FCS THE MAGAZINE

DECEMBER 2020

New Tactics:

Fight against cancer adapts to pandemic

SARAH CANNON Research Institute | FLORIDA CANCER SPECIALISTS & Research Institute | ION Solutions AmerisourceBergen

THE **FIRST AND ONLY** ADC FDA APPROVED FOR ADULT PATIENTS WITH mTNBC WHO HAVE RECEIVED AT LEAST 2 PRIOR THERAPIES FOR METASTATIC DISEASE

33.3%

OVERALL RESPONSE RATE (n=36/108; CR+PR)

(95% CI: 24.6; 43.1)

7.7 MEDIAN MONTHS

DURATION OF RESPONSE (range: 1.9, 30.4)

(95% CI: 4.9; 10.8)

Based on investigator assessment.

TRODELVY was evaluated in an open-label, uncontrolled, single-arm phase 1/2 trial of 108 patients with mTNBC who had received at least 2 prior treatments for metastatic disease. TRODELVY was administered intravenously at a dose of 10 mg/kg on Days 1 and 8 of continuous 21-day treatment cycles, and patients were treated until disease progression or unacceptable toxicity. Major efficacy outcome measures were investigator-assessed overall response rate (ORR) using RECIST 1.1 and duration of response.

CI=confidence interval; CR=complete response; PR=partial response.

INDICATION

TRODELVY™ (sacituzumab govitecan-hziy) is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least 2 prior therapies for metastatic disease.

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 confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNING: NEUTROPENIA AND DIARRHEA

TRODELVY can cause severe or life-threatening neutropenia. Withhold TRODELVY for absolute neutrophil count (ANC) below 1500/mm^3 on Day 1 of any cycle or ANC below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

Monitor blood cell counts periodically during treatment. Consider Granulocyte Colony-Stimulating Factor (G-CSF) for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.

- Dose modifications may be required due to neutropenia. Febrile neutropenia occurred in 6% (24/408) of patients treated with TRODELVY, including 8% (9/108) of patients with mTNBC after at least 2 prior therapies. Less than 1% (1/408) of patients had febrile neutropenia leading to permanent discontinuation. The incidence of Grade 1-4 neutropenia was 64% in patients with mTNBC (n=108). In all patients treated with TRODELVY (n=408), the incidence of Grade 1-4 neutropenia was 54%; Grade 4 neutropenia occurred in 13%. Less than 1% (2/408) of patients permanently discontinued treatment due to neutropenia.

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.

- Diarrhea occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3-4 occurred in 9% (10/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY

Contraindications: Severe hypersensitivity reaction to TRODELVY.

Hypersensitivity

- TRODELVY can cause severe and life-threatening hypersensitivity, including anaphylactic reactions. Hypersensitivity reactions occurred within 24 hours of dosing in 37% (151/408) and Grade 3-4 hypersensitivity occurred in 1% (6/408) of all patients treated with TRODELVY (n=408). The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (3/408).
- Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY 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.

Nausea and Vomiting

- TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively. Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

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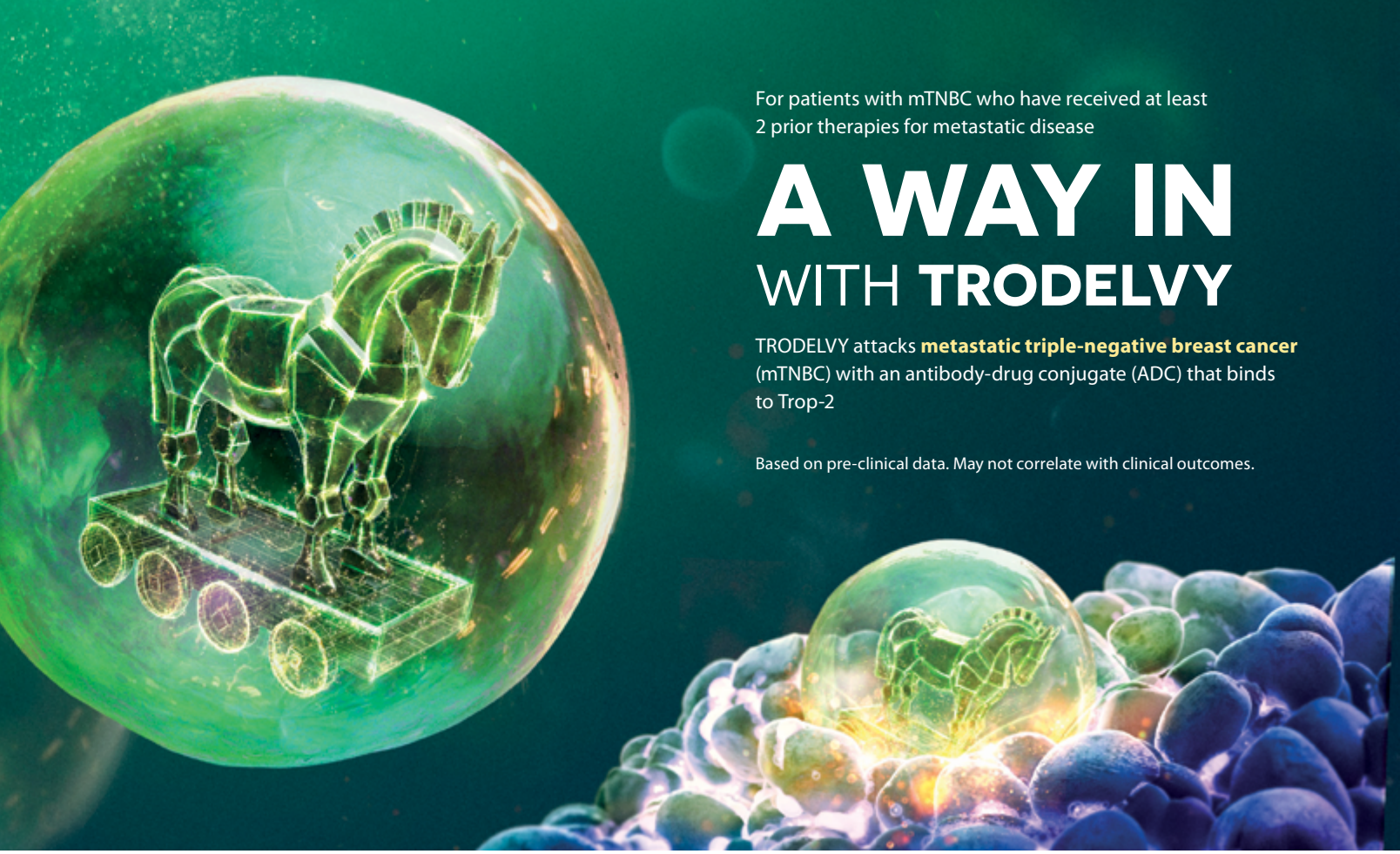

For patients with mTNBC who have received at least 2 prior therapies for metastatic disease

A WAY IN WITH TRODELVY

TRODELVY attacks **metastatic triple-negative breast cancer** (mTNBC) with an antibody-drug conjugate (ADC) that binds to Trop-2

Based on pre-clinical data. May not correlate with clinical outcomes.

- Premedicate with a 2- or 3-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 at the time of scheduled treatment administration 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.

Use in Patients with Reduced UGT1A1 Activity

- Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse events following initiation of TRODELVY treatment. Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.
- In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele, and 11% (16/149) in patients homozygous for the wild-type allele.

Embryo-Fetal Toxicity

- TRODELVY contains a genotoxic component and can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. 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 following 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.

Lactation

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.

Adverse Reactions

Most common adverse reactions (incidence >25%) in patients with mTNBC are nausea (69%), neutropenia (64%), diarrhea (63%), fatigue (57%), anemia (52%), vomiting (49%), alopecia (38%), constipation (34%), rash (31%), decreased appetite (30%), abdominal pain (26%), and respiratory infection (26%).

Please see the Brief Summary of full Prescribing Information, including boxed Warning, on the pages that follow.

Efficacy. Directed.

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

VISIT TRODELVY.COM TO LEARN MORE.

Brief Summary of Prescribing Information

TRODELVY™ (sacituzumab govitecan-hziy) for injection, for intravenous use

See package insert for full Prescribing Information.

INDICATIONS AND USAGE

TRODELVY is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

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 confirmatory trials.

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe 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 *[see Warnings and Precautions]*.**
- **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 *[see Warnings and Precautions]*. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.**

CONTRAINDICATIONS

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Neutropenia

TRODELVY can cause severe or life-threatening neutropenia. Withhold TRODELVY for absolute neutrophil count 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.

Febrile neutropenia occurred in 6% (24/408) patients treated with TRODELVY, including 8% (9/108) patients with mTNBC after at least two prior therapies. Less than 1% (1/408) of patients had febrile neutropenia leading to permanent discontinuation.

The incidence of Grade 1-4 neutropenia was 64% in patients with mTNBC (n=108). In all patients treated with TRODELVY (n=408), the incidence of Grade1-4 neutropenia was 54%; Grade 4 neutropenia occurred in 13%. Less than 1% (2/408) of patients permanently discontinued treatment due to neutropenia.

Diarrhea

TRODELVY can cause severe diarrhea. 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.

Diarrhea occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3-4 occurred in 9% (10/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY.

Hypersensitivity

TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY.

Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1% (6/408) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (3/408).

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY 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.

Nausea and Vomiting

TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively.

Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

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 at the time of scheduled treatment administration 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.

Use in Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele and 11% (16/149) in patients homozygous for the wild-type allele.

Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.

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 *[see Use in Specific Populations]*.

ADVERSE REACTIONS

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

- Neutropenia *[see Warnings and Precautions]*
- Diarrhea *[see Warnings and Precautions]*
- Hypersensitivity *[see Warnings and Precautions]*
- Nausea and Vomiting *[see Warnings and Precautions]*

Clinical Trials Experience

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

The data described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in a single-arm, open-label study (IMMU-132-01) in 408 patients with mTNBC and other malignancies who had received prior systemic therapeutic regimen for advanced disease. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses up to 10 mg/kg until disease progression or unacceptable toxicity.

The data in Table 2 reflect exposure to TRODELVY in a subset of 108 patients with mTNBC who had received at least two prior treatments for metastatic disease in study (IMMU-132-01). Patients received TRODELVY 10 mg/kg via intravenous infusion on Days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity. The median treatment duration in these 108 patients was 5.1 months (range: 0-51 months).

Serious adverse reactions were reported in 31% of the patients. The most frequent serious adverse reactions (reported in >1%) of the patients receiving TRODELVY were febrile neutropenia (6%) vomiting (5%), nausea (3%), dyspnea (3%), diarrhea (4%), anemia (2%), pleural effusion, neutropenia, pneumonia, dehydration (each 2%).

TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to discontinuation were anaphylaxis, anorexia/fatigue, and headache (each <1%, 1 patient for each event). Forty-five percent (45%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 33% of patients treated with TRODELVY, with 24% having one dose reduction and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/febrile neutropenia.

Adverse reactions occurring in ≥10% of patients with mTNBC in the IMMU-132-01 study are summarized in Table 2.

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any adverse reaction	100	71
Gastrointestinal disorders	95	21
Nausea	69	6
Diarrhea	63	9
Vomiting	49	6
Constipation	34	1
Abdominal pain[i]	26	1
Mucositis[ii]	14	1
General disorders and administration site conditions	77	9
Fatigue[iii]	57	8
Edema[iv]	19	0
Pyrexia	14	0
Blood and lymphatic system disorders	74	37
Neutropenia	64	43
Anemia	52	12
Thrombocytopenia	14	3
Metabolism and nutrition disorders	68	22
Decreased appetite	30	1
Hyperglycemia	24	4
Hypomagnesemia	21	1
Hypokalemia	19	2
Hypophosphatemia	16	9
Dehydration	13	5
Skin and subcutaneous tissue disorders	63	4
Alopecia	38	0
Rash[v]	31	3
Pruritus	17	0
Dry Skin	15	0
Nervous system disorders	56	4
Headache	23	1
Dizziness	22	0
Neuropathy[vi]	24	0
Dysgeusia	11	0
Infections and infestations	55	12
Urinary Tract Infection	21	3
Respiratory Infection[vii]	26	3
Musculoskeletal and connective tissue disorders	54	1
Back pain	23	0
Arthralgia	17	0
Pain in extremity	11	0

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2020-US-TROT-00025

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01 *(cont'd)*

Respiratory, thoracic and mediastinal disorders	54	5
Cough[viii]	22	0
Dyspnea[ix]	21	3
Psychiatric disorders	26	1
Insomnia	13	0

Graded per NCI CTCAE v. 4.0

[i]Including abdominal pain, distention, pain (upper), discomfort, tenderness

[ii]Including stomatitis, esophagitis, and mucosal inflammation

[iii]Including fatigue and asthenia

[iv]Including edema; and peripheral, localized, and periorbital edema

[v]Including rash; maculopapular, erythematous, generalized rash; dermatitis acneiform; skin disorder, irritation, and exfoliation

[vi]Including gait disturbance, hypoesthesia, muscular weakness, paresthesia, peripheral and sensory neuropathy

[vii]Including lower and upper respiratory tract infection, pneumonia, influenza, viral upper respiratory infection, bronchitis and respiratory syncytial virus infection

[viii]Includes cough and productive cough

[ix]Includes dyspnea and exertional dyspnea

Table 3: Laboratory Abnormalities observed in >10% of Patients while receiving TRODELVY

Laboratory Abnormality	TRODELVY (n=108)	
	All Grades (%)	Grade 3-4 (%)
Hematology		
Decreased hemoglobin	93	6
Decreased leukocytes	91	26
Decreased neutrophils	82	32
Increased activated partial thromboplastin time	60	12
Decreased platelets	30	3
Chemistry		
Increased alkaline phosphatase	57	2
Decreased magnesium	51	3
Decreased calcium	49	3
Increased glucose	48	3
Increased aspartate aminotransferase	45	3
Decreased albumin	39	1
Increased alanine aminotransferase	35	2
Decreased potassium	30	3
Decreased phosphate	29	5
Decreased sodium	25	4.7
Increased magnesium	24	4
Decreased glucose	19	2

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other sacituzumab govitecan products may be misleading.

The analysis of immunogenicity of TRODELVY in serum samples from 106 patients with mTNBC was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-sacituzumab govitecan-hziy antibodies. Detection of the anti-sacituzumab govitecan-hziy antibodies was done using a 3-tier approach: screen, confirm, and titer. Persistent anti-sacituzumab govitecan-hziy antibodies developed in 2% (2/106) of patients.

DRUG INTERACTIONS

Effect of Other Drugs on TRODELVY

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 *[see Warning and Precaution]*. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers *[see Warning and Precaution]*. Avoid administering UGT1A1 inducers with TRODELVY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, 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. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

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

Data

Animal data

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan-hziy.

Lactation

Risk Summary

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

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Contraception

Females

TRODELVY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males

Because of the potential for genotoxicity, 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

Females

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, 19/108 (18%) patients with mTNBC and 144/408 (35%) of all patients were ≥ 65 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 less than or equal to 1.5 ULN and AST/ALT < 3 ULN).

The exposure of TRODELVY in patients with mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN, or bilirubin greater than 1.0 to 1.5 ULN and AST of any level; n=12) was similar to patients with normal hepatic function (bilirubin or AST less than ULN; n=45).

The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin > 1.5 ULN, or AST and ALT > 3 ULN, or AST and ALT > 5 ULN and associated with liver metastases.

No dedicated trial was performed to investigate the tolerability of TRODELVY in patients with moderate or severe hepatic impairment. No recommendations can be made for the starting dose in these patients.

OVERDOSAGE

In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

Pharmacogenomics

SN-38 is metabolized via UGT1A1. Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from TRODELVY *[see Warnings and Precautions]*. Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations.

PATIENT COUNSELING INFORMATION

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

Neutropenia

Advise patients of the risk of neutropenia. Instruct patients to immediately contact their healthcare provider if they experience fever, chills, or other signs of infection *[see Warnings and Precautions]*.

Diarrhea

Advise patients of the risk of diarrhea. Instruct patients to immediately contact their healthcare provider if they experience diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours *[see Warnings and Precautions]*.

Hypersensitivity

Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, tongue, or throat swelling, urticaria, difficulty breathing, lightheadedness, dizziness, chills, rigors, wheezing, pruritus, flushing, rash, hypotension or fever, that occur during or within 24 hours following the infusion *[see Warnings and Precautions]*.

Nausea/Vomiting

Advise patients of the risk of nausea and vomiting. Premedication according to established guidelines with a two or three drug regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) is also recommended. Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated. All patients should receive take-home medications for preventing and treating delayed nausea and vomiting, with clear instructions. Instruct patients to immediately contact their healthcare provider if they experience uncontrolled nausea or vomiting *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise female patients to contact their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations]*.

Contraception

Advise female patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of TRODELVY *[see Use in Specific Populations]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TRODELVY *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY *[see Use in Specific Populations]*.

Infertility

Advise females of reproductive potential that TRODELVY may impair fertility *[see Use in Specific Populations]*.

Manufactured by:
Immunomedics, Inc.
300 The American Road
Morris Plains, NJ 07950, USA U.S. License No. 1737

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

NATHAN H. WALCKER, CHIEF EXECUTIVE OFFICER:

As much as the COVID-19 pandemic has challenged us, it has taught us the importance of so many things. Here at FCS, I continue to witness the strength of our teams and the value of partnerships.

This became evident months ago with the swift actions taken to keep our employees and patients safe amidst COVID-19, plus the innovative approaches devised to serve our patients without disruption.

In this issue of *FCS Magazine*, you'll appreciate the behind-the-scenes look at our FCS Procurement team. In the early days of the pandemic, these skilled professionals navigated a supply chain stretched beyond thin to secure critical equipment and supplies. They were successful due in large part to the strength of long-established relationships with an extensive network of vendors and suppliers.

One of my favorite aspects of *FCS Magazine* is our People & Places section. Despite the distractions and challenges of 2020, we've continued moving forward. Together and in partnership with our communities, we're growing and expanding to ensure that all patients have access to world-class care close to home.

As the year draws to a close, I couldn't be more proud of our FCS physicians and team members. Together, you have risen to the challenges and exceeded all expectations. Thank you for your efforts to support our patients and one another every step of the way.

LUCIO GORDAN, MD, PRESIDENT & MANAGING PHYSICIAN:

The ongoing pandemic is causing new concerns in oncology care. Our feature article examines a recent study showing a troubling reduction in cancer screenings and treatment. We at FCS are taking an active role in reversing the trend.

FCS continues to participate in clinical research activities that are leading to medical breakthroughs in cancer treatment.

Across our FCS network, over 60 active clinical trials are underway in collaboration with Sarah Cannon Research Institute. In this issue's Clinical Research Update, Drs. Manish Patel, Judy Wang and Shekeab Jauhari, who comprise our Drug Development Unit leadership team, share insights on how, why and when clinical trials are made available.

Our recently announced genetics program seeks to reduce deaths and suffering from hereditary cancers. With the addition of a specially trained genetic professional and a powerful technology tool, we have begun to identify patients who have an increased likelihood of developing cancer.

There perhaps has been no more exciting time to be involved in scientific discoveries that are enabling us to provide our patients with access to the most advanced treatment options.

FCS THE MAGAZINE

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We welcome your feedback, article suggestions and photos (high resolution please).

Email to FCSCommunications@FLCancer.com

FCS is participating in a national awareness campaign to encourage cancer screenings.

COVID-19

COVID-19: A Dangerous Delay

New study reveals COVID-19's negative impact on cancer screenings, diagnosis and treatment

Dr. Michael Diaz

Dr. Lucio Gordan

A new national study that details the devastating effect the COVID-19 crisis has had on cancer screenings, diagnosis and treatment is garnering headlines across the nation. Lucio Gordan, MD, President and Managing Physician of Florida Cancer Specialists & Research Institute (FCS), and FCS Assistant Managing Physician Michael Diaz, MD are co-authors of the study, which was conducted for the Community Oncology Alliance (COA) by Avalere Health and published in the November issue of the journal JCO Clinical Cancer Informatics. Its findings show a substantial decrease in the number of cancer screenings, diagnosis and treatment for senior adults and Medicare beneficiaries in 2020.

FCS Clinics Already Seeing A Dangerous Trend

Dr. Gordan, Dr. Diaz and colleagues were part of the study's research team of oncologists who reported that they are already seeing patients being diagnosed with later stage cancers, which require more complex treatment and often result in higher morbidity and mortality rates. "In the early months of the pandemic," Dr. Gordan explained, "many people chose or had to delay or even skip regular screenings, such as mammograms, prostate exams, PSA testing or colonoscopies, among others, for various types of cancer. This has resulted in later diagnoses for some patients and delays in beginning treatment. Oncologists are preparing their practices for significant impact in cancer patient outcomes due to these delays."

Dr. Diaz, who also serves as President of COA, concurs. "If cancers are not diagnosed at an early stage, we could face rising death rates for several years to come," he said. "It is critical that adults with a family history of cancer and others who may be experiencing symptoms do not delay their screenings for the fear of being exposed to or contracting coronavirus. Medical practices now have numerous strategies in place to protect the safety and health of patients, doctors, nurses and other staff members."

The COA study revealed a drastic drop in screening procedures, surgeries and treatments for patients with colon, prostate, lung and breast cancer in a group comprised of greater than six million

seniors (Medicare population); if this trend continues, physicians warn, it will lead to a public health catastrophe, as the number of undiagnosed/untreated cancer patients rise and cancer mortality increases.

Community Oncology's Quick Response

One positive cited in the study was the rapid adoption of telehealth and other strategies by community oncology practices, such as Florida Cancer Specialists. Dr. Gordan said, "Community oncologists and their team members showed incredible resilience and resolve to deal with this severe crisis, by adopting telehealth very quickly, reorganizing workflows, enhancing safety processes at their clinics and migrating staff to work from home, among other strategies. Although a decrease in services was inevitable, the resolve of these practitioners and staff handled and avoided what could have been a much worse situation."

FCS Working with COA to Develop National Awareness Campaign

FCS, along with other organizations, is leading a nationwide effort to obtain sponsorship that will support a crucial initiative from COA to create a national awareness campaign calling attention to the importance of getting recommended cancer screenings or treatment and not delaying because of the COVID-19 pandemic.

Plans include producing a national public service announcement that will drive awareness. The campaign will communicate and reinforce these important messages:

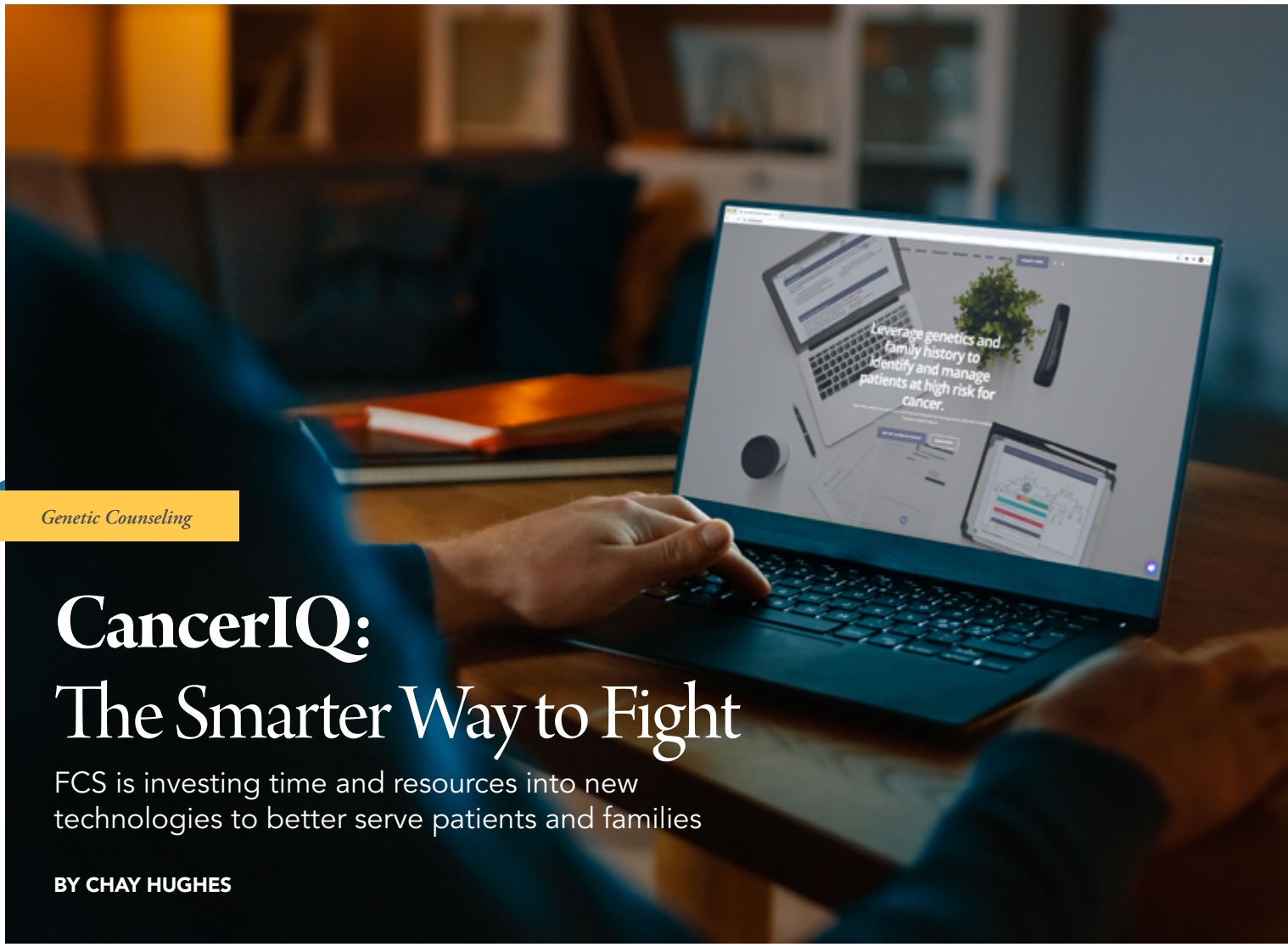
- Do not delay getting screened for cancer, whether it is a routine or annual screening, or if you think something is "wrong."
- Early cancer detection and treatment saves lives.
- Screening is safe and conducted in facilities that are COVID-19 free and making patient safety the top priority.

Cancer Is Not Quarantined — We Must Take Action to Save Lives

In the early months of the pandemic, shelter-in-place orders and a general uncertainty about the virus caused an enormous decline in the number of screenings. While screening numbers have risen in the past few months, they still have not reached pre-pandemic levels. Many Floridians remain scared and unsure of whether or not to get annual routine screenings, particularly if they are older or in a high-risk category for the coronavirus.

With the current third wave of COVID-19 sweeping across the country, it's no wonder that people are fearful and confused about what to do, even though the majority of Americans recognize the importance of cancer screenings. Adding to the disarray is the fact that, once again, hospitals (where many screening facilities are located) are facing shortages in both personnel and resources, which could affect screening schedules.

Despite these concerns, however, we must take action. That's why the COA campaign is so important. We are convinced that resuming regular cancer screenings will save lives, not only in cancer care but also, hopefully, in other areas of medicine as well.



Genetic Counseling

CancerIQ: The Smarter Way to Fight

FCS is investing time and resources into new technologies to better serve patients and families

BY CHAY HUGHES

Leveraging the latest innovation in emerging technologies is a critical component of Florida Cancer Specialists' strategy in the fight against cancer. Under the leadership of FCS President and Managing Physician Dr. Lucio Gordan, FCS is adding a genetic risk assessment software to identify and manage patients at high risk of cancer.

CancerIQ is a new digital platform designed to identify genetic risk factors for entire families. According to Dr. Gordan, the goal is to diagnose increased risk of cancer, preventing its development in a person with potential high genetic risk.

"We hope that we will not only diagnose patients before they have cancer just based on their family history and inherent risk, but also help patients who have a history of cancer already, as there are therapies that can be tailored based on germline genetic features," said Dr. Gordan.

The Details: How CancerIQ Works

The program launched in fall 2020 at FCS's Tallahassee location. There, patients were invited to opt into the program by answering questions on an iPad or other hand-held mobile device.

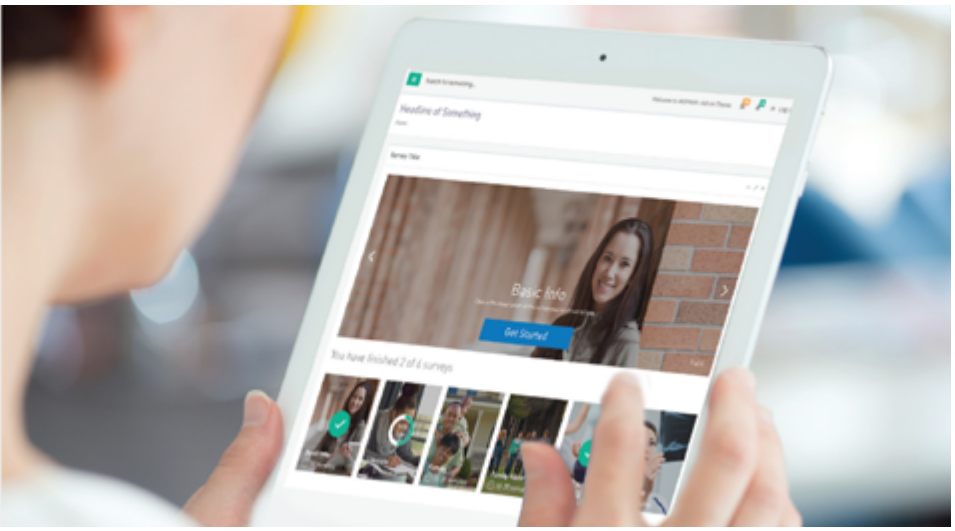
Just a few, simple multiple-choice questions later and a patient's healthcare team was able to have a fuller picture of potential risk factors. CancerIQ acts as a catalyst for a larger conversation (usually 45 minutes to an hour) in assessing risks and talking through individual options.

"What we're trying to do is bridge this gap by formalizing a process in which we'll capture a patient's family history electronically," explained Dr. Gordan. "Patients will enter the information via an iPad or whatever electronic format they choose. Their responses will trigger an analysis and response: 'Does this patient qualify for genetic testing or not?' 'What is the risk?' And it will alert the providers to order the appropriate tests for that patient."

Those flagged as high-risk are referred for genetic counseling, testing and personalized care management by a multidisciplinary team.

Dr. Lucio Gordan

Vicki Caraway, RN, BSN, MBA, NE-BC



On the provider's side, individualized data, analytics and a genetic roadmap for risk factors based on their patient's needs will be created instantly by CancerIQ. From that point, physicians will be able to select which additional testing applies to their patient. Panels will test anywhere from 30 to 80 genes, depending on which commercial platform the provider selects.

Informed Patients + Enhanced Technology = Better Outcomes

FCS Vice President of Clinical Services, Vicki Caraway, RN, BSN, MBA, NE-BC has had nearly 30 years of experience helping oncology patients heal. Together with Dr. Gordan, Caraway has championed CancerIQ as a necessity for the FCS team.

According to Caraway, patients today are savvier than in years past when it comes to their options. Most patients, she said, are aware of genetic testing and are ready and willing to take the steps needed to assess their risks.

"Cancer IQ is the platform that allows us to screen all new patients to understand who needs to undergo hereditary cancer genetic testing," explained Caraway. "From that, patients who meet societal guidelines for genetic testing will hopefully opt in and agree to move forward with genetic testing. What happens next is that once we get the results back from the lab, CancerIQ will automatically flag patients who require treatment changes or increased surveillance for a secondary cancer. It's a powerful tool, and we're super excited."

CancerIQ's cutting-edge software technology will be available across FCS' 89 treatment facilities in 2021.

MEET GENETICS COUNSELOR CATHY MARINAK

The software technology could not have arrived at FCS at a more ideal time. With new advances in genetic counseling seemingly every day, leadership at FCS has made the investment to add an entirely new position to the staff.

Nurse Practitioner Cathy Marinak, AOCNP will serve as the organization's new genetics counselor. Vice President of Clinical Services Vicki Caraway, RN, BSN, MBA, NE-BC said the organization is looking forward to tapping into Marinak's expertise.

"I really wanted to have someone in our organization who's done it, lived it, breathed it and knows the best way to reach the most patients," said Vicki. "We hired someone who has a lot of experience and has done this for many years. Cathy and I are going to work together to figure out how to expand CancerIQ across the state."

PROCUREMENT

FCS Procurement 101

Keeping FCS equipped during COVID

BY KARI C. BARLOW

As Chief Procurement Officer for FCS, Paul Chadwick is used to a certain amount of chaos.

After all, global supply chains can be complex and unpredictable. But COVID-19 sent the regular chaos of navigating and managing very complex material and pharmaceutical contracting, purchasing and logistics systems to an entirely new level. The FCS procurement team was additionally tasked with sourcing the much-needed PPE to protect FCS team members and patients.

"There was a greater concern about infecting patients and having patients infect staff," he said. "Normally it would be masks for physicians and nurses, but in this crisis, everyone needed masks."

Masks were needed — as well as gloves, gowns and countless other pieces of equipment that were rapidly disappearing from the market.

"The challenge has been that those massive hospital systems that are treating COVID-19 are consuming all the PPE they can get their hands on," said Paul, who has worked for FCS for almost two years. "We are a very large, well-organized health system/health group, but we can't compete on that scale."

The industry underwent a massive shift in a short amount of time, and like many other facilities, FCS clinics started running out of vital supplies. Items were not only more difficult to replenish, they took longer to arrive.

To Paul and FCS Director of Procurement Rose Ann Meyers, it was clear their team would have to get creative.

"It was chaos!" said Rose Ann, who has worked for FCS for 11 ½ years. "We didn't have a lot of time. We had to make quick decisions based on what the clinical team was saying."

Harnessing that energy, they morphed into a team of detectives, relentless in their quest to buy the PPE the clinics needed.

"Honestly, we tracked down every lead,

"We cannot take our eye off of the ball ... the clinics are depending on us. That's the bottom line."

every I-know-someone-who-knows-someone," Chadwick said. "Our first big order came through the brother of someone who works for the company."

The bulk of that work fell to Cindy Richardson, a sourcing analyst who tirelessly investigated every tip and vetted companies and websites to make sure they were legitimate.

"Initially, when things ran out, Cindy was texting people on the weekends," Paul said. "She was reaching out to all of her contacts. She really was the eye of the storm."

Working at such a pace certainly has taken its toll on Paul and the team. There are still long days — many of them packed with Zoom and Teams meetings — but the team has rallied to meet every challenge.

"They're so good at all of it," Paul said. "Some

of them have a great setup and some of them are working from their kitchen table all day, and they have all just sort of done it. All of them have worked harder through this."

For Rose Ann — who found it easier to work at her office at corporate headquarters in Fort Myers a few days each week — physical activity was a lifesaver.

"I walked the parking lot quite a bit," she said. "There were days when I just had to step away."

Paul — who normally travels weekly to Fort Myers, Tampa and Gainesville but has been grounded at his Brooklyn, New York home since March — took comfort in being closer to his wife, Suzanne, and kids, 11-year-old Colin and seven-year-old Hazel.

"Having a little more time with the family has really helped," he said. "Just to be home more has helped with that balance."

When he looks back to the early days of the pandemic, he's proud of what his team has accomplished.

"We would always have a 'Plan B,' " he said. "It was really kind of knowing there was always one more stone to turn over that really kept us going."

And even today, scarcity in multiple areas continues to be a problem. As soon as gloves or masks are at acceptable levels, another item falls short and the urgency returns.

Paul Chadwick

Rose Ann Meyers

"Something is always short," Chadwick notes. "Even down to the flu vaccine, which we've managed to source from a couple of places."

This year, because of the heightened awareness of coronavirus, more people, both staff and patients, want flu shots, he added.

"And flu shots are something you order in January, and in January we were not in a COVID world," he said.

All of that means the procurement team has no time to slow down.

"We cannot take our eye off of the ball," said Rose Ann. "No matter what, the clinics are depending on us. That's the bottom line."

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DRUG REVIEW

INREBIC® (fedratinib) capsules 100 mg

A Treatment Option for Patients with Intermediate-2 or High Risk Myelofibrosis

Ralph V. Boccia, MD, FACP, is board certified in hematology, medical oncology and internal medicine by the American Board of Internal Medicine. He practices out of the Center for Cancer and Blood Disorders, an AON practice of which he is the founder and medical director, located in Bethesda, Maryland and Germantown, Maryland.

Dr. Boccia is a clinical associate professor of medicine at Georgetown University.

This promotional article was created and funded by Bristol Myers Squibb Company. Dr. Boccia was compensated by Bristol Myers Squibb Company for his participation.

INDICATION

INREBIC® (fedratinib) is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).

IMPORTANT SAFETY INFORMATION

WARNING: ENCEPHALOPATHY INCLUDING WERNICKE'S

Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with INREBIC. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

WARNINGS AND PRECAUTIONS

Encephalopathy, including Wernicke's: Serious and fatal encephalopathy, including Wernicke's encephalopathy, has occurred in INREBIC-treated patients. Serious cases were reported in 1.3% (8/608) of patients treated with INREBIC in clinical trials and 0.16% (1/608) of cases were fatal.

Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia). Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including Wernicke's, and prompt a full evaluation including a neurologic examination, assessment of thiamine levels, and imaging. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately

The first JAK (Janus kinase) inhibitor for the treatment of myelofibrosis was introduced in 2011.[1,2] In August 2019, the FDA approved the selective JAK2 inhibitor INREBIC (fedratinib) for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.[3,4] This indication statement is broad; therefore, INREBIC could be an option for patients who are naïve to JAK inhibitors or for patients previously treated with the JAK2 inhibitor ruxolitinib. INREBIC contains a boxed warning for encephalopathy, including Wernicke's encephalopathy.[4]

The FDA approval of INREBIC was based on the results from the pivotal phase 3 JAKARTA trial in JAK-inhibitor-naïve patients with intermediate-2 or high-risk primary or secondary myelofibrosis with splenomegaly.[3,4] Patients were randomized 1:1:1 to receive INREBIC 500 mg (n=97), 400 mg (n=96), or placebo (n=96) once daily for at least 6 cycles. Patients continued to receive INREBIC as long as they were having clinical benefit, defined as complete or partial remission, clinical improvement, or stable disease, and had not experienced disease progression or relapse (as defined by the modified IWG-MRT criteria) or unacceptable toxicity requiring discontinuation. Crossover from the placebo arm was allowed after the randomization period, and crossover patients were randomized 1:1 to one of the 2 INREBIC arms. The primary endpoint was the proportion of patients achieving ≥35% reduction from baseline in spleen volume at the end of cycle 6 as measured by MRI or CT and confirmed with a scan 4 weeks later. The main secondary endpoint was the proportion of patients achieving ≥50% reduction from baseline to the end of cycle 6 in Total Symptom Score (TSS) as measured by the MF-SAF v2.0 diary, which captures the 6 core symptoms of MF: night sweats, itching, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain.[4,5]

In the intent-to-treat population, 37% (35 of 96) of patients receiving the FDA-approved dose of 400 mg once daily achieved the primary endpoint of ≥35% reduction from baseline in spleen volume at the end of cycle 6 as measured by MRI or CT and confirmed with a scan 4 weeks later. The median duration of the spleen response was 18.2 months. In the placebo arm, one patient (1%) had a spleen volume reduction of ≥35%. In the symptom evaluable population, 40% (36 of 89) of patients in the INREBIC 400 mg arm and 9% (7 of 81)

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discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

Anemia: New or worsening Grade 3 anemia occurred in 34% of INREBIC-treated patients. The median time to onset of the first Grade 3 anemia was approximately 2 months, with 75% of cases occurring within 3 months. Mean hemoglobin levels reached nadir after 12 to 16 weeks with partial recovery and stabilization after 16 weeks. Red blood cell transfusions were received by 51% of INREBIC-treated patients and permanent discontinuation of INREBIC occurred due to anemia in 1% of patients. Consider dose reduction for patients who become red blood cell transfusion dependent.

Thrombocytopenia: New or worsening Grade ≥3 thrombocytopenia during the randomized treatment period occurred in 12% of INREBIC-treated patients. The median time to onset of the first Grade 3 thrombocytopenia was approximately 1 month; with 75% of cases occurring within 4 months. Platelet transfusions were received by 3.1% of INREBIC-treated patients. Permanent discontinuation of treatment due to thrombocytopenia and bleeding that required clinical intervention both occurred in 2.1% of INREBIC-treated patients. Obtain a complete blood count (CBC) at baseline, periodically during treatment, and as clinically indicated. For Grade 3 thrombocytopenia with active bleeding or Grade 4 thrombocytopenia, interrupt INREBIC until resolved to less than or equal to Grade 2 or baseline. Restart dose at 100 mg daily below the last given dose and monitor platelets as clinically indicated.

Gastrointestinal Toxicity: Gastrointestinal toxicities are the most frequent adverse reactions in INREBIC-treated patients. During the randomized treatment period, diarrhea occurred in 66% of patients, nausea in 62% of patients, and vomiting in 39% of patients. Grade 3 diarrhea 5% and vomiting 3.1% occurred. The median time to onset of any grade nausea, vomiting, and diarrhea was 1 day, with 75% of cases occurring within 2 weeks of treatment. Consider providing appropriate prophylactic anti-emetic therapy (e.g., 5-HT3 receptor antagonists) during INREBIC treatment. Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms. Grade 3 or higher nausea, vomiting, or diarrhea not responsive to supportive measures

in the placebo arm had a ≥50% reduction in TSS at the end of cycle 6. In the JAKARTA trial, the most common adverse reactions (reported in ≥20% of patients) included diarrhea (66%), nausea (62%), vomiting (39%), and anemia (40%). Serious adverse reactions occurred in 21% of patients, and included cardiac failure (5%) and anemia (2%). INREBIC was associated with hematologic laboratory abnormalities, such as anemia (74%), thrombocytopenia (47%), and neutropenia (23%).[4]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend fedratinib as initial therapy (category 2B) for patients with intermediate-2 or high-risk myelofibrosis and platelet count ≥50 × 10^9/L and who are transplant ineligible.[6]

It is important to note that INREBIC has a boxed warning for encephalopathy, including Wernicke's. Serious encephalopathy, including Wernicke's, occurred in 8 out of 608 patients in the development program, one of whom had a fatal outcome. Wernicke's is a neurologic emergency resulting from thiamine (vitamin B) deficiency. As such, it is important to assess thiamine levels in all patients prior to starting INREBIC and periodically during treatment as clinically indicated. INREBIC should not be started in patients with thiamine deficiency, and thiamine should be repleted prior to treatment initiation.[4]

In addition to the pivotal study, there was a single-arm phase 2 study in patients who were previously treated with ruxolitinib. The JAKARTA2 study was prematurely terminated, which therefore impacts the interpretability of the data. No conclusions can be drawn regarding the benefit or risk of INREBIC in this patient population and these data are not in the INREBIC label. The JAKARTA2 study included 97 patients with primary or secondary myelofibrosis who were resistant or intolerant to ruxolitinib per investigator assessment. The primary endpoint was the proportion of patients achieving ≥35% reduction from baseline in spleen volume at the end of Cycle 6. Median exposure to ruxolitinib prior to enrollment in the study was 10.7 months. Median exposure to INREBIC during the study was 24 weeks. 30.9% of patients had a confirmed spleen reduction of ≥35% from baseline at the end of Cycle 6 and 26.7% had ≥50% reduction in TSS from baseline at the end of Cycle 6. In patients previously treated with ruxolitinib, hematologic adverse events were observed, including anemia (99.0%), thrombocytopenia (70.1%), and neutropenia (24.0%). The most common (selected)

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within 48 hours, interrupt INREBIC until resolved to Grade 1 or less or baseline. Restart dose at 100 mg daily below the last given dose. Monitor thiamine levels and replete as needed.

Hepatic Toxicity: Elevations of ALT and AST (all grades) during the randomized treatment period occurred in 43% and 40%, respectively, with Grade 3 or 4 in 1% and 0%, respectively, of INREBIC-treated patients. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months. Monitor hepatic function at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher ALT and/or AST elevations (greater than 5 × ULN), interrupt INREBIC dose until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose. If re-occurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with INREBIC.

Amylase and Lipase Elevation: Grade 3 or higher amylase 2% and/or lipase 10% elevations developed in INREBIC-treated patients. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. One patient developed pancreatitis in the fedratinib clinical development program (n=608) and pancreatitis resolved with treatment discontinuation. Monitor amylase and lipase at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher amylase and/or lipase elevations, interrupt INREBIC until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose.

ADVERSE REACTIONS:

The most common adverse reactions for INREBIC treated vs. placebo were diarrhea (66% vs. 16%), nausea (62% vs. 15%), anemia (40% vs. 14%), and vomiting (39% vs. 5%). Dosage interruptions due to an adverse reaction during the randomized treatment period occurred in 21% of patients who received INREBIC. Adverse reactions requiring dosage interruption in >3% of patients who received INREBIC included diarrhea and nausea. Dosage reductions due to an adverse reaction during the randomized treatment period occurred in 19% of patients who received INREBIC. Adverse reactions requiring dosage reduction in >2% of patients who received INREBIC included anemia (6%), diarrhea (3%), vomiting (3%), and thrombocytopenia (2%).

adverse reactions (reported in >30% of patients) included increased creatinine (74.2%), diarrhea (61.9%), nausea (55.7%), increased AST and ALT (47.4% and 45.4%, respectively), and vomiting (41%).[7]

The NCCN Guidelines® also recommend fedratinib (category 2A) for patients with intermediate-2 or high-risk myelofibrosis previously treated with ruxolitinib with no response or loss of response and who have platelet count ≥50 × 10^9/L and who are transplant ineligible.[6] It is important to remember that this guideline should be considered with the following limitations: JAKARTA2, a phase-2, single-arm, open-label study, was prematurely terminated, which impacts the interpretability of the data. No conclusions regarding the benefits or risks of fedratinib in patients who are resistant or intolerant to ruxolitinib can be established based on this study. These data are not included in the Prescribing Information. It is important to assess the patient and the available data before making a decision on what is right for your patient.

Please see Important Safety Information and accompanying Brief Summary, including Boxed WARNING, for INREBIC.

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6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.1.2020. © National Comprehensive Cancer Network, Inc 2020. All rights reserved. Accessed May 21, 2020. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaimers any responsibility for their application or use in any way.
7. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myeloproliferative neoplasm-associated myelofibrosis previously treated with ruxolitinib: a reanalysis of the phase II JAKARTA-2 study. Presented at 2019 ASCO Annual Meeting; May 31- June 4, 2019; Chicago, IL. Abstract 7057.

DRUG INTERACTIONS:

Coadministration of INREBIC with a strong CYP3A4 inhibitor increases fedratinib exposure. Increased exposure may increase the risk of adverse reactions. Consider alternative therapies that do not strongly inhibit CYP3A4 activity. Alternatively, reduce the dose of INREBIC when administering with a strong CYP3A4 inhibitor. Avoid INREBIC with strong and moderate CYP3A4 inducers. Avoid INREBIC with dual CYP3A4 and CYP2C19 inhibitor. Coadministration of INREBIC with drugs that are CYP3A4 substrates, CYP2C19 substrates, or CYP2D6 substrates increases the concentrations of these drugs, which may increase the risk of adverse reactions of these drugs. Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when coadministered with INREBIC.

PREGNANCY/LACTATION:

Consider the benefits and risks of INREBIC for the mother and possible risks to the fetus when prescribing INREBIC to a pregnant woman. Due to the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with INREBIC, and for at least 1 month after the last dose.

RENAL IMPAIRMENT:

Reduce INREBIC dose when administered to patients with severe renal impairment. No modification of the starting dose is recommended for patients with mild to moderate renal impairment. Due to potential increase of exposure, patients with preexisting moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions.

HEPATIC IMPAIRMENT:

Avoid use of INREBIC in patients with severe hepatic impairment.

Please see accompanying Brief Summary, including Boxed WARNING.

INREBIC® [fedratinib], Capsules for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

WARNING: ENCEPHALOPATHY INCLUDING WERNICKE'S

Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with INREBIC. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize *[see Dosage and Administration (2.6), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

INREBIC® (fedratinib) is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Conduct baseline testing of thiamine (Vitamin B1) levels prior to initiation of INREBIC *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

The recommended dosage of INREBIC is 400 mg taken orally once daily for patients with a baseline platelet count of greater than or equal to 50 x 10^9/L.

INREBIC may be taken with or without food. Administration with a high fat meal may reduce the incidence of nausea and vomiting.

Modify the dose for patients using concomitant strong CYP3A4 inhibitors, and in patients with severe renal impairment (creatinine clearance (CL_{cr}) 15 mL/min to 29 mL/min) *[see Dosage and Administration (2.3, 2.4)]*.

If a dose of INREBIC is missed, the next scheduled dose should be taken the following day.

Patients that are on treatment with ruxolitinib before the initiation of INREBIC must taper and discontinue according to the ruxolitinib prescribing information.

2.2 Monitoring for Safety

Obtain the following blood tests prior to starting treatment with INREBIC, periodically during treatment, and as clinically indicated *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5)]:*

- Thiamine (Vitamin B1) level
- Complete blood count with platelets
- Creatinine and BUN
- Hepatic panel
- Amylase and lipase

2.3 Dose Modifications with Concomitant Use of Strong CYP3A4 Inhibitors

Reduce INREBIC dose when administering with strong CYP3A4 inhibitors to 200 mg once daily.

In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, INREBIC dosage should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg once daily thereafter as tolerated *[see Drug Interactions (7.1)]*.

2.4 Dose Modifications for Severe Renal Impairment

Reduce INREBIC dose to 200 mg once daily in patients with severe renal impairment (creatinine clearance (CL_{cr}) 15 mL/min to 29 mL/min as estimated by Cockcroft-Gault (C-G) equation).

2.5 Dose Modifications for Adverse Reactions

Modify dose for hematologic and non-hematologic adverse reactions per Table 1 and Table 2. Discontinue INREBIC in patients unable to tolerate a dose of 200 mg daily. See Warnings and Precautions for other mitigating strategies.

Table 1: Dose Modifications for Hematologic Adverse Reactions

Hematologic Adverse Reactions	Dose Reduction
Grade 4 Thrombocytopenia or Grade 3 Thrombocytopenia with active bleeding	Interrupt dose until resolved to Grade 2 or lower or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 4 Neutropenia	Interrupt dose until resolved to Grade 2 or lower or baseline. Restart dose at 100 mg daily below the last given dose.

Consider dose reductions for patients who become transfusion-dependent during treatment with INREBIC.

Table 2: Dose Reductions for Non-hematologic Adverse Reactions

Non-hematologic Adverse Reactions	Dose Reduction
Grade 3 or higher Nausea, Vomiting, or Diarrhea not responding to supportive measures within 48 hours	Interrupt dose until resolved to Grade 1 or lower or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 3 or higher ALT, AST, or Bilirubin	Interrupt dose until resolved to Grade 1 or lower or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST, and bilirubin (total and direct) more frequently following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment with INREBIC.
Grade 3 or higher Other Non-hematologic Toxicities	Interrupt dose until resolved to Grade 1 or lower or baseline. Restart dose at 100 mg daily below the last given dose.

2.6 Management of Thiamine Levels and Wernicke's Encephalopathy (WE)

Assess thiamine levels and nutritional status prior to starting INREBIC and periodically during treatment and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation and during treatment if thiamine levels are low. If Wernicke's encephalopathy is suspected, immediately discontinue treatment with INREBIC and initiate parenteral thiamine treatment. Monitor until symptoms resolve or improve and thiamine levels normalize *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Encephalopathy, Including Wernicke's

Serious and fatal encephalopathy, including Wernicke's encephalopathy, has occurred in INREBIC-treated patients. Serious cases were reported in 1.3% (8/608) of patients treated with INREBIC in clinical trials and 0.16% (1/608) of cases were fatal.

Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia). Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including Wernicke's, and prompt a full evaluation including a neurologic examination, assessment of thiamine levels, and imaging. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize *[see Dosage and Administration (2.6) and Clinical Trials Experience (6.1)]*.

5.2 Anemia and Thrombocytopenia

Treatment with INREBIC can cause anemia and thrombocytopenia.

Anemia

New or worsening Grade 3 anemia occurred in 34% of INREBIC-treated patients. The median time to onset of the first Grade 3 anemia was approximately 2 months, with 75% of cases occurring within 3 months. Mean hemoglobin levels reached nadir after 12 to 16 weeks with partial recovery and stabilization after 16 weeks. Red blood cell transfusions were received by 51% of INREBIC-treated patients and permanent discontinuation of INREBIC occurred due to anemia in 1% of patients. Consider dose reduction for patients who become red blood cell transfusion dependent *[see Dosage and Administration (2.5)]*.

Thrombocytopenia

New or worsening Grade ≥3 thrombocytopenia during the randomized treatment period occurred in 12% of INREBIC-treated patients. The median time to onset of the first Grade 3 thrombocytopenia was approximately 1 month; with 75% of cases occurring within 4 months. Platelet transfusions were received by 3.1% of INREBIC-treated patients. Permanent discontinuation of treatment due to thrombocytopenia and bleeding that required clinical intervention both occurred in 2.1% of INREBIC-treated patients.

Obtain a complete blood count (CBC) at baseline, periodically during treatment, and as clinically indicated. For Grade 3 thrombocytopenia with active bleeding or Grade 4 thrombocytopenia, interrupt INREBIC until resolved to less than or equal to Grade 2 or baseline. Restart dose at 100 mg daily below the last given dose and monitor platelets as clinically indicated *[see Dosage and Administration (2.5)]*.

5.3 Gastrointestinal Toxicity

Gastrointestinal toxicities are the most frequent adverse reactions in INREBIC-treated patients. During the randomized treatment period, diarrhea occurred in 66% of patients, nausea in 62% of patients, and vomiting in 39% of patients. Grade 3 diarrhea and vomiting occurred in 5% and 3.1% of patients, respectively. The median time to onset of any grade nausea, vomiting, and diarrhea was 1 day, with 75% of cases occurring within 2 weeks of treatment.

Consider providing appropriate prophylactic anti-emetic therapy (e.g., 5-HT3 receptor antagonists) during INREBIC treatment. Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms. For Grade 3 or higher nausea, vomiting, or diarrhea not responsive to supportive measures within 48 hours, interrupt INREBIC until resolved to Grade 1 or less or baseline. Restart dose at 100 mg daily below the last given dose *[see Dosage and Administration (2.5)]*. Monitor thiamine levels and replete as needed.

5.4 Hepatic Toxicity

Elevations of ALT and AST (all grades) during the randomized treatment period occurred in 43% and 40%, respectively, with Grade 3 or 4 in 1% and 0%, respectively, of INREBIC-treated patients. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months.

Monitor hepatic function at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher ALT and/or AST elevations (greater than 5 × ULN), interrupt INREBIC dose until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose. If re-occurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with INREBIC *[see Dosage and Administration (2.5)]*.

5.5 Amylase and Lipase Elevation

Grade 3 or higher amylase and/or lipase elevations developed in 2% and 10%, respectively, of INREBIC-treated patients. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. One patient developed pancreatitis in the fedratinib clinical development program (n=608) and pancreatitis resolved with treatment discontinuation.

Monitor amylase and lipase at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher amylase and/or lipase elevations, interrupt INREBIC until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose *[see Dosage and Administration (2.5)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Encephalopathy, including Wernicke's *[see Warnings and Precautions (5.1)]*
- Anemia and Thrombocytopenia *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.3)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.4)]*
- Amylase and Lipase Elevation *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS Section 5.1 Encephalopathy, including Wernicke's, reflect exposure to INREBIC as a single agent in 608 patients who received more than one dose (ranging from 30 mg to 800 mg) in Studies JAKARTA, ARD11936, JAKARTA2, ARD12042, ARD12888, TED12037/TED12015, INT12497, and TES13519, of whom 459 were patients with myelofibrosis, including 97 patients previously treated with ruxolitinib. Among the 608 patients receiving INREBIC, the median drug exposure was 37 weeks and the median number of cycles initiated was 9 cycles. Fifty-nine percent of 608 patients were exposed for 6 months or longer and 39% were exposed for 12 months or longer.

Using the dataset described above, the most common adverse reactions in >20% of patients (N=608) were diarrhea, nausea, anemia, vomiting, fatigue, thrombocytopenia, and constipation.

JAKARTA Trial

The safety of INREBIC was evaluated in the randomized treatment period of the JAKARTA trial *[see Clinical Studies (14)]*. Key eligibility criteria included adult patients with intermediate-2 or high-risk primary MF or post-PV MF or post-ET MF with splenomegaly, platelet count ≥50 x 10^9/L, and no splenectomy. Patients received INREBIC at 400 mg daily (n=96) or placebo (n=95). Among patients receiving INREBIC, 82% were exposed for more than 6 months and 65% for more than one year. Patients had a median duration of exposure to INREBIC 400 mg daily of 15.5 months compared with placebo where patients were treated for 6 months or until disease progression after which patients were allowed to crossover to active treatment. The median age of patients who received INREBIC was 65 years (range: 27 to 86 years), 59% were male, 90% were White, 8% were Asian, 1% were Black, 1% were Other, and 92% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

Serious adverse reactions occurred in 21% of INREBIC-treated patients. Serious adverse reactions in ≥2% of patients receiving INREBIC 400 mg daily included cardiac failure (5%) and anemia (2%). Fatal adverse reactions of cardiogenic shock occurred in 1% of patients receiving INREBIC 400 mg daily.

Permanent discontinuation due to an adverse reaction occurred in 14% of patients receiving INREBIC. Most frequent reasons for permanent discontinuation in ≥2% of patients receiving INREBIC included cardiac failure (3%), thrombocytopenia, myocardial ischemia, diarrhea, and increased blood creatinine (2% each).

Dosage interruptions due to an adverse reaction during the randomized treatment period occurred in 21% of patients who received INREBIC. Adverse reactions requiring dosage interruption in >3% of patients who received INREBIC included diarrhea and nausea.

Dosage reductions due to an adverse reaction during the randomized treatment period occurred in 19% of patients who received INREBIC. Adverse reactions requiring dosage reduction in >2% of patients who received INREBIC included anemia (6%), diarrhea (3%), vomiting (3%), and thrombocytopenia (2%).

The most common adverse reactions (reported in ≥20%) were diarrhea, nausea, anemia, and vomiting.

Tables 3 and 4 summarize the common adverse reactions and laboratory abnormalities, respectively, in JAKARTA during randomized treatment.

Table 3: Adverse Reactions Reported in ≥5% Patients Receiving INREBIC 400 mg with a Difference between Arms of >5% during Randomized Treatment

Adverse Reaction[a]	INREBIC 400 mg (n=96)		Placebo (n=95)	
	All Grades %	Grade ≥3[b] %	All Grades %	Grade ≥3 %
Diarrhea	66	5	16	0
Nausea	62	0	15	0
Anemia	40	30	14	7
Vomiting	39	3.1	5	0
Fatigue or asthenia	19	5	16	1.1
Muscle spasms	12	0	1.1	0
Blood creatinine increased	10	1	1.1	0
Pain in extremity	10	0	4.2	0
Alanine aminotransferase Increased	9	0	1.1	0
Headache	9	0	1.1	0
Weight increased	9	0	4.2	0
Dizziness	8	0	3.2	0
Bone pain	8	0	2.1	0
Urinary tract infection[c]	6	0	1.1	0
Dysuria	6	0	0	0
Aspartate aminotransferase increased	5	0	1.1	0

[a] CTCAE version 4.03.
[b] Only 1 Grade 4 event (anemia).
[c] Includes cystitis.

Clinically significant adverse reactions reported in 5% or less of patients: hypertension of all grades was reported in 4.2% of patients and Grade 3 or higher in 3% of INREBIC-treated patients.

Changes in selected post-baseline laboratory values that were observed are shown in Table 4 for the JAKARTA trial during randomized treatment.

Table 4: Selected Laboratory Abnormalities That Have Worsened from Baseline (≥20%) in Patients Receiving INREBIC with a Difference between Arms of >10% When Compared to Placebo in JAKARTA during Randomized Treatment

Laboratory Parameter	INREBIC 400 mg (n=96)		Placebo (n=95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Hematology				
Anemia	74	34	32	10
Thrombocytopenia	47	12	26	10
Neutropenia	23	5	13	3.3
Biochemistry				
Creatinine increased	59	3.1	19	1.1
ALT increased	43	1	14	0
AST increased	40	0	16	1.1
Lipase increased	35	10	7	2.2
Hyponatremia	26	5	11	4.3
Amylase increased	24	2.1	5	0

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on INREBIC

Strong CYP3A4 Inhibitors

Coadministration of INREBIC with a strong CYP3A4 inhibitor increases fedratinib exposure *[see Clinical Pharmacology (12.3)]*. Increased exposure may increase the risk of adverse reactions *[see Warnings and Precautions (5), and Adverse Reactions (6.1)]*. Consider alternative therapies that do not strongly inhibit CYP3A4 activity. Alternatively, reduce the dose of INREBIC when administering with a strong CYP3A4 inhibitor *[see Dosage and Administration (2.3)]*.

Strong and Moderate CYP3A4 Inducers

Avoid INREBIC with strong and moderate CYP3A4 inducers. The effect of concomitant administration of a strong or moderate CYP3A4 inducer with INREBIC has not been studied *[see Clinical Pharmacology (12.3)]*.

Dual CYP3A4 and CYP2C19 Inhibitors

Avoid INREBIC with dual CYP3A4 and CYP2C19 inhibitor. The effect of concomitant administration of a dual CYP3A4 and CYP2C19 inhibitor with INREBIC has not been studied *[see Clinical Pharmacology (12.3)]*.

7.2 Effect of INREBIC on Other Drugs

CYP3A4, CYP2C19, or CYP2D6 Substrate Drugs

Coadministration of INREBIC with drugs that are CYP3A4 substrates, CYP2C19 substrates, or CYP2D6 substrates increases the concentrations of these drugs, which may increase the risk of adverse reactions of these drugs *[see Clinical Pharmacology (12.3)]*. Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when coadministered with INREBIC.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on INREBIC use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of fedratinib to pregnant rats during organogenesis at doses considerably lower than the recommended human daily dose of 400 mg/day resulted in adverse developmental outcomes *(see Data)*. Consider the benefits and risks of INREBIC for the mother and possible risks to the fetus when prescribing INREBIC to a pregnant woman.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. 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, fedratinib administration at a dose of 30 mg/kg/day during organogenesis (gestation days 6 to 17) was associated with adverse developmental outcomes including skeletal variations (such as additional ossification center of neuronal arches). These effects occurred in rats at approximately 0.1 times the clinical exposure based on AUC at the recommended daily dose. At lower doses of 10 mg/kg/day (0.01 times the clinical exposure at the recommended daily dose), fedratinib administered to pregnant rats resulted in maternal toxicity of decreased gestational weight gain.

In an embryo-fetal development study in pregnant rabbits, fedratinib administration during organogenesis (gestation Days 6 to 18) did not produce developmental or maternal toxicity at doses up to the highest dose level tested, 30 mg/kg/day (approximately 0.08 times the clinical exposure at the recommended daily dose). In a separate study, administration of 80 mg/kg/day fedratinib to rabbits resulted in maternal mortality.

In a pre- and postnatal study in rats, fedratinib was administered to pregnant female rats at doses of 3, 10, or 30 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. A slight decrease in maternal body weight gain during gestation occurred at 30 mg/kg/day. The offspring from the high dose (30 mg/kg) had decreased body weight preweaning in both sexes and postweaning through the maturation phase in males. These effects occurred at exposures approximately 0.1 times the clinical exposure at the recommended daily dose.

8.2 Lactation

Risk Summary

There are no data on the presence of fedratinib or its metabolites 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 patients not to breastfeed during treatment with INREBIC, and for at least 1 month after the last dose.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of patients with myelofibrosis who received an INREBIC dose of 400 mg in the clinical studies, 47.3% were greater than 65 years of age and 12.3% were greater than 75 years of age. No overall differences in safety or effectiveness of INREBIC were observed between these patients and younger patients.

8.6 Renal Impairment

Reduce INREBIC dose when administered to patients with severe renal impairment (CL_{cr} 15 mL/min to 29 mL/min by Cockcroft-Gault) *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. No modification of the starting dose is recommended for patients with mild to moderate renal impairment (CLcr 30 mL/min to 89 mL/min by Cockcroft-Gault). Due to potential increase of exposure, patients with pre-existing moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions *[see Dosage and Administration (2.5)]*.

8.7 Hepatic Impairment

INREBIC pharmacokinetics has not been evaluated in patients with severe hepatic impairment (total bilirubin > 3 times ULN and any AST). Avoid use of INREBIC in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

17 PATIENT COUNSELING INFORMATION

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

Discuss the following with patients prior to and during treatment with INREBIC.

Encephalopathy, including Wernicke's

Advise patients that serious and fatal encephalopathy, including Wernicke's, has occurred in patients taking INREBIC. Wernicke's encephalopathy is a neurological emergency resulting from acute thiamine (Vitamin B1) deficiency. Advise patients of the need to monitor thiamine levels *[see Dosage and Administration (2.1, 2.2, 2.6), and Warnings and Precautions (5.1)]*. Advise patients to seek emergency medical attention for any change in mental status such as confusion, drowsiness or memory impairment, cerebellar abnormalities such as ataxia, and ophthalmic abnormalities such as diplopia and nystagmus. Advise patients to contact their healthcare provider right away if they experience nausea, vomiting, diarrhea, and weight loss unresponsive to treatment resulting in malnutrition and lower thiamine levels, which may lead to Wernicke's encephalopathy *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Anemia and Thrombocytopenia

Advise patients that INREBIC is associated with anemia and thrombocytopenia, and of the need to monitor complete blood counts before and during treatment *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider if they experience intractable diarrhea, nausea, or vomiting. Prescribers should advise patients of the potential complications of severe diarrhea, nausea, or vomiting *[see Warnings and Precautions (5.3)]*.

Hepatic Toxicity

Advise patients that INREBIC may increase liver enzymes and of the need to monitor liver enzyme levels *[see Warnings and Precautions (5.4)]*.

Amylase and Lipase Elevation

Advise patients that INREBIC may increase amylase and lipase and of the need to monitor amylase and lipase *[see Warnings and Precautions (5.5)]*.

Lactation

Advise patients not to breastfeed during treatment with INREBIC and for at least 1 month after the final dose *[see Use in Specific Populations (8.2)]*.

Dosing and Storage Instructions

- Instruct patients that if they miss a dose of INREBIC, skip the dose and take it the next day and return to normal schedule *[see Dosage and Administration (2.1)]*. Warn patients not to take 2 doses to make up for the missed dose.

Manufactured for and marketed by:
Celgene Corporation
Summit, NJ 07901

Pat. www.celgene.com/therapies

FCS Foundation News & Events

Stay safe and wear a mask with the FCS Foundation two-ply face masks. A two-pack of Foundation masks is available for purchase at FCSFstore.com.

Grab these unique greeting cards and support the FCS Foundation at the same time. Now on sale, these beautiful greeting cards are created by cancer patients participating in the Healing Arts Program at the Florida Cancer Specialists Vero Beach office. A pack of 10 is available with envelopes at FCSFstore.com. All proceeds benefit the FCS Foundation.

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Go to the FCS Foundation's Facebook page, and let us know why you support the Foundation. "Like" the page, post a hello and share why you support the FCS Foundation. Each week through December, one random name will be pulled, and the winner will receive a thank you gift.

Share your support on Amazon. Go to Smile.Amazon.com, log-in and select Florida Cancer Specialists Foundation as your charity. For eligible purchases at AmazonSmile, the AmazonSmile Foundation will donate 0.5% of the purchase price to the customer's selected charitable organization.

Clinical Trials

Phase 1 Clinical Trials Bring Early Access to Patients

The clinical research team at FCS is conducting more than 60 Phase 1 clinical trials in partnership with Sarah Cannon Research Institute — at this very moment.

BY CHAY HUGHES

If "intrepid" isn't the first adjective that comes to mind when you think of oncologists, then you haven't met the trailblazers leading clinical research at Florida Cancer Specialists in action.

At Phase 1 Drug Development Units in Sarasota and the Orlando area, FCS doctors are playing a key role in the advancement of cancer research. In collaboration with Sarah Cannon Research Institute, they're conducting 60-to-65 early Phase 1 clinical trials every day.

It's an exciting period for developmental therapeutics in oncology.

In 2015, Dr. Judy Wang joined Dr. Manish Patel at the Phase 1 Unit he directs in Sarasota. Together with their colleague Dr. Shekeab Jauhari in Lake Mary, these medical oncologists bring ground-breaking cancer research and treatments to their patients within the local, community-based care of FCS.

Phase 1: The Next Frontier

According to Dr. Wang, researchers are engineering new potential cancer treatments at an unprecedented rate. But in order to have a drug move along in the approval process, Phase 1 trials like the ones conducted at FCS are essential in establishing baseline data, proper dosage and expectant side effects.

"Now, you're seeing new drugs being approved at an accelerated pace — at times, it can feel like almost every week — which is a promising sign that governing regulatory agencies and pharmaceutical industries acknowledge the unmet needs for oncology patients," said Dr. Wang. "In the developmental journey of bringing a drug from experimental trials to FDA-approved access for the general public, the first crucial step really lies with us in the initial Phase 1 studies."

Sarah Cannon and FCS: A Network of Researchers

During his tenure at FCS, Dr. Patel has seen these studies grow in proportion with the public's demand for more treatment options.

"Doctors, patients and the industry as a whole want these drugs to come out faster, so we're starting to see these early phase trials become much larger," explained Dr. Patel. "The goal is trying to get these drugs approved as early and as safely as possible."

Giving FCS patients "first access" to life-saving medications means connecting with other experts in the field. In order to have a broader network, FCS collaborates with Sarah Cannon Research Institute, which acts as a hub to connect oncology practices nationwide conducting similar studies. Data collected from these separate sites will unify to push research forward.

According to Dr. Patel, FCS's large clinical trial menu allows patients access to local trials so that many no longer have to fly. Now, physicians from any of FCS's 89 locations are able to refer their metastatic patients to one of two Phase 1 Clinical Trial units.

During the first surge of COVID-19 cases in the U.S., many academic centers paused enrollment to clinical trials. Despite the challenge of coordinating these studies during a pandemic, clinical trials at FCS have continued, with additional protocols in place to optimize patient safety. Dr. Shekeab Jauhari explains, "We've stayed focused on the mission of providing excellent care. Our Phase 1 trials allow for earlier access to the newest cancer treatments in development. This has motivated us to continue our work without any interruptions."

Dr. Manish Patel

Dr. Shekeab Jauhari

Dr. Judy Wang

The Patient's Perspective: What You Need to Know

Patients involved in clinical trials at FCS are monitored with extreme precision.

Every ache, pang and downtick in lab tests is meticulously documented.

"Not only do our trials allow access to exciting therapies," says Dr. Wang, "but our trial patients find it rewarding to be part of the development process and establishing the management of these drugs for future patients."

Patients should know that their participation will help physicians and researchers like Dr. Patel, Dr. Wang and Dr. Jauhari push innovation in cancer research forward — and that they'll be well cared for every step of the way.

NORTH PORT GROUNDBREAKING

This November, we commemorated the start of construction of our new North Port office, which will replace the current North Port location. Once complete in 2021, the new facility will include medical oncology, hematology, clinical research and next-generation PET/CT imaging technology along with 16 exam rooms and 45 chairs for chemotherapy and other infusions.

LAKE WORTH RIBBON CUTTING

The ribbon was cut officially opening our new location in Lake Worth in October. The clinic is an expansion that includes 9,000 more square feet, nine private exam rooms and 22 chemotherapy infusion chairs. Patients have access to all existing services and providers — all in a comfortable, spacious setting.

RX TO GO RIBBON CUTTING

Also in October, we celebrated the opening of our new 20,000-square-foot Rx To Go specialty pharmacy facility in Fort Myers. The new facility is an expansion and enhancement of a previous location and is equipped with updated technologies, such as digital screens and focus boards for metric testing, LED lighting through the entire building, a ductless VRF HVAC system and a full building generator.

WE WELCOME THE FOLLOWING PHYSICIANS

Kristen Gonter-Aubin, MD
Medical oncologist/hematologist in Englewood and Venice HealthPark

Shaachi Gupta, MD
Medical oncologist/hematologist in Lake Worth and West Palm Beach

Jennifer Muller, MD
Medical oncologist in Naples Napa Ridge

Swati Pathak, MD
Medical oncologist/hematologist in Davenport and Lake Wales

Ahsan Shah, MD
Medical oncologist in the Fort Myers Colonial office and Fort Myers Cancer Center

From Our Patients

★★★★★

ONLINE REVIEW: 5 STARS

In November 2019, I got the news that no one wants to get — cancer. I was diagnosed with Stage 3 tonsil cancer and liver cancer. Treating cancer takes a team of doctors, nurses, technicians and support staff at multiple locations. Over the past year, an important part of my team has been Dr. Rasha Beg at Florida Cancer Specialists in Oviedo. I am happy and proud to have Dr. Beg and her staff fighting for me. Throughout my treatment, they have kept me informed on what I was going to go through, what to expect the effects of my treatment to be and provided detailed explanations of the therapies and treatments I was to undergo. Their interactions with me were always done with compassion and understanding. As part of what I would call an 'A++ team,' Dr. Beg and her staff engaged with the rest of my treatment team, and each engagement was timely, comprehensive and resulted in clear understandings and issues resolution.

To Dr. Schroff, Rochelle, Dr. Z, Courtney, Kathie, Dana and to simply address the entire wonderful staff of Florida Cancer Specialists:

Thirty-two years ago, the love story of Dana and Doug began. It was a love story that many called a fairy tale. But as with every fairy tale, there was a "bad guy," "bad apple" or "big bad wolf" — ours came in the form of cancer. Once again, as with every fairy tale, we had a knight in shining armor, or in our case (after Dr. Z retired) some female knights (dames) who came to the rescue of Dana and Doug. We are so, so incredibly thankful to the "kingdom" of FCS for giving us 10 more years to live our fairy tale. Absolutely everyone from check-in to checkout on every visit was simply wonderful. You brought us comfort, help and hope.

All of you are true angels! After every visit, Doug always commented on how comfortable he felt at FCS. This is because of each of you! When my knight was happy, my fairy tale was coming true!

With much love and gratitude,
Dana Hopper and sons Drew and Dustin

Have something to add?

You can submit your feedback by emailing us at FCSCommunications@FLCancer.com

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I have always had great care from Dr. Raymond and her staff since 2007. When my port clotted and I had emergency surgery, everyone was great, attentive and compassionate. Dr. Raymond is the best. Thank you.

★★★★★

ONLINE REVIEW: 5 STARS

Incredible experience and guidance with total commitment to the patient. Dr. Steven Newman has been an incredible doctor for me.

★★★★★

ONLINE REVIEW: 5 STARS

Dr. Soori guided me through four months of chemo in the first quarter of 2020. His knowledge and experience, combined with an empathetic and caring approach, set me at ease throughout the experience. Dr. Soori easily deserves five stars. He is a Florida Cancer Specialist!

★★★★★

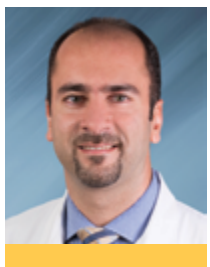
ONLINE REVIEW: 5 STARS

Dr. Sennabaum made me feel so comfortable and actually got a laugh out of me, which I hadn't been able to do for a while. Really like this doctor!

★★★★★

ONLINE REVIEW: 5 STARS

Dr. Barakat is the best! He is always prepared when I see him, and he stays abreast of concerns that I have as I work my way through the process of being declared cured. I got first-class care while I was undergoing treatment, and I am getting excellent follow-up during the "watch and wait" period. Highly recommend!



ONUREG® (azacitidine) tablets, for oral use Rx ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

ONUREG (azacitidine) is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

DOSAGE AND ADMINISTRATION

Important Administration Information

Do not substitute ONUREG for intravenous or subcutaneous azacitidine. The indications and dosing regimen for ONUREG differ from that of intravenous or subcutaneous azacitidine *[see Warnings and Precautions]*.

Recommended Dosage

The recommended dosage of ONUREG is 300 mg orally once daily with or without food on Days 1 through 14 of each 28-day cycle. Continue ONUREG until disease progression or unacceptable toxicity.

Administer an antiemetic 30 minutes prior to each dose of ONUREG for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.

If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on Day 1 of a cycle, do not administer ONUREG. Delay the start of the cycle until the ANC is 0.5 Gi/L or more.

Instruct patients on the following:

- Do not split, crush, or chew ONUREG tablets.
- Take a dose about the same time each day.
- If a dose of ONUREG is missed, or not taken at the usual time, take the dose as soon as possible on the same day, and resume the normal schedule the following day. Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day. Resume the normal schedule the following day.

ONUREG is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Monitoring and Dosage Modifications for Adverse Reactions

Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression.

The recommended dosage modifications for adverse reactions are provided in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Recommended Dosage Modification
Myelosuppression *[see Warnings and Precautions]*	Neutrophils less than 0.5 Gi/L on Cycle Day 1	• Interrupt treatment. Resume at the same dose once neutrophils return to 0.5 Gi/L or higher.
	Neutrophils less than 1 Gi/L with fever at anytime	First Occurrence • Interrupt treatment. Resume at the same dose once neutrophils return to 1 Gi/L or higher. Occurrence in 2 Consecutive Cycles • Interrupt treatment. After neutrophils return to 1 Gi/L or higher, resume at reduced dose of 200 mg. • If a patient continues to experience febrile neutropenia after dose reduction, reduce the treatment duration by 7 days. • If febrile neutropenia reoccurs after dose and schedule reduction, discontinue ONUREG.
	Platelets less than 50 Gi/L with bleeding	First Occurrence • Interrupt dose. Resume at the same dose once platelets return to 50 Gi/L or higher. Occurrence in 2 Consecutive Cycles • Interrupt dose. After platelets return to 50 Gi/L or higher, resume at reduced dose of 200 mg. • If a patient continues to experience thrombocytopenia with bleeding after dose reduction, reduce the treatment duration by 7 days. • If thrombocytopenia with bleeding reoccurs after dose and schedule reduction, discontinue ONUREG.
Gastrointestinal Toxicity *[see Adverse Reactions]*	Grade 3 or 4 Nausea or Vomiting	• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG (azacitidine).
	Grade 3 or 4 Diarrhea	• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.
Other Adverse Reactions *[see Adverse Reactions]*	Grade 3 or 4	• Interrupt dose and provide medical support. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity re-occurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.

CONTRAINDICATIONS

ONUREG is contraindicated in patients with known severe hypersensitivity to azacitidine or its components *[see Adverse Reactions and Description (11) in full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters *[see Clinical Pharmacology (12.3) in full Prescribing Information]*, the recommended dose and schedule for ONUREG are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG may result in a fatal adverse reaction. Treatment of patients using ONUREG at the doses recommended for intravenous or subcutaneous azacitidine may not be effective.

Do not substitute ONUREG for intravenous or subcutaneous azacitidine *[see Dosage and Administration]*.

Myelosuppression

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG, respectively. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia, respectively. Less than 1% of patients discontinued ONUREG due to either neutropenia or thrombocytopenia.

Monitor complete blood counts and modify the dosage as recommended *[see Dosage and Administration]*. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes

In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodysplastic syndromes were randomized to ONUREG or placebo. One-hundred and seven patients received a median of 5 cycles of ONUREG 300 mg daily for 21 days of a 28-day cycle. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in patients who received ONUREG compared with placebo. The most frequent fatal adverse reaction was sepsis. The safety and effectiveness of ONUREG for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG is not recommended outside of controlled trials.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant

rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis caused fetal death and anomalies.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG (azacitidine) and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions]*

Clinical Trials Experience

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

Acute Myeloid Leukemia

The safety of ONUREG was evaluated in QUAZAR *[see Clinical Studies (14) in full Prescribing Information]*. Patients received ONUREG 300 mg (N=236) or placebo (N=233) orally once daily on Days 1 through 14 of each 28-day cycle. Among patients who received ONUREG, 71% were exposed for 6 months or longer, and 49% were exposed for greater than one year. The median duration of exposure to ONUREG was 11.6 months (range: 0.5 to 74.3 months) and the median number of cycles was 12 (range; 1 to 82 cycles).

Serious adverse reactions occurred in 15% of patients who received ONUREG. Serious adverse reactions in ≥ 2% of patients who received ONUREG were pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG.

Permanent discontinuation of ONUREG due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ONUREG in > 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%). Interruptions of ONUREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required an interruption of ONUREG in > 5% of patients included neutropenia (20%), thrombocytopenia (8%), and nausea (6%).

Dose reductions of ONUREG due to an adverse reaction occurred in 14% of patients. Adverse reactions which required a dose reduction in > 1% of patients included neutropenia (6%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

The most common (≥ 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.

Table 2 summarizes the adverse reactions in QUAZAR.

Table 2: Adverse Reactions (≥ 5%) in Patients with AML Who Received ONUREG with a Difference Between Arms of > 2% Compared to Placebo in QUAZAR

Adverse Reaction	ONUREG (N=236)		Placebo (N=233)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	65	3	24	< 1
Vomiting	60	3	10	0
Diarrhea	50	5	21	1
Constipation	39	1	24	0
Abdominal pain[a]	22	2	13	< 1
General disorders and administration site conditions				
Fatigue/asthenia[b]	44	4	25	1
Infections				
Pneumonia[c]	27	9	17	5
Musculoskeletal and connective tissue disorders				
Arthralgia	14	1	10	< 1
Pain in extremity	11	< 1	5	0
Metabolism and nutrition disorders				
Decreased appetite	13	1	6	1
Blood and lymphatic disorders				
Febrile neutropenia	12	11	8	8
Nervous system disorders				
Dizziness	11	0	9	0

[a] Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain.

[b] Grouped term includes fatigue and asthenia.

[c] Broad scope term includes influenza, pneumonia, respiratory tract infection, respiratory tract infection viral, bronchopulmonary aspergillosis, lung infection, Staphylococcal infection, atypical pneumonia, lower respiratory tract infection, lung abscess, Pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia fungal, Pseudomonas infection, hemoptysis, productive cough, pleural effusion, atelectasis, pleuritic pain, rales, Enterobacter test positive, and Hemophilus test positive.

Clinically relevant adverse reactions that did not meet criteria for inclusion in Table 1 were weight decreased (4%) in patients who received ONUREG (azacitidine).

Neutropenia, thrombocytopenia, and anemia of any grade occurred in 74%, 65%, and 25% of patients treated with ONUREG. Table 3 summarizes select Grades 3 or 4 hematological laboratory abnormalities in QUAZAR.

Table 3: Selected Hematological Laboratory Abnormalities That Worsened from Baseline in Patients Who Received ONUREG in QUAZAR

Laboratory Abnormality	ONUREG		Placebo	
	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)
Neutropenia	223	109 (49)	217	50 (23)
Thrombocytopenia	222	46 (21)	212	22 (10)
Anemia	229	10 (4)	223	7 (3)

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of intravenous or subcutaneous azacitidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reaction
- Interstitial lung disease
- Tumor lysis syndrome
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]* and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. There are no available data on ONUREG use in pregnant women to evaluate for a drug-associated risk. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis *(see Data)*. Advise pregnant women of the potential risk to the fetus.

The estimated background 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

No reproductive or developmental toxicity studies have been conducted with oral azacitidine.

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of 6 mg/m^2 azacitidine (at doses less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis) on gestation Day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation Day 15 at doses of approximately 3 to 12 mg/m^2 (at doses less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis).

In rats, azacitidine was clearly embryotoxic when given an intraperitoneal injection on gestation Days 4 to 8 (postimplantation) at a dose of 6 mg/m^2 (at doses less than the recommended human daily dose on a mg/m^2 basis), although treatment in the preimplantation period (on gestation Days 1 to 3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single intraperitoneal dose of 3 to 12 mg/m^2 (at doses less than the recommended human daily dose on a mg/m^2 basis) given on gestation Days 9, 10, 11, or 12. In this study, azacitidine caused fetal death when administered at 3 to 12 mg/m^2 on gestation Days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation Day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

Lactation

Risk Summary

There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose.

Females and Males of Reproductive Potential

ONUREG can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting ONUREG.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ONUREG (azacitidine) and for at least 6 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose.

Infertility

Based on animal data, ONUREG may impair male or female fertility *[see Nonclinical Toxicology (13.1) in full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Of the 238 patients in QUAZAR who received ONUREG, 72% were 65 years of age or older, while 12% were 75 years of age or older. No overall differences in safety or effectiveness of ONUREG were observed between these patients and younger patients.

Renal Impairment

Monitor patients with severe renal impairment (creatinine clearance [CLcr] 15 to 29 mL/min calculated by Cockcroft-Gault formula) more frequently for adverse reactions and modify the ONUREG dosage for adverse reactions *[see Dosage and Administration]*.

No dose adjustment of ONUREG is recommended for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min) *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

ONUREG has not been studied in patients with pre-existing severe hepatic impairment (total bilirubin > 3 × ULN).

A recommended dosage of ONUREG has not been established for patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN).

No dose adjustment of ONUREG is recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

PATIENT COUNSELING INFORMATION

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

Myelosuppression

Advise patients of the risk of myelosuppression with ONUREG and of the need to monitor complete blood counts before and during treatment *[see Warnings and Precautions]*.

Gastrointestinal Toxicity

Advise patients of the risk of gastrointestinal toxicity with ONUREG (azacitidine) and of the potential need to use anti-emetic or anti-diarrheal medications during treatment *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose *[see Use in Specific Populations]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients to take ONUREG with or without food at about the same time each day and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to cut, split, crush, or chew the tablets *[see Dosage and Administration]*.

Storage Instructions

Advise patients to keep ONUREG in the original container. Advise patients to keep the container tightly closed with both desiccant canisters inside and to not eat the desiccant canisters *[see How Supplied/Storage and Handling (16) in full Prescribing Information]*.

REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

Manufactured by:
Celgene Corporation
A Wholly Owned Subsidiary of Bristol-Myers Squibb
86 Morris Avenue
Summit, NJ 07901

ONUPI.001 September 2020

ONU_HCP_BSv.001 09/2020

Bristol Myers Squibb™

ONUREG™ (azacitidine) tablets 300 mg • 200 mg

ORAL AML TREATMENT THAT DEMONSTRATED OVER 2 YEARS MEDIAN OVERALL SURVIVAL[1]*

THERE'S SOMETHING YOU DON'T SEE EVERY DAY

ONUREG® is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

THE FIRST AND ONLY FDA-APPROVED CONTINUED AML TREATMENT FOR PATIENTS IN FIRST REMISSION[1,2]

***QUAZAR® AML-001[1]**

The efficacy of ONUREG® was evaluated in QUAZAR® AML-001, a multicenter, randomized, double-blind, placebo-controlled, phase III study. Eligible patients were ages 55 years or older, had AML, and were within 4 months of achieving first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) with intensive induction chemotherapy. A total of 472 patients who completed induction with or without consolidation therapy were randomized 1:1 to receive ONUREG® 300 mg (n=238) or placebo (n=234) orally on Days 1 to 14 of each 28-day treatment cycle. Efficacy was established on the basis of overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to ONUREG® compared with placebo. In the trial, ONUREG® showed a median OS of 24.7 months (95% CI: 18.7, 30.5) vs 14.8 months (95% CI: 11.7, 17.6) for patients receiving placebo (HR 0.69 [95% CI: 0.55, 0.86; *P*=0.0009]).

AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ONUREG® is contraindicated in patients with known severe hypersensitivity to azacitidine or its components.

WARNINGS AND PRECAUTIONS

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters, the recommended dose and schedule for ONUREG® are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG® may result in a fatal adverse reaction. Treatment with ONUREG® at the doses recommended for intravenous or subcutaneous azacitidine may not be effective. Do not substitute ONUREG® for intravenous or subcutaneous azacitidine.

Myelosuppression

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG®. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia. Less than 1% of patients discontinued ONUREG® due to either neutropenia or thrombocytopenia. Monitor complete blood counts and modify the dosage as recommended. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes (MDS)

In AZA-MDS-003, 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to MDS were randomized to ONUREG® or placebo. 107 received a median of 5 cycles of ONUREG® 300 mg daily for 21 days of a 28-day cycle. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in the ONUREG® arm compared with placebo. The most frequent fatal adverse reaction was sepsis. Safety and effectiveness of ONUREG® for MDS have not been established. Treatment of MDS with ONUREG® is not recommended outside of controlled trials.

Embryo-Fetal Toxicity

ONUREG® can cause fetal harm when administered to a pregnant woman. Azacitidine caused fetal death and anomalies in pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG® and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG® and for at least 3 months after the last dose.

ADVERSE REACTIONS

Serious adverse reactions occurred in 15% of patients who received ONUREG®. Serious adverse reactions in ≥2% included pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG®.

Most common (≥10%) adverse reactions with ONUREG® vs placebo were nausea (65%, 24%), vomiting (60%, 10%), diarrhea (50%, 21%), fatigue/asthenia (44%, 25%), constipation (39%, 24%), pneumonia (27%, 17%), abdominal pain (22%, 13%), arthralgia (14%, 10%), decreased appetite (13%, 6%), febrile neutropenia (12%, 8%), dizziness (11%, 9%), pain in extremity (11%, 5%).

LACTATION

There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG® and for 1 week after the last dose.

Please see the Brief Summary of full Prescribing Information for ONUREG® on the following pages.

References: 1. ONUREG® [Prescribing Information]. Summit, NJ: Celgene Corporation; 2020. **2.** U.S. Food and Drug Administration approves Onureg® (azacitidine tablets), a new oral therapy, as continued treatment for adults in first remission with acute myeloid leukemia [press release]. Bristol Myers Squibb website. https://news.bms.com/press-release/corporatefinancial-news/us-food-and-drug-administration-approves-onureg-azacitidine-ta. Published September 1, 2020. Accessed September 1, 2020.

Bristol Myers Squibb™

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Learn more, sign up for updates, and find out how to access ONUREG® at
ONUREGpro.com/explore