not available.

and the choroid posteriorly. Choroidal metastases typically present as raised amelanotic choroidopathy with patchy pigmentation of the RPE. They are often accompanied by an upper serous retinal detachment disproportionate to the lesion itself. Symptoms depend on the location of the metastases: peripheral metastases containing a small amount of serous fluid may be asymptomatic, whereas macular involvement or subretinal fluid can cause flash hallucinations (subjective perception of flashes, sparks, or color), visual distortion, floaters, blurred vision, difficulty focusing, and dyschromia (an abnormal ability to perceive colors). Although some of these symptoms may mimic drug toxicity, mydriatic fundus examination (often combined with ocular ultrasonography and optical coherence tomography) can often differentiate choroidal metastases from drug-induced retinopathy.[34,35] Orbital or optic nerve metastases can cause optic disc edema, which can be secondary to papilledema due to brain metastases. In such cases, cross-sectional imaging of the head can assist in the diagnosis.[36] Retinal metastases can cause retinal inflammation and intraretinal hemorrhage, and vitreous metastases cause the accumulation of white blood cells in the vitreous, which may manifest as vitritis (inflammation of the vitreous body). Mydriatic fundus examination and vitreous biopsy can help differentiate true vitritis from vitreous metastases.[37]

Management of ocular AEs associated with MEK inhibitors

The US package inserts for trametinib and cobimetinib recommend that patients receive regular eye examinations during treatment and whenever new or worsening visual disturbances occur. Because most ocular toxicities are mild or moderate (and almost always reversible), patients and oncologists should pay attention to these AEs, but more comprehensive ophthalmology evaluations should be received at the onset of clinical symptoms. If retinal detachment has been diagnosed, trametinib should be withheld; it should be restarted at the same or a lower dose only if the retinal detachment resolves within 3 weeks. Clinicians should discontinue the drug, or restart at a lower dose, if there is no improvement after 3 weeks, if the disease recurs, or if RVO occurs. For serous retinopathy caused by cobimetinib, treatment should be interrupted until visual symptoms improve. Treatment can be resumed at a lower dose only if symptoms improve within 4 weeks. Clinicians should permanently discontinue treatment if symptoms recur or RVO occurs. In a similar vein, if serous retinopathy is caused by binimetinib, treatment should be withheld and then resumed at a lower dose if symptoms improve within 10 days. Otherwise, permanently discontinue if no improvement or RVO occurs. Moreover, selumetinib was the same (Table 3). Currently, there are no validated treatment options available for retinal detachment and RVO. The fluid accumulation is usually reabsorbed

TABLE 3. **Management of Ocular Adverse Events Recommended During Treatment With MEK Inhibitors**

MEK inhibitor	Eye examination frequency	Management
Trametinib	Periodically, at any time new or worsening visual disturbances occur	Retinal detachment: Withhold trametinib for up to 3 wk. ▪ If improved, resume trametinib at same or lower dose. ▪ If not improved, permanently discontinue trametinib or resume trametinib at lower dose. RVO: Permanently discontinue trametinib.
Cobimetinib	Periodically, at any time new or worsening visual disturbances occur	Serous retinopathy: Withhold cobimetinib for up to 4 wk. ▪ If signs and symptoms improve, resume at the next lower dose level. ▪ If not improved or symptoms recur at the lower dose within 4 wk, permanently discontinue. RVO: Permanently discontinue cobimetinib.
Binimetinib	Periodically, at any time new or worsening visual disturbances occur	Serous retinopathy: Withhold binimetinib for up to 10 d. ▪ If improved and becomes asymptomatic, resume at same dose. ▪ If not improved, resume at a lower dose level or permanently discontinue binimetinib. RVO: Permanently discontinue binimetinib.
Selumetinib	Periodically, at any time new or worsening visual disturbances occur	Retinal detachment: Withhold until resolution. Resume at reduced dose. RVO: Permanently discontinue selumetinib.

d, days; RVO, retinal vein occlusion; wk, weeks.

in retinal detachment, with symptoms resolving and no need for treatment. RVO is a more serious AE requiring therapeutic intervention. Drug discontinuation should inform consent from patients first, for they have the right to decide. They may maintain eyesight or suffer blindness under the following MEK inhibitor treatment, drug discontinuation should be carefully evaluated for metastatic patients. A range of treatments, including vascular endothelial growth factor receptor inhibitors, anticoagulants, corticosteroids, and thrombolytic agents, have attempted to solve this problem but have no validated evidence to date.[38,39] The lack of available treatment options requires oncologists, ophthalmologists, and patients to mind this problem, and favors ophthalmologic examinations before and after the start of MEK inhibitor treatment to achieve quick diagnoses and close monitoring.

Conclusion

MEK inhibitors are novel targeted anticancer agents of the MAPK pathway and have been approved to treat melanoma, NSCLC, and various *BRAF* V600–mutant solid tumors. However, they seem to cause common and unique ocular toxicities. Treatment with MEK inhibitors combined with targeted drugs or chemotherapy (vs targeted therapy or chemotherapy without MEK inhibitors) seems to increase overall ocular AEs, especially blurred vision, chorioretinopathy, and retinal detachment. To overcome this limitation, oncologists and ophthalmologists need to enhance communication to safeguard patient health during MEK inhibitor therapy. ■

FUNDING: This work was supported by a grant from the Leading Talent Cultivation Project of Henan Health Science and Technology Innovation Talents (No. YXKC2020009), Henan International Joint Laboratory of Drug Resistance and Reversal of Targeted Therapy for Lung Cancer (No. [2021]10), Henan Medical Key Laboratory of Refractory Lung Cancer (No. [2020]27), and Henan Refractory Lung Cancer Drug Treatment Engineering Technology Research Center (No. [2020]4). The funders had no role in the study design, data collection/analysis, decision to publish, or preparation of the manuscript.

AFFILIATIONS: [1]Department of Internal Medicine, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China
[2]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China

CORRESPONDING AUTHOR: Qiming Wang, MD, PhD
Department of Internal Medicine
The Affiliated Cancer Hospital of Zhengzhou University
Henan Cancer Hospital
Zhengzhou, China
Email: qimingwang1006@126.com

For references and supplementary figures, visit cancernetwork.com/MEK_3.23

THE X

INDICATION

XPOVIO® (selinexor) is a prescription medicine approved:

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

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

Monitor sodium level at baseline and throughout treatment.

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

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

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

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

XPOVIO®
(selinexor)

In multiple myeloma

RESTORE YOUR PATIENTS' OWN CANCER DEFENSES

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

FACTOR

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

See the clinical results at xpoviopro.com.

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

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

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

ADVERSE REACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

Please see full Prescribing Information.

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

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

Karyopharm® Therapeutics

US-XPOV-11/20-00075 (05/21)

XPOVIO Brief Summary

XPOVIO®
(selinexor)

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

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

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

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

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

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

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

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

Gastrointestinal Toxicity
XPOVIO can cause severe gastrointestinal toxicities.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Key: S=selinexor, Vd=bortezomib-dexamethasone

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

Females and Males

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

Pediatric Use

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

Geriatric Use

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

PATIENT COUNSELING INFORMATION

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

Dosing Instructions:

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

Hematologic Adverse Reactions

Thrombocytopenia

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

Anemia

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

Neutropenia

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

Gastrointestinal Adverse Reactions

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

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

Hyponatremia

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

Serious Infection

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

Neurotoxicity

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

Embryo-Fetal Toxicity

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

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

Cataract

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

Fatigue

Advise patients that they may experience fatigue.

Lactation

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

Concomitant Medications

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

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

Karyopharm® Therapeutics

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

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

RAPID REPORTER®

ONCOLOGY® Reviews Key Presentations From the
2023 Gastrointestinal Cancers Symposium

ctDNA May Be Ideal Biomarker for Early Response Assessment in Advanced Colorectal Cancer

The short half-life of circulating tumor DNA (ctDNA) compared with other tumor biomarkers makes it ideal for early response assessment in patients with advanced colorectal cancer and may enable use of adaptive clinical study designs in the future.

Investigators reported that molecular nonresponders had an HR for death 5.9 times higher than that of molecular responders, and a time to next treatment (TTNT) HR twice as high; this was done using an MR cut point of more than a 50% decrease in ctDNA.

The median overall survival (OS) in patients who responded or did not respond to chemotherapy was not reached (NR; 95% CI, 26.3-NR; Cox Proportional HR, 0.17; 95% CI, 0.08-0.36; *P*<.005) and 11.8 months (95% CI, 8.7-14.6; HR, 5.92; 95% CI, 2.78-12.63; *P*<.005). Additionally, in patients who responded or did not respond to all regimens, the median OS was NR (95% CI, 23.7-NR; 0.43; 95% CI, 0.24-0.76; *P*<.005) and 17.8 months (95% CI, 10.5-23.4; HR, 2.43; 95% CI, 1.31-4.18; *P*<.005).

Moreover, among patients treated with chemotherapy, the median TTNT for responders and nonresponders was 10.3 months (95% CI, 7.3-NR; HR, 0.51; 95% CI, 0.28-0.92; *P*=.26) and 5.8 months (95% CI, 4.0-7.4; HR, 1.97; 1.08-3.58; *P*=.026), respectively. In the population that received all regimens, the responders and nonresponders had a median TTNT of 10.1 months (95% CI, 8.2-16.1; HR, 0.48; 95% CI, 0.30-0.76; *P*<.005) and 6.1 months (95% CI, 4.5-7.6; HR, 2.09; 95% CI, 1.31-3.34; *P*<.005).

Molecular responders treated with chemotherapy had the most notable reduction in TTNT and OS HR, as identified by thresholds of ctDNA decrease of 50% or greater; a similar trend was observed across several thresholds. Moreover, molecular responders experienced a decrease in HR for OS and TTNT.

→ **To read the full article, visit:** Cancernetwork.com/ASCOGI23_ctDNA

Atezolizumab ± Bevacizumab Combo Yields Modest Benefit in Advanced Biliary Tract Cancer

Atezolizumab (Tecentriq) plus cisplatin/gemcitabine with or without bevacizumab (Avastin) resulted in a modest clinical benefit in a population diagnosed with advanced biliary tract cancer, according to data from the dual experimental arm of the phase 2 IMbrave 151 trial (NCT04677504).

Data presented showed that treatment-naïve patients who

received bevacizumab, atezolizumab, and cisplatin/gemcitabine (n = 79) had a median progression-free survival (PFS) of 8.3 months (95% CI, 6.8-10.0) vs 7.9 months (95% CI, 6.2-8.4) among those who received placebo plus atezolizumab and cisplatin/gemcitabine (n = 83; HR, 0.76; 95% CI, 0.51-1.14). The 6-month PFS rates were 78.2% (95% CI, 68.8%-87.7%) and 63.1% (95% CI, 52.6%-73.6%), respectively.

A key secondary end point was objective response rate (ORR). The confirmed ORR was 24.1% (95% CI, 15.1%-35.0%) with the addition of bevacizumab vs 25.3% (95% CI, 16.4%-36.0%) without the VEGF inhibitor. Complete responses were observed in 1 patient in each arm. More than half the patients in each arm (63.3% and 54.2%, respectively) had stable disease. The disease control rate with bevacizumab was 78.5% vs 75.9% without.

Duration of response (DOR) was prolonged in the bevacizumab arm with 88.5% (95% CI, 73.6%-100.0%) of responders having a response lasting at least 6 months, compared with 47.4% (95% CI, 23.0%-71.8%) of responders in the placebo arm. The median DOR was not estimable (NE; 95% CI, 6.4-NE) in the bevacizumab arm compared with 5.8 months (95% CI, 4.3-6.7) without bevacizumab.

Overall survival (OS) data were immature at the time of analysis. The median OS was NE (95% CI, 11.0-NE) in the bevacizumab arm vs 11.4 months (95% CI, 10.6-NE) in the placebo arm (HR, 0.74; 95% CI, 0.43-1.27). The 6-month OS rates were 92.0% (95% CI, 85.8%-98.1%) vs 80.5% (95% CI, 72.0%-89.1%), respectively.

Treatment-related adverse effects (TRAEs) linked to atezolizumab were experienced by 47.4% vs 38.3% of patients in the bevacizumab and placebo arms, respectively. TRAEs related to bevacizumab or placebo were experienced by 56.4% vs 38.3%, respectively.

→ **To read the full article, visit:** Cancernetwork.com/ASCOGI23_atezolizumab

Pembrolizumab Combo Produces Comparable QOL vs Lenvatinib in Liver Cancer Subtype

Pembrolizumab (Keytruda) plus lenvatinib (Lenvima) yielded comparable health-related quality of life (HRQOL) outcomes vs placebo plus lenvatinib in patients with advanced hepatocellular carcinoma (HCC), according to findings from the phase 3 LEAP-002 study (NCT03713593).

Patients receiving lenvatinib plus pembrolizumab reported, at baseline, a mean European Organisation for Research and Treatment of Cancer Quality of Life (EuroQOL) Questionnaire Core 30 global health score/quality of life score of 71.59 and, at week 27, a score of 66.77, resulting in a least square mean (LSM) change of –8.13 (95% CI, –10.38 to –5.87). For patients receiving the placebo in addition to lenvatinib, the mean baseline score was 72.43, and the mean score at week 27 was 66.60, yielding a LSM change of –8.58 (95% CI, –10.83 to –6.33). Across the total study population, the difference in LSM change from baseline to week 27 was 0.45 (95% CI, –2.53 to 3.44).

Further, patients receiving lenvatinib plus pembrolizumab reported a mean baseline EuroQOL 5-dimension, 5-level visual analog scale score of 76.82 at baseline and a score of 72.61 at week 27, resulting in an LSM change of –6.92 (95% CI, –8.82 to –5.03). For patients receiving the placebo in addition to lenvatinib, the mean baseline score was 76.10 and the mean score at week 27 was 71.93, yielding an LSM change of –7.53 (95% CI, –9.43 to –5.64).

Although first-line lenvatinib plus pembrolizumab demonstrated numerical improvements in progression-free survival and overall survival in LEAP-002, the combination did not meet the prespecified statistical significance criteria for these domains. Nevertheless, investigators concluded that the HRQOL analysis warrants further investigation into immunotherapy's role in HCC.

→ **To read the full article, visit:** Cancernetwork.com/ASCOGI23_lenvatinib

Tremelimumab/Durvalumab Demonstrates Safety, Activity in Gastric/GEJ Adenocarcinoma

In patients with mismatch repair deficient and microsatellite instability-high Epstein-Barr virus–negative gastric or gastroesophageal (GEJ) junction cancer, preoperative combination therapy with tremelimumab (Imjudo) and durvalumab (Imfinzi) was safe and clinically active, according to findings from the phase 2 INFINITY trial (NCT04817826).

In the efficacy-evaluable population, the pathological complete response (pCR) rate for patients treated with tremelimumab plus durvalumab was 60%, and the rate of major to pCR in those with less than 10% of viable cells was 80%.

Investigators evaluated tremelimumab plus durvalumab combination therapy among patients with resectable gastric or GEJ cancer. Patients received 300 mg of tremelimumab for 12 weeks with 1500 mg of durvalumab every 4 weeks for 3 cycles followed by surgery.

In an analysis of exploratory end points, the pCR rate was 17% for those with T4 disease and 89% for those with T2 or T3 tumors (P = .011). Moreover, PD-1 combined positive score was not associated with outcomes, and tumor mutational burden demonstrated a nonsignificant trend toward correlation with pCR.

The most common any-grade immune-related adverse effects (AEs) included pruritus (22%), thyroiditis (22%), hepatitis (17%), and skin rash (17%). Investigators observed grade 3 or higher AEs including hepatitis (n = 1), colitis (n = 1), and pneumonitis (n = 1).

→ **To read the full article, visit:** Cancernetwork.com/ASCOGI23_GEJ

Bevacizumab Combo Yields Survival, DCR Benefits in mCRC

Improved overall survival (OS) and disease control rate were reported in patients with metastatic colorectal cancer (CRC) who were given bevacizumab (Avastin) plus trifluridine (FTD) and tipiracil (TPI, Lonsurf), vs those who received trifluridine and tipiracil alone, according to findings from the phase 3 SUNLIGHT study (NCT04737187).

Median OS was 10.8 months in the treatment arm and 7.5 months in the control arm (HR, 0.61; 95% CI, 0.49-0.77; P <.001). At 6 months, the OS rate was 77% vs 61%, respectively, and at 12 months, the OS rate was 43% vs 30%, respectively.

Median progression-free survival (PFS) was 5.6 months in the treatment arm and 2.4 months in the control arm (HR, 0.44; 95% CI, 0.36-0.54; P <.001). The 6-month PFS rate was 43% vs 16%, respectively, and the 12-month PFS rate was 16% vs 1%, respectively. A PFS analysis by prespecified subgroup showed similar findings as the OS subgroup analysis, with all subgroups experiencing benefits.

The median time to deterioration in global health status in the treatment arm was 8.5 months vs 4.7 months in the control arm (HR, 0.50; 95% CI, 0.38-0.65; P <.001). The time to worsening to an ECOG performance status of 2 or greater was superior for patients receiving FTD/TPI with bevacizumab (9.3 months) vs FTD/TPI alone (6.3 months; HR, 0.54; 95% CI, 0.43-0.67; P <.001).

Overall adverse events (AEs) were equally frequent in both arms. Investigators reported no treatment-related deaths. The rates of severe AEs were 72% in the treatment arm and 70% in the control arm; and 13% of patients in both arms experienced AEs leading to withdrawal from the study.

→ **To read the full article, visit:** Cancernetwork.com/ASCOGI23_bevacizumab

Sorafenib/SBRT Yields OS Benefit in Locally Advanced Hepatocellular Carcinoma

Treatment with sorafenib (Nexavar) and stereotactic body radiation therapy (SBRT) improved overall survival (OS), progression-free survival (PFS), and time to disease progression vs sorafenib alone in patients with locally advanced hepatocellular carcinoma, according to data from the phase 3 NRG/RTOG1112 study (NCT01730937).

The results demonstrated a median OS of 15.8 months (90% CI, 11.4-19.2) with sorafenib/SBRT vs 12.3 months (90% CI, 10.6-14.3) with sorafenib alone (HR, 0.77; 90% CI, 0.59-1.01; 1-sided P = .55). The median PFS was 9.2 months (95% CI, 7.5-11.9) with SBRT/sorafenib vs 5.5 months (95% CI, 3.4-6.3) with sorafenib alone (HR, 0.55; 95% CI, 0.40-0.75; P = .0001). Time to progression with sorafenib/SBRT and sorafenib alone was 18.5 months and 9.5 months, respectively (HR, 0.69; 95% CI, 0.48-0.99; P = .034).

Most patients (94%) in the combination arm received SBRT as intended; 12 patients received SBRT without sorafenib. In the sorafenib arm, 3 patients did not receive the tyrosine kinase inhibitor and 21% proceeded to SBRT after sorafenib discontinuation.

The 6-month and 12-month PFS rates with SBRT/sorafenib were 71% (95% CI, 62%-81%) and 37% (95% CI, 26%-47%), respectively, vs 41% (95% CI, 30%-51%) and 20% (95% CI, 12%-29%), respectively, with sorafenib alone. The 6-month and 12-month time to progression rates were 23% (95% CI, 14%-32%) and 43% (95% CI, 32%-53%), respectively, with SBRT/sorafenib vs 44% (95% CI, 33%-54%) and 57% (95% CI, 46%-67%), respectively, with sorafenib alone.

Regarding safety, gastrointestinal (GI) bleeds occurred in 4% (n = 3) of patients in the combination arm vs 6% (n = 5) of those in the monotherapy arm. In the combination and monotherapy arms, respectively, patients experienced GI disorders (10% vs 7%), bloodwork abnormalities (27% vs 19%), and hepatobiliary disorders (1% vs 3%). ■

→ **The read the full article, visit:** Cancernetwork.com/ASCOGI23_sorafenib

Read this and more online at
www.cancernetwork.com/conference

Medical World News
STREAMING NETWORK
powered by MJH life sciences

A 24-hour streaming program

For Health Care Professionals, By Health Care Professionals

Season 8 is streaming now!

www.medicalworldnews.com

CONTINUING MEDICAL EDUCATION (CME)

Recent Updates in Monitoring and Sequencing Treatment in Chronic Lymphocytic Leukemia

FACULTY

William G. Wierda, MD, PhD
Executive Medical Director and Center Medical Director
Department of Leukemia, Division of Cancer Medicine
Professor of Medicine, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

This activity was written by PER® editorial staff under faculty guidance and review.

CME PROVIDER CONTACT INFORMATION

Physicians' Education Resource®, LLC
2 Clarke Drive, Suite 110
Cranbury, NJ 08512
Toll-Free: 888-949-0045
Local: 609-378-3701
Fax: 609-257-0705
info@gotoper.com

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Assess recent clinical evidence on current and emerging therapeutic approaches that have been evaluated for the treatment of patients with CLL across lines of care
- Translate pivotal trial data on evolving therapeutic options in CLL to develop patient-adapted treatment decisions and sequencing strategies

Release Date: March 2022
Expiration Date: March 2023

INSTRUCTIONS FOR PARTICIPATION & HOW TO RECEIVE CREDIT

1. Read this activity in its entirety.
2. Go to **www.gotoper.com/ash23cll-art** to access and complete the posttest
3. Answer the evaluation questions.
4. Request credit using the drop down menu.

YOU MAY IMMEDIATELY DOWNLOAD YOUR CERTIFICATE

FACULTY, STAFF, AND PLANNERS' DISCLOSURES

In accordance with ACCME Guidelines, PER® has identified and resolved all COI for faculty, staff, and planners prior to the start of this activity by using a multistep process.

Disclosures (William Wierda): *Grant/Research Support:* GSK/Novartis, AbbVie, Genentech, Pharmacyclics LLC, AstraZeneca/Acerta Pharma, Gilead Sciences, Bristol Myers Squibb (Juno & Celgene), KITE Pharma, Sunesis, Miragen, Oncternal Therapeutics, Cyclacel, Loxo Oncology/Lilly, Janssen, Xencor; *Other:* Chair of the CLL National Comprehensive Cancer Network

The staff of PER® have no relevant financial relationships with commercial interests to disclose.

OFF-LABEL DISCLOSURE AND DISCLAIMER

This activity may or may not discuss investigational, unapproved, or off-label use of drugs. Learners are advised to consult prescribing information for any products discussed. The information provided in this activity is for accredited continuing education purposes only and is not meant to substitute for the independent clinical judgment of a health care professional relative to diagnostic, treatment, or management options for a specific patient's medical condition. The opinions expressed in the content are solely those of the individual faculty members and do not reflect those of PER® or any of the companies that provided commercial support for this activity.

This activity is supported by an educational grant from Genentech, a member of the Roche Group.

ACCREDITATION/CREDIT DESIGNATION

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PER® Physicians' Education Resource, LLC
gotoper.com

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia diagnosed in adults, with an estimated 18,740 new cases forecast for the United States in 2023.[1] Diagnosis frequently occurs upon discovering lymphocytosis in routine blood tests at an average age of 72 years.[2] Since the disease often has no symptoms for many patients, it is characterized by the proliferation and accumulation of CD5-positive B cells in the blood, bone marrow, lymph nodes, and spleen.[3,4] For asymptomatic patients with CLL, a "watch-and-wait" approach is generally the appropriate clinical course.[2,3]

Among symptomatic patients who may be experiencing anemia, increased lymphocyte count, night sweats, lymphadenopathy, excessive fatigue, or other symptoms, chemoimmunotherapy was previously used as frontline therapy.[4] However, chemotherapy-free regimens using targeted therapeutics—such as inhibitors of Bruton tyrosine kinase (BTK), B-cell lymphoma 2 (BCL2), and phosphatidylinositol 3-kinase (PI3K) — have yielded significant improvements in overall survival (OS), progression-free survival (PFS), and reduced toxicity when compared with chemoimmunotherapy.[5] This article will cover 3 things you should know about CLL and ways to apply evolving therapeutic options to patient treatment.

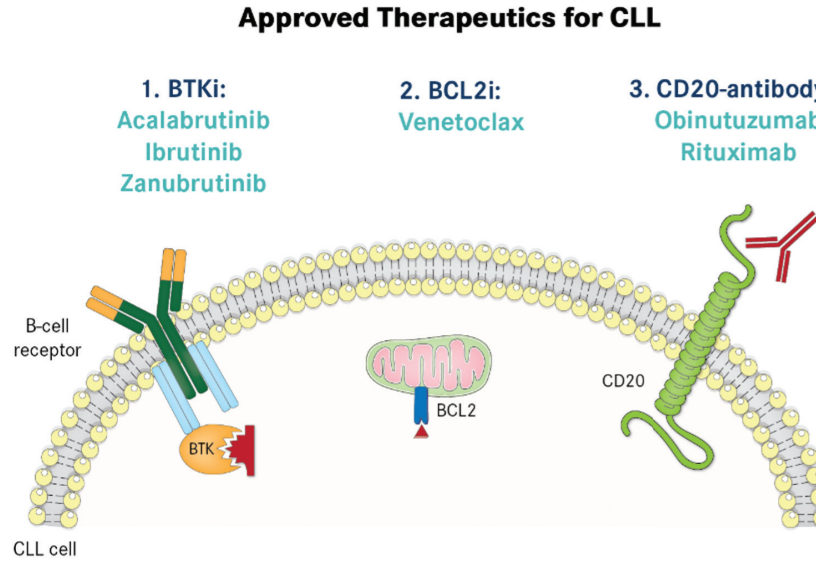
Doublet and triplet targeted therapy combinations are effective frontline options

The treatment armamentarium for CLL and the number of clinical trials have expanded quickly, testing combinations of BTK inhibitors (eg, ibrutinib, acalabrutinib, zanubrutinib), monoclonal antibodies (eg, rituximab, obinutuzumab) and the BCL2 inhibitor venetoclax (**Figure**).[3] In the phase 3 CLL14 trial (NCT02242942), patients with CLL were treated with 12 cycles of chlorambucil and 6 cycles of obinutuzumab vs 12 cycles of venetoclax and 6 cycles of obinutuzumab.[6] At a median follow-up of 65.4 months, median PFS for chlorambucil-obinutuzumab was 36.4 months and was not reached in the venetoclax-obinutuzumab cohort. The 5-year PFS rates were 27.0% and 62.6%, respectively (HR 0.35; 95% CI, 0.26-0.46; $P < .0001$). The phase 3 GLOW trial (NCT03462719) confirmed the inferiority of Clb-Obi treatment to ibrutinib plus venetoclax in older, unfit patients: at a median follow-up of 4 years, the estimated 3.5-year PFS rates were 24.8% and 74.6%, respectively (HR 0.214; 95% CI, 0.138-0.334; $P < .0001$).[7]

Following the results from doublet-therapy clinical trials, time-limited triplet combinations have been investigated using a BTK inhibitor with venetoclax and obinutuzumab.[8] In the phase 3 GAIA/CLL13 trial (NCT02950051), the combination of ibrutinib, obinutuzumab, and venetoclax produced improved 3-year PFS rates when compared against chemoimmunotherapy or other venetoclax-based doublet therapies; however, the addition of ibrutinib appeared to increase the occurrence of atrial fibrillation and bleeding events.[9,10]

The second-generation selective BTK inhibitor acalabrutinib has been associated with fewer toxicities than ibrutinib, yet it has similar efficacy in patients with previously treated CLL.[3,5,11] The ongoing, single-arm, phase 2 AVO trial (NCT03580928) evaluating acalabrutinib, obinutuzumab, and venetoclax in the frontline setting showed that 86% of the 56 evaluable patients achieved the primary endpoint of undetectable minimal residual disease (uMRD) in bone marrow at cycle 16.[12] The best overall response rate (ORR) was 98%, with complete responses (CRs) noted in in 48% of patients and partial responses (PRs) seen in 50% of patients. The most common non-hematological toxicities were headache (78%), fatigue (76%), and bruising (66%). Grade 2 and 3 atrial fibrillations occurred in 1 patient each (3% total), and 21% required dose reductions.

FIGURE. **Drug Mechanisms of Action for Targeted Therapies in CLL[8]**



BCL2i, B-cell lymphoma 2 (BCL2) inhibitor; BTKi, Bruton tyrosine kinase (BTK) inhibitor.

Minimal residual disease guides clinical decisions for patients treated with venetoclax-based regimens

MRD describes the number of CLL cells present in leukocytes after treatment. The absence of MRD (< 10^{-4} CLL cells) is also called MRD negativity or defined precisely as uMRD; it exists as a primary goal for patients treated with venetoclax-based regimens.[13] MRD negativity has been correlated with prolonged PFS and OS, as observed in the CLL14 trial among patients treated with venetoclax-obinutuzumab who had uMRD compared with those with MRD greater than or equal to 10^{-4} detected.[6]

Clinical trials among patients with CLL use MRD measurements to assess drug efficacy and continual MRD assessment to define therapy duration. In the phase 3 FLAIR trial (ISRCTN01844152), varying doses of ibrutinib and venetoclax were used, with established rules of MRD negativity required to stop treatment.[14] At 24 months, 42.6% of patients in the venetoclax-ibrutinib group reached uMRD less than 10^{-4} and were able to halt therapy.

Patients with uMRD exhibit increased OS

MRD was also examined to determine whether it could aid treatment decisions about venetoclax continuation or consolidation therapy. Researchers concluded from the phase 3 MURANO trial (NCT02005471) that half of the patients who had positive CLL clonal growth while on venetoclax were unlikely to achieve uMRD with treatment extension in contrast to those with negative growth.[15] In a phase 2, response-adaptive trial, venetoclax consolidation therapy was examined among patients with high-risk CLL treated with long-term ibrutinib.[16] After 1 year of combination treatment, the best cumulative rate of uMRD in bone marrow was 73%. Ten patients discontinued treatment early based on this MRD-directed approach, and MRD-positive patients continued to receive targeted maintenance therapy. In the phase 2 CLARITY trial (ISCRTN13751862), achievement of uMRD within 6 months (or a 2-log reduction at 2 months) with venetoclax plus ibrutinib treatment was correlated with sustained uMRD at a 3-year follow-up.[17]

The phase 2 CAPTIVATE trial (NCT02910583) used "confirmed uMRD" to randomize patients to placebo or single-agent ibrutinib after 15 cycles of first-line combination ibrutinib plus venetoclax therapy.[18] The 4-year PFS rates remained similar between treatment arms (88% with placebo and 95% with continued ibrutinib). Lastly, posttreatment uMRD measurements were used in the GLOW study to define a sustainable therapeutic response.[7]

Novel BTK inhibitors are approved for relapsed/refractory CLL

Treatment options for relapsed/refractory (R/R) CLL depend upon previous frontline therapies, duration of remission, and acquired resistance.[19] If remission duration exceeds 36 months, then first-line therapy may be repeated.[3] For patients who are intolerant to ibrutinib, the second-generation BTK inhibitors acalabrutinib and zanubrutinib are potential options.[20]

In the randomized, open-label, phase 3 ASCEND trial (NCT02970318), acalabrutinib monotherapy resulted in significantly longer median PFS compared with investigator's choice of therapy (rituximab plus either idelalisib or bendamustine).[21] In the 4-year update, acalabrutinib remained superior to the investigator's choice, with a 42-month PFS rate of 62% vs 19%, respectively.[22] Similarly, in the phase 3 ELEVATE-RR trial (NCT02477696), acalabrutinib was compared head-to-head with ibrutinib in patients with previously treated CLL.[11] Acalabrutinib was noninferior to ibrutinib, with a median PFS of 38.4 months for both treatments (acalabrutinib [95% CI, 33.0-38.6]; ibrutinib [95% CI, 33.0-41.6]; HR, 1.00; 95% CI, 0.79-1.27). Acalabrutinib was also associated with a lower incidence of hypertension (9.4% vs 23.2%), bleeding events (38.0% vs 51.3%), and arthralgia (15.8% vs 22.8%) compared with ibrutinib.

The recently approved drug zanubrutinib is a highly specific, second-generation BTK inhibitor that was compared head-to-head against ibrutinib in the phase 3 ALPINE trial (NCT03734016) in patients with R/R CLL.[3,23] At a median follow-up of 29.6 months, zanubrutinib produced superior PFS to ibrutinib (HR, 0.65; 95% CI, 0.49-0.86; P = .0024); median PFS was 35.0 months (95% CI, 33.2-44.3) with ibrutinib and not reached with zanubrutinib.[24] Furthermore, atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% vs 13.3%; P = .0004).

Zanubrutinib is now approved for the treatment of R/R CLL

Several noncovalent, reversible BTK inhibitors and protein degraders are currently in development.[25] The phase 1/2 BRUIN trial (NCT03740529) examined the efficacy and safety of the highly selective, noncovalent BTK inhibitor pirtobrutinib in patients with previously treated B-cell malignancies, including CLL and small lymphocytic leukemia (SLL).[26] Among 247 patients who had received a prior covalent BTK inhibitor alone, the ORR was 82% (95% CI, 76.8%-86.7%), including reported CRs in 4 patients (1.6%) and PRs in 177 patients (71.7%); among 100 patients also given venetoclax, the ORR was 79.0% (95% CI, 69.7%-86.5%), with PRs noted in 70 patients (70.0%).

In conclusion, second-generation BTK inhibitors have become treatment options as part of triplet therapy for frontline treatment (ie, acalabrutinib, venetoclax, and obinutuzumab) as well as zanubrutinib monotherapy in the R/R setting. Furthermore, MRD status has several advantages for monitoring venetoclax-based treatment efficacy and can be used to determine the timing of treatment discontinuation, predict durability of response, and select next treatment options for patients with CLL. ■

Key References

12. Ryan CE, Lampson BL, Tyekucheva S, et al. Updated results from a multicenter, phase 2 study of acalabrutinib, venetoclax, obinutuzumab (AVO) in a population of previously untreated patients with CLL enriched for high-risk disease. *Blood*. 2022;140(suppl 1):837-838. doi:10.1182/blood-2022-168003

24. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): results from final analysis of ALPINE randomized phase 3 study. *Blood*. 2022;140(suppl 2):LBA-6. doi:10.1182/blood-2022-171538

26. Mato AR, Woyach JA, Brown JR, et al. Efficacy of pirtobrutinib in covalent BTK-inhibitor pre-treated relapsed / refractory CLL/SLL: additional patients and extended follow-up from the phase 1/2 BRUIN study. *Blood*. 2022;140(suppl 1):2316-2320. doi:10.1182/blood-2022-159497

For references visit
www.gotoper.com/ash23cll-art


WE ASPIRE
TO CURE CANCER.
At Takeda Oncology,
we aspire to cure cancer,
with inspiration from
patients and innovation
from everywhere.
@TakedaOncology
Learn more at TakedaOncology.com
©2022 Takeda Pharmaceuticals U.S.A., Inc.
Takeda
ONCOLOGY