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PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

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GASTROINTESTINAL CANCER: SPECIAL ISSUE

Clinical Trials Examining ctDNA-Guided Approaches to Treating Early Colon Cancer

INTERVIEW

Paolo Tarantino, MD, Spotlights Treatment Trends for Breast Cancer Awareness Month

PAOLA TARANTINO, MD

EXKIVITY® (mobocertinib)

The first and only oral therapy designed to target *EGFR* Exon20 insertion+ mNSCLC[1,2]

FOR PATIENTS WITH *EGFR* EXON20 INSERTION+ mNSCLC POST PLATINUM-BASED CHEMOTHERAPY[1]

INDICATION

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLONGATION and TORSADES DE POINTES

See full prescribing information for complete boxed warning.

- **EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation.**
- **Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc.**
- **Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation.**

EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction.

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EGFR Exon20 insertions are distinct targetable driver mutations —Use an FDA-approved NGS test to identify patients[3-5]

***EGFR* Exon20 insertions are the third most common type of *EGFR* driver mutation; different from exon 19 deletions and exon 21 L858R mutations, as well as from T790M point mutations[4,6]**

- **~10%** of all *EGFR* mutations are Exon20 insertions[7]
- About **2,000-4,000** new patients may present in the US every year[8]
- **~50%** of patients can be missed by relying on PCR testing*[5]

*PCR can only detect ≤5 out of 60+ *EGFR* Exon20 insertion variants. The variants detected by PCR are the most common, representing ~50% of cases.[5]

Discover EXKIVITY to see what may be possible for your patients post platinum-based chemotherapy:

EXKIVITY is the first and only oral therapy designed to target *EGFR* Exon20 insertion+ mNSCLC[1,2]

National Comprehensive Cancer Network® (NCCN®) recommends mobocertinib as a Category 2A second-line treatment option*†[9]

Use an FDA-approved NGS test to identify patients in your practice who may benefit from treatment with EXKIVITY[5]

*For eligible patients with mNSCLC.
†See the NCCN Guidelines for NSCLC for detailed recommendations, including other treatment options.[9]

EXPLORE THE STUDY RESULTS

VISIT EXKIVITYhcp.com

WARNINGS AND PRECAUTIONS

QTc Prolongation and Torsades de Pointes

EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250 patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs), 1.2% of patients had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with baseline QTc greater than 470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation.

Please see Important Safety Information and Brief Summary of full Prescribing Information, including Boxed Warning, on the following pages.

EXKIVITY®
mobocertinib
40 mg capsules

EXKIVITY®
mobocertinib
40 mg capsules

IMPORTANT SAFETY INFORMATION (CONT'D)

Interstitial Lung Disease (ILD)/Pneumonitis

EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population, ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.

Cardiac Toxicity

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population, heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%), and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY. Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity.

Diarrhea

EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population, diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days, but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY.

ADVERSE REACTIONS

The most common (>20%) adverse reactions are diarrhea (92%), rash (78%), stomatitis (46%), vomiting (40%), decreased appetite (39%), paronychia (39%), nausea (37%), musculoskeletal pain (34%), dry skin (32%), fatigue (29%), pruritus (24%), cough (24%) and decreased weight (21%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (15%), increased amylase (13%), increased lipase (10%), decreased potassium (5.3%), decreased red blood cells (3.5%), increased creatinine (2.7%), decreased magnesium (2.7%), and increased alanine aminotransferase (2.7%).

DRUG INTERACTIONS

CYP3A Inhibitors

Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations, which may increase the risk of adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs.

EXPLORE THE STUDY RESULTS

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CYP3A Inducers

Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations, which may reduce EXKIVITY anti-tumor activity. Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

CYP3A Substrates

Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of hormonal contraceptives with EXKIVITY. Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information.

Prolonged QTc Interval

EXKIVITY can cause QTc interval prolongation. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Females and Males of Reproductive Potential

EXKIVITY can cause fetal harm when administered to pregnant women. Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose. Based on animal studies EXKIVITY may impair fertility in males and females of reproductive potential.

Lactation

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

Geriatric

Of the 114 patients who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence rate of Grade 3 and 4 adverse reactions (69% vs 47%) and serious adverse reactions (64% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at **1-844-217-6468** or the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on the following pages.

References: 1. Exkivity. Prescribing information. Takeda Pharmaceuticals America, Inc; 2021. **2.** Zhou C et al. Published correction appears in 2022 Feb 24. *JAMA Oncol*. 2021;7(12):e214761. doi:10.1001/jamaoncol.2021.4761 **3.** Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4:5. doi:10.1038/s41392-019-00389 **4.** Wang F, Li C, Wu Q, Lu H. *Transl Cancer Res*. 2020;9(4):2982-2991. **5.** Bauml JM et al. Presented at: IASLC 2020 World Conference on Lung Cancer; January 28-31, 2021; Singapore. Oral presentation 3399. **6.** Arcila ME et al. *Mol Cancer Ther*. 2013;12(2):220-229. **7.** Remon J et al. *Cancer Treat Rev*. 2020;90:102105. doi:10.1016/j.ctrv.2020.102105 **8.** Oxnard GR et al. *J Thorac Oncol*. 2013;8(2):179-184. **9.** Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V3.2022.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
EXKIVITY® (MOBOCERTINIB)

These highlights do not include all the information needed to use EXKIVITY safely and effectively. See full prescribing information at EXKIVITYhcp.com

WARNING: QTc PROLONGATION and TORSADES DE POINTES

- **EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolyte correction at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation *[see Warnings and Precautions (5.1)]*.**
- **Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc *[see Warnings and Precautions (5.1), Drug Interactions (7.1, 7.3)]*.**
- **Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation *[see Dosage and Administration (2.3)]*.**

1 INDICATIONS AND USAGE

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*, whose disease has progressed on or after platinum-based chemotherapy.

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with locally advanced or metastatic NSCLC for treatment with EXKIVITY based on the presence of EGFR exon 20 insertion mutations *[see Clinical Studies (14)]*. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of EXKIVITY is 160 mg orally once daily until disease progression or unacceptable toxicity.

Take EXKIVITY with or without food *[see Clinical Pharmacology 12.3]*, at the same time each day. Swallow EXKIVITY capsules whole. Do not open, chew or dissolve the contents of the capsules.

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time.

If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

2.3 Dosage Modifications for Adverse Reactions

EXKIVITY dose reduction levels for adverse reactions are summarized in Table 1.

Table 1: Recommended EXKIVITY Dose Reductions

Dose Reductions	Dose Level
First dose reduction	120 mg once daily
Second dose reduction	80 mg once daily

Recommended dosage modifications of EXKIVITY for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions

Adverse Reaction	Severity*	EXKIVITY Dosage Modification
QTc Interval Prolongation and Torsades de Pointes *[see Warnings and Precautions (5.1)]*	Grade 2 (QTc interval 481-500 msec)	First Occurrence • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the same dose. Recurrence • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.
	Grade 3 (QTc interval ≥501 msec or QTc interval increase of >60 msec from baseline)	First Occurrence • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY. Recurrence • Permanently discontinue EXKIVITY.
	Grade 4 (Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	• Permanently discontinue EXKIVITY.
Interstitial Lung Disease (ILD)/pneumonitis *[see Warnings and Precautions (5.2)]*	Any grade	• Withhold EXKIVITY if ILD/pneumonitis is suspected. • Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.
Decreased Ejection Fraction or Heart Failure *[see Warnings and Precautions (5.3)]*	Grade 2 decreased ejection fraction	• Withhold EXKIVITY until ≤ Grade 1 or baseline. • If recovered to baseline within 2 weeks, resume EXKIVITY at the same dose or the next lower dose. • If not recovered to baseline within 2 weeks, permanently discontinue EXKIVITY.
	≥ Grade 2 heart failure or Grade 3 or 4 decreased ejection fraction	• Permanently discontinue EXKIVITY.
Diarrhea *[see Warnings and Precautions (5.4)]*	Intolerable or recurrent Grade 2 or Grade 3	• Withhold EXKIVITY until ≤ Grade 1. • Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	First Occurrence • Withhold EXKIVITY until ≤ Grade 1. • Resume EXKIVITY at the next lower dose. Recurrence • Permanently discontinue EXKIVITY.

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions (cont'd)

Adverse Reaction	Severity*	EXKIVITY Dosage Modification
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Intolerable or recurrent Grade 2 or Grade 3	• Withhold EXKIVITY until ≤ Grade 1. • Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	First Occurrence • Withhold EXKIVITY until ≤ Grade 1. • Resume EXKIVITY at the next lower dose if recovery occurs within 2 weeks. • Permanently discontinue EXKIVITY if recovery does not occur within 2 weeks. Recurrence • Permanently discontinue EXKIVITY.

ULN = upper limit of normal

* Graded per Common Terminology Criteria for Adverse Events Version 5.0.

2.4 Dosage Modifications for Moderate CYP3A Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors with EXKIVITY. If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce the EXKIVITY dose by approximately 50% (i.e., from 160 to 80 mg, 120 to 40 mg, or 80 to 40 mg) and monitor the QTc interval more frequently. After the moderate CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume EXKIVITY at the dose taken prior to initiating the moderate CYP3A inhibitor *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 QTc Prolongation and Torsades de Pointes

EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250 patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*, 1.2% of patients had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with a baseline QTc greater than 470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY *[see Drug Interactions (7.1)]*, which may further prolong the QTc *[see Drug Interactions (7.3)]*.

Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation *[see Dosage and Administration (2.3)]*.

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population *[see Adverse Reactions (6.1)]*, ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events.

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.3)]*.

5.3 Cardiac Toxicity

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population *[see Adverse Reactions (6.1)]*, heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes *[see Warnings and Precautions (5.1)]*. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first-degree atrioventricular block (0.4%), second-degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%) and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY.

Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity *[see Dosage and Administration (2.3)]*.

5.4 Diarrhea

EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population *[see Adverse Reactions (6.1)]*, diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake.

Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity *[see Dosage and Administration (2.3)]*.

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryolethality at maternal exposures 1.7 times the human exposure based on area under the curve (AUC) at the 160-mg once-daily clinical dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY *[see Drug Interactions (7.2)]* and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to EXKIVITY as a single agent at a dose of 160 mg orally once daily in 256 patients, including 114 patients with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC from Study AP32788-15-101, and patients with other solid tumors. Forty-eight percent (48%) were exposed for 6 months or longer and 12% were exposed for greater than one year. The most common (>20%) adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

EGFR Exon 20 Insertion Mutation-Positive Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC who received prior platinum-based chemotherapy *[see Clinical Studies (14)]*. Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment; significant, uncontrolled, active cardiovascular disease; or prolonged QTc interval were excluded from enrollment in this trial. A total of 114 patients received EXKIVITY 160 mg once daily until disease progression or unacceptable toxicity; 60% were exposed for 6 months or longer and 14% were exposed for greater than 1 year.

Serious adverse reactions occurred in 46% of patients who received EXKIVITY. Serious adverse reactions in ≥2% of patients included diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. Fatal adverse reactions occurred in 1.8% of patients who received EXKIVITY, including cardiac failure (0.9%), and pneumonitis (0.9%).

Permanent discontinuation occurred in 17% of patients who received EXKIVITY. Adverse reactions requiring permanent discontinuation of EXKIVITY in at least ≥2% of patients were diarrhea and nausea.

Dosage interruptions of EXKIVITY due to an adverse reaction occurred in 51% of patients. Adverse reactions which required dosage interruption in >5% of patients included diarrhea, nausea and vomiting.

Dose reductions of EXKIVITY due to an adverse reaction occurred in 25% of patients. The adverse reaction requiring dose reduction in >5% of patients was diarrhea.

Table 3 summarizes the adverse reactions in Study AP32788-15-101.

Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation-Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

Adverse Reaction	EXKIVITY (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal Disorders		
Diarrhea	92	22
Stomatitis[a]	46	4.4**
Vomiting	40	2.6**
Decreased appetite	39	0.9**
Nausea	37	4.4**
Decreased weight	21	0
Abdominal pain[b]	18	1.8**
Gastroesophageal reflux disease	15	0
Dyspepsia	11	0
Skin and Subcutaneous Tissue Disorders		
Rash[c]	78	1.8**
Paronychia[d]	39	0.9**
Dry skin	32	0
Pruritus	24	0.9**
Alopecia	19	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[e]	34	2.6**
General Disorders and Administration Site Conditions		
Fatigue[f]	29	3.5**
Respiratory, Thoracic and Mediastinal Disorders		
Cough[g]	24	0
Upper respiratory tract infection[h]	16	0
Dyspnea[i]	15	4.4
Rhinorrhea	13	0
Eye Disorders		
Ocular Toxicity[j]	11	0
Cardiac Disorders		
QTc interval prolongation[k]	10	3.5
Hypertension[l]	10	4.4**
Nervous System Disorders		
Headache	10	0

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5).

** Events of Grade 3 only (no Grade 4 occurred).

a. Stomatitis includes angular cheilitis, aphthous ulcer, cheilitis, mouth ulceration, mucosal inflammation, odynophagia, and stomatitis.

b. Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

c. Rash includes acne, dermatitis, dermatitis acneiform, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and urticaria.

d. Paronychia includes nail bed tenderness, nail disorder, nail infection, onycholysis, and paronychia.

e. Musculoskeletal pain includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.

f. Fatigue includes asthenia, and fatigue.

g. Cough includes cough, productive cough, and upper-airway cough syndrome.

h. Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.

i. Dyspnea includes dyspnea and dyspnea exertional.

j. Ocular toxicity includes dry eye, eye pruritis, abnormal sensation in eye, eye discharge, blepharitis, trichiasis, conjunctival hemorrhage, vitreous floaters, blurred vision and corneal edema.

k. QTc interval prolongation includes electrocardiogram QT prolonged and ventricular arrhythmia.

l. Hypertension includes blood pressure increase and hypertension.

Clinically relevant adverse reactions in <10% of patients receiving EXKIVITY included edema (9%), acute kidney injury (8%), peripheral neuropathy (7%), palmar-plantar erythrodysaesthesia (4.4%), pneumonitis (2.6%) and cardiac failure (2.6%).

Table 4 summarizes the laboratory abnormalities in Study AP32788-15-101.

Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with EGFR Exon 20 Insertion Mutation-Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

Laboratory Abnormality	EXKIVITY** (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Hematology		
Decreased red blood cells	59	3.5
Decreased lymphocytes	52	15
Decreased platelets	26	0.9
Decreased leukocytes	25	0
Chemistry		
Increased creatinine	52	2.7
Increased amylase	40	13
Increased lipase	35	10
Decreased potassium	29	5.3
Increased alkaline phosphatase	25	1.8
Decreased albumin	23	1.8
Decreased magnesium	23	2.7
Increased alanine aminotransferase	22	2.7
Increased aspartate aminotransferase	21	1.8
Decreased sodium	20	0.9

* Grades per NCI CTCAE v5.0.

** The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from baseline.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on EXKIVITY

Strong or Moderate CYP3A Inhibitors	
Clinical Impact	• Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions, including QTc interval prolongation.
Prevention or Management	• Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*.
Strong or Moderate CYP3A Inducers	
Clinical Impact	• Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce EXKIVITY anti-tumor activity.
Prevention or Management	• Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

7.2 Effect of EXKIVITY on Other Drugs

CYP3A Substrates	
Clinical Impact	• Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates.
Prevention or Management	• Avoid concomitant use of hormonal contraceptives with EXKIVITY *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3)]*. • Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information.

7.3 Drugs that Prolong the QTc Interval

Drugs that Prolong the QTc Interval	
Clinical Impact	• EXKIVITY can cause QTc interval prolongation *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)]*. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)]*.
Prevention or Management	• Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryolethality (embryo-fetal death) and maternal toxicity at plasma exposures approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose (*see Data*). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In an embryo-fetal development study, once-daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose). Adverse effects on embryo-fetal development at this dose level included embryolethality due to post-implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high-dose level (10 mg/kg).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

EXKIVITY can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

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

Infertility

Based on animal studies, EXKIVITY may impair fertility in males and females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 114 patients *[see Clinical Studies (14)]* who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (69% vs 47%) and serious adverse reactions (64% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

8.6 Renal Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m^2 by Modification of Diet in Renal Disease [MDRD] equation). The recommended dosage of EXKIVITY has not been established for patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin ≥1.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

17 PATIENT COUNSELING INFORMATION

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

QTc Interval Prolongation and Torsades de Pointes

Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain *[see Warnings and Precautions (5.2)]*.

Cardiac Toxicity

Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope *[see Warnings and Precautions (5.3)]*.

Diarrhea

Inform patients that EXKIVITY may cause diarrhea, which may be severe in some cases and should be treated promptly. Advise patients to have antidiarrheal medicine readily available and promptly start antidiarrheal treatment (e.g., loperamide), increase oral fluids and electrolyte intake, and contact their healthcare provider if diarrhea occurs *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females and males of reproductive potential that EXKIVITY may impair fertility *[see Use in Specific Populations (8.3)]*.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

Missed Dose

Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day *[see Dosage and Administration (2.2)]*.

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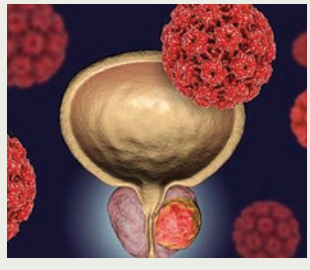

VIDEO

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PODCAST

Oncology Peer Review On-The-Go: Cancer-Related Fatigue Outcome Measures in Integrative Oncology

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BEHIND THE BEST HOSPITALS FOR CANCER

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Medical World News™

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BEHIND THE BEST HOSPITALS FOR CANCER

Recently, US News and World Report released its annual rankings on "Best Hospitals for Cancer." Among the top centers were the Hospitals of the University of Pennsylvania and the Siteman Cancer Center at Barnes-Jewish Hospital. CancerNetwork® editors sat down with Robert H. Vonderheide, MD, DPhil, director of the Abramson Cancer Center at the University of Pennsylvania in Philadelphia, and Timothy Eberlein, MD, director of the Alvin J. Siteman Cancer Center in St Louis, Missouri, about what makes their centers stand out from the rest.

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PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

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Howard S. Hochster, MD
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You Can Help Set New Paradigms Involving ctDNA

Welcome to a special issue of *ONCOLOGY®* focusing on exciting trials that may set future standards for adjuvant therapy in colon cancer. We are very pleased to highlight these trials, particularly the recently opened phase 2/3 CIRCULATE-US trial (NCT05174169).

What is circulating tumor DNA (ctDNA)? DNA is released into the blood stream by all dying cells, including tumor cells. With advances in DNA amplification and sequencing, it is now possible to identify cell-free DNA, which derives from cancer cells rather than normal cells. Ideally, such a test would be 100% positive in colon cancer preoperatively and would be negative if the tumor was completely resected with no other tumor cells left in the body. If we had a diagnostic test with 100% accuracy, we would be able to treat every patient with microscopic residual disease and avoid treating those who could be cured with surgery alone. In stage III colon cancer, for example, on average we could identify the 35 out of 100 patients destined to recur after "curative" surgery for adjuvant therapy and avoid treating the other 65 patients who actually were cured with surgery.

Some of the preliminary data on the various ctDNA tests look very promising in prospective cohort trials involving patients treated according to standard of care regimens. For example, results of the 1500-patient GALAXY-Japan study (jRCT1031200006), presented at the Gastrointestinal Cancers Symposium in January 2022, showed a highly predictive value for positive ctDNA in risk of relapse and benefit of chemotherapy. The results also suggested no benefit for adjuvant chemotherapy in patients with negative ctDNA. However, such data are contaminated by stage-based treatment and bias in treatment selection. We therefore need prospective randomized trials.

In this issue of *ONCOLOGY®*, leaders of these key prospective trials and experts in the area of ctDNA further explain the trials and their goals. For our American readers, I would direct your attention to the National Cancer Institute–sponsored COBRA trial (NCT04068103) for patients with stage IIA disease and the CIRCULATE-US trial for patients with stage II or stage III disease. These are the best opportunities to use this technology for your patients with colon cancer who are eligible for adjuvant treatment. These trials, which will study the outcome of ctDNA-directed treatment with appropriate controls, are needed to demonstrate that by using guidance of ctDNA results, we can do better than our current approach of treating only patients with high-risk pathologic stage II and all pathologic stage III colon cancer with adjuvant chemotherapy.

We need your help and the help of your patients to make this advance in treatment a reality; these are large, randomized trials. Your participation, and that of your colleagues, can help bring this technology into the guidelines and standard of care in the quickest time frame possible.

Please enjoy these state-of-the-art articles and see the Clinical Trials in Progress section for a quick reference guide (*see pages 608-609*). We hope this issue will aide your participation in these trials. I would like to express my heartfelt thanks to all the authors of articles in this issue of *ONCOLOGY®* and also my coeditor for this special edition, **Thomas J. George Jr, MD, FACP.** ■

ISSUE COEDITOR

Thomas J. George Jr, MD, FACP
University of Florida
Gastrointestinal Cancer Committee, NRG Oncology

MEET OUR EXPERT

Paolo Tarantino, MD is a clinical research fellow at Dana-Farber Cancer Institute in Boston, Massachusetts, and an investigator at the European Institute of Oncology in Milan, Italy.

Paolo Tarantino, MD, Spotlights Treatment Trends for Breast Cancer Awareness Month

"The care of patients with breast cancer and most other cancers is like an orchestra. Each physician is part of an orchestra and is needed for...the appropriate treatment for each tumor."

Antibody-drug conjugates (ADCs) have been at the forefront of care for patients with breast cancer in recent years. Recently, the ADC fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) was approved for patients with HER2-positive breast cancer and patients with HER2-low breast cancer.[1,2]

In an interview with *ONCOLOGY*® ahead of Breast Cancer Awareness Month, **Paolo Tarantino, MD**, talked about the importance of multidisciplinary care for patients with breast cancer, the most exciting data presented this year in the HER2-positive and HER2-low space, where future research should be focused to improve treatment and patient care, and the possibility of using T-DXd in the HER-negative setting.

Q: What is your role as part of a multidisciplinary care team?

TARANTINO: Oncology has evolved over time and has become more of a multidisciplinary practice, especially in breast cancer. It's impossible to treat a patient with either early-stage or advanced-stage breast cancer without the involvement of a large multidisciplinary team, which in most cases includes medical oncologists, surgeons, radiation oncologists, geneticists, pulmonologists, and cardiologists among many others. The care of patients with breast cancer and most other cancers is like an orchestra. Each physician is part of an orchestra and is needed for the final symphony, the final treatment, the appropriate treatment for each tumor.

Q: What has been the biggest breakthrough in the management of breast cancer within the past year?

TARANTINO: At the [2022 American Society of Clinical Oncology Annual Meeting] during the plenary presentation of the DESTINY-Breast04 trial [NCT03734029],[3] there was this impressive standing ovation. It was an emotional moment. This was related to the fact that something unprecedented [was shared] during that presentation. [We told the audience that we had] observed the benefit of anti-HER2 drugs for the first time expanding from HER2-positive breast cancer, which accounts for [approximately] 20% of all patients with breast cancer, toward what we now call HER2-low breast cancer, which is an additional 50% or 60% of all patients with breast cancer.

This ADC, T-DXd, which delivers a highly potent chemotherapy payload in a targeted way, has shown to be much more effective than standard traditional chemotherapy for patients with metastatic breast cancer and low HER2 expression. This was unprecedented because it not only showed a benefit to progression-free but also overall survival, which is something we don't see every day in metastatic breast cancer. That standing ovation was the highlight of this

year. At the same time, ADCs are reshaping the way we [manage] breast cancer because they're bringing chemotherapy, which we've developed in the past 50 to 60 years, to a new age. [This is] a targeted delivery of chemotherapy that is more effective and can avoid some [adverse] effects. In general, ADCs are the drug of the year and DESTINY-Breast04 is the highlight of 2022.

Q: What are some barriers to optimal care in patients with breast cancer that need to be overcome in the near future?

TARANTINO: As an Italian physician who has moved to the United States, I've experienced the striking disparity in access to drugs among countries. In the US, it is easier to get access to some new drugs as compared with Europe, and particularly Italy where I was practicing before. Nonetheless, there is a wide disparity in the access to many drugs. This is an important barrier to optimal care because sometimes there is a highly effective treatment but you cannot always use it the way you would want. This is where we need to work hard to ensure access to highly effective drugs for all the patients who might benefit.

A second important aspect is that we still are working on the right sizing of treatments. This is true in the metastatic setting, but even more for the [management] of early breast cancer. I'm lucky to work at Dana-Farber Cancer Institute] with Sara M. Tolaney, MD, MPH, who has worked a lot in this field and has developed de-escalated regimens that allow us to treat patients with fewer toxicities, but with the same efficacy of treatments. We still need to work hard on this because still many patients are overtreated. We are developing promising tools that may allow us to achieve right-sized treatments, including circulating tumor DNA, gene signatures, and other biomarkers that can help us understand which patients need more and which patients need less. In the end, the aim is treating and curing patients with cancer with the least possible amount of adverse effects. This is one important barrier right now because we don't have the tools or the biomarkers readily available. We are still developing them, but I think we are getting there.

Q: Which ongoing clinical trials are you most excited to see the results of?

TARANTINO: Usually we start developing drugs in the pretreated metastatic setting, then we slowly bring them into the earlier-line settings, and finally into the curable setting. This is what is happening now and we are [seeing] the benefit of ADCs in early-line settings. We have seen it already with T-DM1 [ado-trastuzumab emtansine; Kadcyla], which is the first ADC to be approved for breast cancer. When it was brought in the early setting, it is shown to be able to improve cure rates in the KATHERINE trial [NCT01772472].[4]

Now there are some trials that are doing the same with novel ADCs. For T-DXd, there is the DESTINY-Breast05 trial [NCT04622319] that is comparing T-DXd with T-DM1 in the adjuvant setting to see if we can further improve cure rates for the HER2-positive disease. Sacituzumab govitecan [Trodelvy] is an anti-TROP2 ADC that is being tested in the SASCIA trial [NCT04595565] in the same setting to try to improve cure rates. In the neoadjuvant setting, there is the NeoSTAR trial [NCT04230109]. In general, there are several trials in the neoadjuvant or adjuvant setting that aim to expand the benefits of ADCs to the early setting. Some of these trials could bring important benefits, but for these we will need to wait a few more years.

A trial we might hear about sooner is the DESTINY-Breast06 trial [NCT04494425], which is testing T-DXd both in patients with HER2-low as well as HER2 0 [immunohistochemistry 0] breast cancer. It's a provocative idea; notably this drug has already shown some early activity in patients with HER2 0 disease, thus T-DXd might work in this category and expand its benefit to a much larger population of patients. This is one of those trials that could further change the way we categorize breast cancer beyond the recent evolutions.

Q: What do we have to look forward to in the breast cancer space?

TARANTINO: Drug development is going fast, and it's going well; we're developing highly efficacious drugs. Now we are understanding how to master their use. In general, there's a lot of optimism regarding several new drugs, some of which have been recently approved and some of which may be approved in the coming months and years. The second point is [regarding] biomarkers. We cannot use the same drugs for all patients, we need to tailor our treatments. We need to dedicate extensive efforts not only to drug development but also to identifying biomarkers that tell us up front which patients require an intensified treatment and who might instead be treated with less. [We also need to know] which patients might derive benefit from a specific drugs. For instance, we use a TROP-2 ADC but we don't assess for TROP-2 expression, although we have some data suggesting there might be increasing benefit [to this therapy] with increased target expression. We need to work on developing biomarkers to tailor treatments in clinical practice. We can be optimistic because we have been developing highly efficacious drugs. In the coming years, we'll better manage breast cancer with increased precision. ■

For references visit
cancernetwork.com/Tarantino_10.22

In adult and pediatric patients 12 years and older

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

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

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

REACH3 Primary Endpoint: ORR at Week 24

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

ORR through Week 24

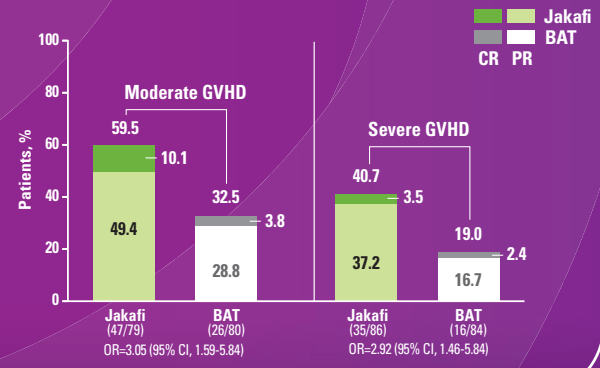
70% (116/165) with Jakafi vs 57% (94/164) with BAT[4‡]

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

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

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

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



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

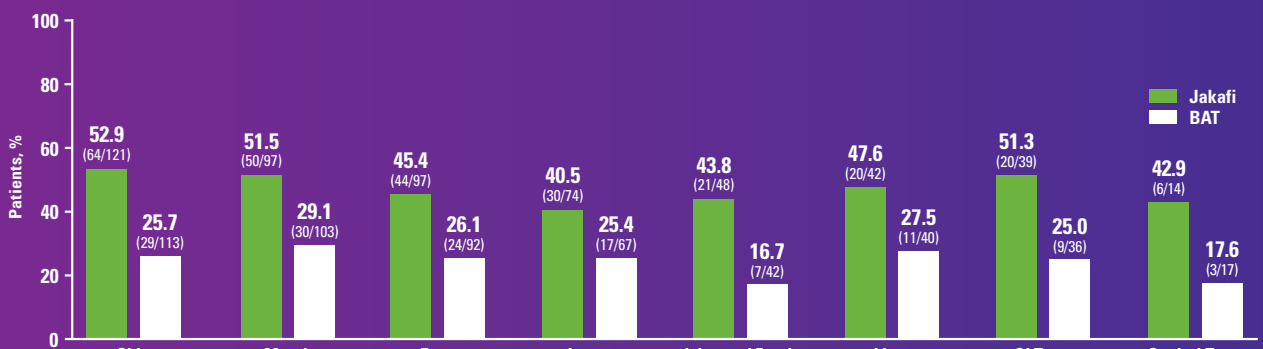
IMPORTANT SAFETY INFORMATION

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

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

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

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



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

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

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

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

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

Intervene with Jakafi in your appropriate patients with cGVHD.

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

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

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

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

Incyte

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

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

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

CONTRAINDICATIONS None.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinically relevant laboratory abnormalities are shown in Table 4.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinically relevant laboratory abnormalities are shown in Table 8.

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

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

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

DRUG INTERACTIONS Fluconazole Concomitant use of Jakafi with fluconazole increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Avoid concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily. Reduce the Jakafi dosage when used concomitantly with fluconazole doses of less than or equal to 200 mg *[see Dosage and Administration (2.5) in Full Prescribing Information]*. **Strong CYP3A4 Inhibitors** Concomitant use of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Reduce the Jakafi dosage when used concomitantly with strong CYP3A4 inhibitors except in patients with aGVHD or cGVHD *[see Dosage and Administration (2.5) in Full Prescribing Information]*. **Strong CYP3A4 Inducers** Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may reduce efficacy of Jakafi. Monitor patients frequently and adjust the Jakafi dose based on safety and efficacy *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

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

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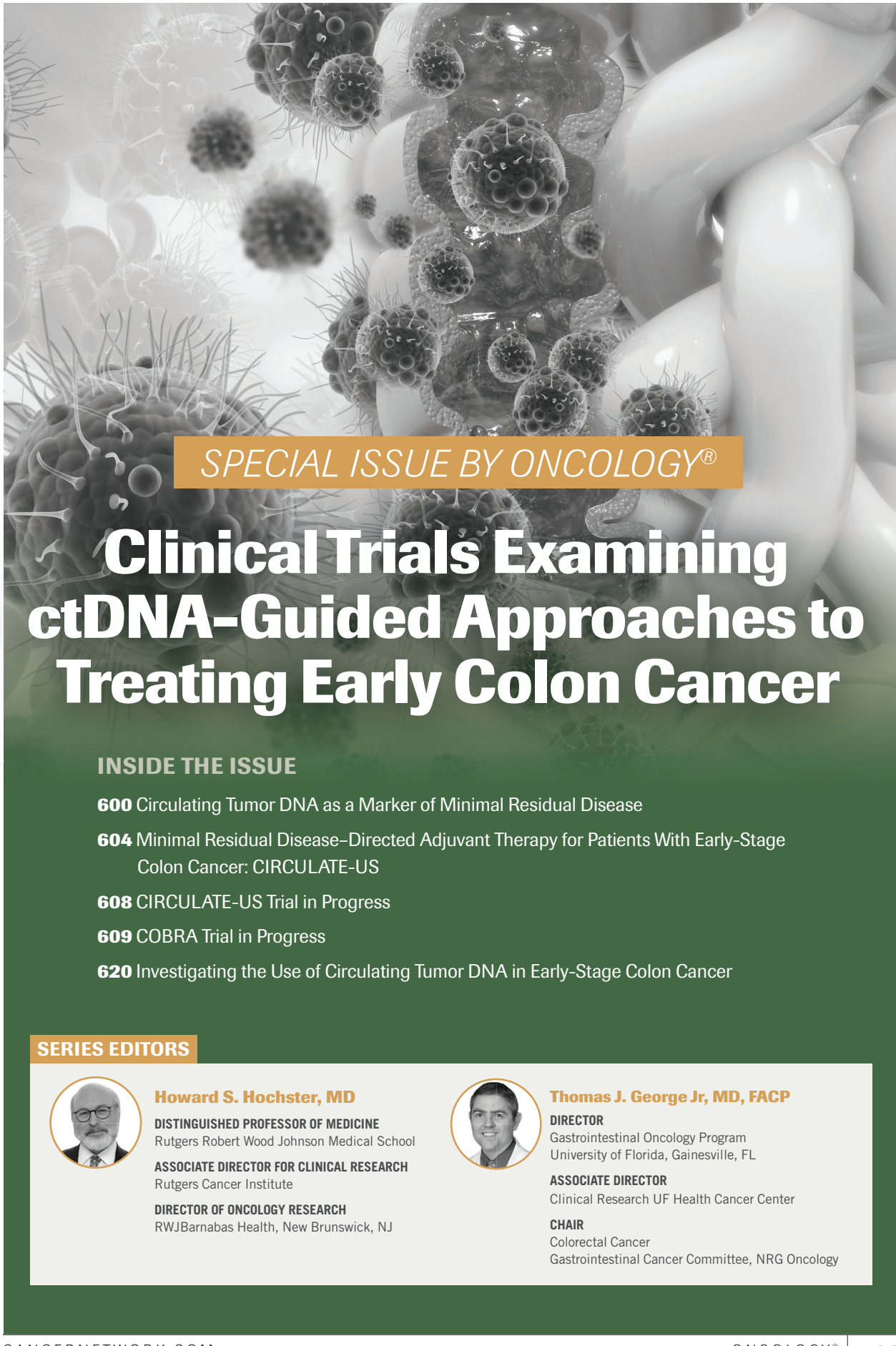

SPECIAL ISSUE BY ONCOLOGY®

Clinical Trials Examining ctDNA-Guided Approaches to Treating Early Colon Cancer

INSIDE THE ISSUE

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Circulating Tumor DNA as a Marker of Minimal Residual Disease

Ben Fangman, MD[1]; Kanwal Raghav, MD[1]; and Scott Kopetz, MD, PhD[1]

Colorectal cancer (CRC) remains the third most common cancer and second most common cause of cancer death in the United States.[1] Traditionally, treatment and prognostication have been based on American Joint Committee on Cancer tumor–node-metastasis staging, relying on the extent of radiographically evident disease; locoregional disease is treated primarily with surgery, with or without adjuvant chemotherapy, and metastatic disease is primarily treated with systemic therapy. The clinical decision regarding use of adjuvant therapy has been based on lymph node status and other clinic pathological risk factors (eg grade or presence of obstruction or perforation).[2] However, this risk stratification is incomplete. With increasingly widespread availability of genomic sequencing methods and subsequent greater sensitivity in detecting microscopic disease in peripheral blood, significant research has been focused on utilizing this capability to improve outcomes in CRC, particularly after curative resection.

A term initially coined in the context of hematologic malignancies after induction therapy, molecular residual disease (MRD)—sometimes also referred to as "minimal residual disease "in solid tumors—is defined as molecular evidence of disease detected via cell-free circulating tumor DNA (ctDNA) or another tumor-derived moiety, in the absence of radiographically evident disease.[3,4] ctDNA is shed from either a primary tumor or metastatic site via secretion, apoptosis, or necrosis into the bloodstream, where it can subsequently be collected by venous sampling.[5] ctDNA has been widely studied for MRD detection in CRC to aid in clinical decision-making.[3,5-9]

The ability to use ctDNA to identify patients with MRD has important clinical relevance in CRC for several reasons. First, it identifies those who have micrometastatic disease and are therefore at highest risk for relapse after curative-intent therapy.[10,11] Second, ctDNA shares the same somatic and epigenetic variants of the tumor from which it was shed, thus providing dynamic information regarding acquired resistance to therapy.[12] Lastly, given that ctDNA allows for higher sensitivity of disease detection, it provides the ability to tailor systemic therapy to a greater degree than do standard imaging modalities. In patients without radiographic evidence of disease, MRD detection allows for earlier intervention, potentially when minimal disease, without a substantial tumor protective microenvironment, may still be curable; this is thereby an extension of a risk-stratified adjuvant approach. In patients with known metastatic disease who are undergoing systemic therapy with palliative intent, MRD may be used as a guide for treatment deescalation or treatment holidays, sparing patients from cumulative therapy-related toxicities.

The utilization of ctDNA in the management of patients with CRC has evolved over time. Advancements in methods of polymerase chain reaction (PCR) and genome-wide sequencing have improved sensitivity of detection, and standardization of practices has allowed for widespread access to genomic profiling capabilities. A key challenge that continues to impede the broad clinical applicability of ctDNA in clinical practice, particularly in the MRD setting, is related to false negative results. This is influenced by a variety of factors, most notably low levels of circulating ctDNA; these low levels can occur because of either low tumor burden or, in some cases, decreased shedding of ctDNA, as is seen in peritoneal disease.[13]

Today, multiple different assays are used clinically, each with differing methodology. There are 2 broad categories of platforms, tumor-informed and tumor-uninformed, each with unique roles, advantages, and disadvantages, as we outline below.

Tumor-Informed Assays

Tumor-informed assays involve sequencing the patient's tumor specimen, utilizing either biopsy or resection sample, to create a tumor-specific signature of detectable unique aberrations such as single nucleotide variants, short indels, chromosomal breakpoints, and others. Depending on the platform, multiple strategies exist for initial profiling, but they are largely based either on next-generation sequencing (NGS) through whole exome sequencing or whole-genome sequencing (WGS) of the surgical tumor specimen. Once the unique alterations have been identified, PCR-based or personalized NGS panels are typically utilized for serial monitoring of ctDNA. If ctDNA harbors a detectable quantity of the same mutations as the tumor-informed probe, the sample is said to be MRD positive.[14] Assays differ in the threshold of number and quantity of ctDNA alterations required to be considered MRD positivity, which impacts the specificity and sensitivity of the resulting assay. The focus on the previously identified alterations in the tumor allows increased depth of coverage of the alterations of interest, which makes these assays more sensitive. Additionally, by using a tumor-informed probe, this approach increases specificity by reducing the impact of sequencing errors or naturally occurring clonal populations not derived from the tumor of interest, such as clonal hematopoiesis of indeterminant potential from white blood cells.

Although a thorough description of available assays is not within the scope of this review, we will describe several of the more commonly utilized assays to provide a perspective on the methodologic differences. There are not yet robust comparisons of the performance of these techniques, although such studies are planned.

The Signatera assay was the first to offer MRD testing commercially, and it is currently the most utilized clinical assay. After whole exome or large targeted panel sequencing, 16 unique alterations are identified and multiplex PCR primer pairs are generated to probe for the identified alterations.[14] The test results are either negative or positive for MRD, based upon whether 2 or more of the alterations are present within the circulating plasma; if the results are positive, quantification of the level of detected ctDNA is provided. The RaDaR assay expands the panel to 48 tumor-informed alterations for amplicon-based sequencing.[15]

SafeSeqS (and the newer methodologic variant, SaferSeqS) is a PCR-based approach that utilizes double-stranded molecular barcoding and hemi-nested PCR for duplex sequencing. This decreases the sequencing error rate and detects mutations at frequencies of 10^{-5} as well.[16] Asaf Zviran, PhD, MSc, and colleagues, created a machine-learning integrated WGS approach using a tumor-informed prior which increased the sensitivity for single nucleotide variations (SNVs) and copy number alterations (CNAs) down to approximately 10^{-5} in the setting of low tumor burden. One notable limitation to this approach is limited ability to confidently identify driver mutations, which would decrease the sensitivity for mutational profiling for treatment decisions. Thus, the utility of this approach in CRC is largely confined to the MRD detection setting.[17]

Targeted error correction sequencing (TEC-Seq) and Cancer Personalization Profiling by Deep Sequencing (CAPP-Seq) are hybrid capture–based NGS methods that target multiple regions of the genome known to be associated with driver mutations in a variety of malignancies. These are subsequently deep sequenced. With this approach, the sensitivity of detection of SNV, indels, CNAs, and fusions is greatly increased.[18] Phased variant enrichment and detection sequencing (PhasED-Seq) is another approach that utilizes WGS and has reported the lowest limits of detection of a plasma-based approach at 10^{-6}.[19]

As a group, tumor-informed assays have important limitations. First, there is an approximate 4-week turnaround time for construction of the tumor-specific probe. However, once the tumor-informed probe is created, the initial and subsequent plasma testing can be completed with rapid turnaround time, typically on the order of 1 to 2 weeks. Second, the creation of tumor-specific probes relies on adequate tissue for genomic sampling, which may not always be available. Currently, the theoretical performance benefit of tumor-informed testing justifies this longer testing timeframe, but this will be a key consideration as clinical experience with tumor-agnostic assays accumulates.

Tumor-Uninformed Assays

Tumor-uninformed assays are plasma-based approaches that do not need to sequence the primary tumor. These assays largely use targeted NGS-based approaches, and each has specific features to improve sensitivity and specificity. We outline the general approaches to these assays below.

To improve its sensitivity, the Reveal assay (Guardant) leverages a fixed gene panel of known CRC-specific mutations with the fact that CRC commonly has aberrant methylated DNA, particularly at C5 positions on cytosine. Aparna Parikh, MD, and colleagues demonstrated a sensitivity of 55% with a single data point, which was improved with serial monitoring to 91%; its specificity was 100% in predicting recurrence after definitive therapy with this approach.[9] Collections of larger prospective data sets are underway.

Other methylation-specific strategies, such as the evaluation of the methylation of *WIF1* and *NPY*, genes commonly hypermethylated in CRC, have been attempted, with evidence of prognostic effect in CRC cohorts.[20] Although this approach benefits from low cost and

simplicity of implementation, neither the sensitivity nor specificity of these assays is as exemplary as those of NGS-based assays.

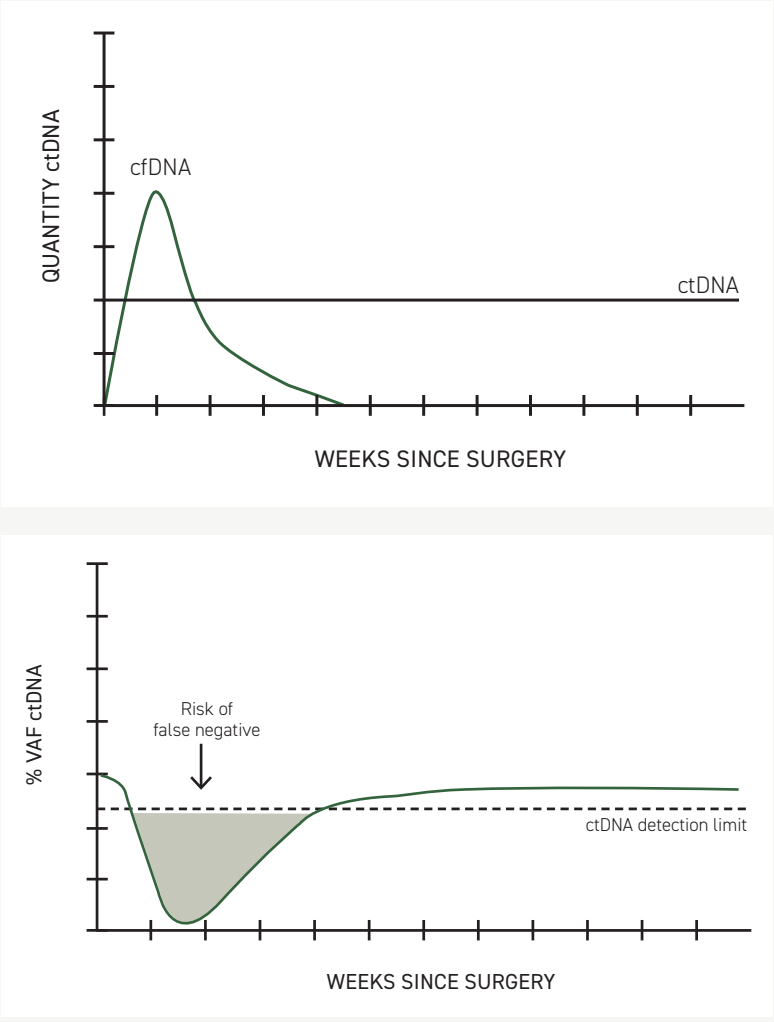
The advantages of tumor-uninformed approaches include quicker turnaround time, lower costs, and lack of need to rely on tissue and biopsy integrity. An added benefit of these approaches is detecting epigenetic information, which tumor-informed or plasma-based genomic panels cannot do.[21]

Assay Performance and Preanalytical Considerations

For the applications envisioned with MRD testing, both high sensitivity and specificity are required. High sensitivity is especially critical for deescalation strategies in which patients may be offered less intense therapy than would otherwise be considered, such as shorter duration or delayed adjuvant therapy, or nonoperative management. In contrast, high specificity is required particularly in studies where escalation would be considered, especially when the escalation is to experimental therapy with less well-defined toxicity. Many of the ongoing trials of novel therapeutics, including unapproved agents and cellular therapies, are possible because of the high specificity of the assays, which reduces the risk of treating patients on the basis of false positives when in fact no MRD is present. Several variables (too numerous to examine in depth in this review) impact the performance of these assays. The need to integrate these outcomes into clinical management mandates their timely turnaround, which represents another variable in consideration of the optimal assay.

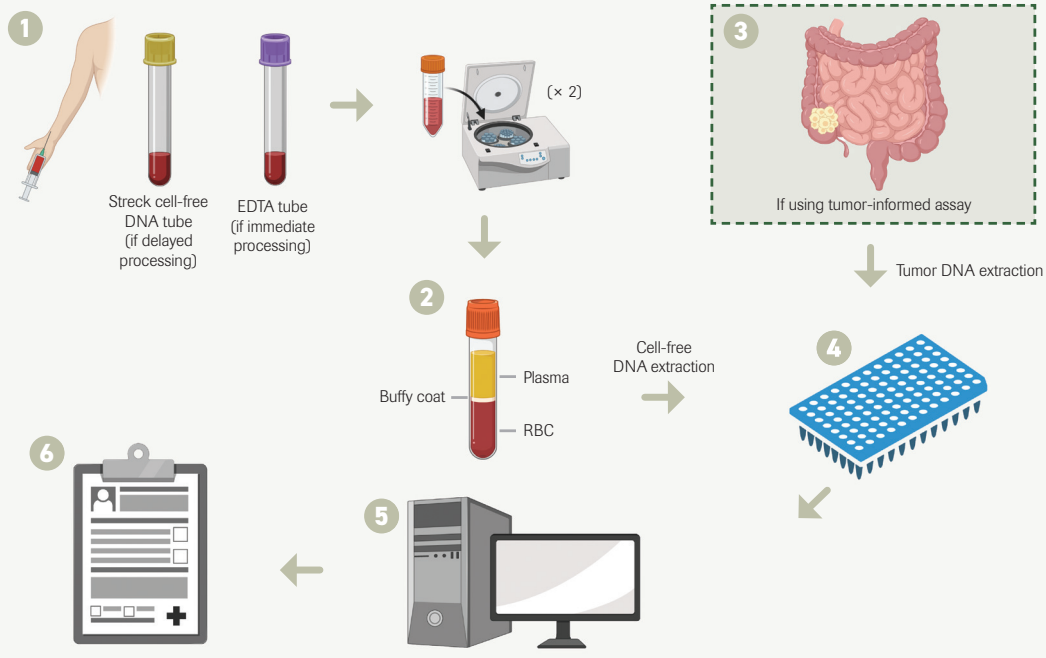
The effective utilization of ctDNA for MRD detection begins with the optimal timing of sample collection, storage, and processing. Ideally, samples should be collected at least 2 weeks postoperatively (**Figure 1**) to allow for the large levels of host cell-free DNA (cfDNA) that may be seen postoperatively to decrease, as increased levels can negatively impact sample sensitivity via ctDNA dilution.[22] **Figure 2** illustrates the optimal process of collecting ctDNA. Samples should be collected in either K2 ethylenediaminetetraacetic blood collection tubes, if white cells are to be able to be separated from plasma within 1 to 2 hours, or Streck cell-free DNA tubes, in which plasma can be stored for days without significant ctDNA degradation.[13] Two sequential centrifugations to isolate plasma are recommended to further reduce the level of germline DNA contamination. Although serum was utilized in earlier studies, it is not recommended for current methodologies because serum contains increased cfDNA from hematologic cells due to lysis from clotting; this dilutes ctDNA in the sample, decreasing assay sensitivity. Thus, current methodologies utilize plasma for ctDNA detection.

FIGURE 1. **Timing of ctDNA Detection**



cf DNA, cell free DNA; ctDNA, circulating tumor DNA; VAF, variant allele frequency.

FIGURE 2. **ctDNA Sampling Process**



EDTA, ethylenediaminetetraacetic acid; RBC, red blood cells.

Opportunities and Next Steps

The rapid progress in the development of ctDNA assays provides substantial opportunities and challenges for integrating them into clinical practice. Several clinical trials are ongoing, as described more fully within this issue; trial results will ultimately define the clinical utility of these assays. Although the clinical oncology community will likely ultimately favor assays with the highest level of clinical data, the rapidly changing field means that studies to understand the relative performance of new assays will be necessary. As the performance of these assays improves, it will be a challenge to integrate their results into clinical practice, as some questions, such as when patients may benefit from adjuvant therapy, may be very dependent on the threshold of detection of the assays. The efforts recently announced by the National Institutes of Health to compare ctDNA assays will be a welcome addition to the landscape and will help define performance more rigorously for future studies.[23] Novel methodologies—including integration of fragmentation patterns (fragmentomics), nucleosomic compartment, and methylomics—will supplement existing approaches and further drive the amount of information discernible from ctDNA. Ultimately, the focus on conducting high-quality trials with rigorously validated assays will be required to unlock the full potential of this technology to benefit patients. ■

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Minimal Residual Disease–Directed Adjuvant Therapy for Patients With Early-Stage Colon Cancer: CIRCULATE-US

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ABSTRACT

BACKGROUND: The ability to detect circulating tumor DNA (ctDNA), a novel surrogate for minimal residual disease (MRD) for patients with solid tumors, has significantly evolved over the past decade. Several studies have shown that ctDNA may provide clinical insight into the biological dynamics of MRD. The CIRCULATE-US (NRG-GI008; NCT05174169) trial will aim to address the role of ctDNA for risk stratification to intensify and deintensify adjuvant chemotherapy for patients with early-stage colon cancer.

METHODS: CIRCULATE-US, a prospective phase 2/3 randomized trial, is investigating the molecular dynamics and prognostic role of ctDNA (evaluated by Natera's Signatera assay) for patients with resected colon cancer. Patients with negative postoperative ctDNA will be enrolled in cohort A and randomized to receive either immediate treatment with 5-fluorouracil and folinic acid or capecitabine plus oxaliplatin (FOLFOX6 or CAPEOX; Arm 1) or serial ctDNA surveillance with delayed adjuvant therapy (Arm 2). Patients randomized to Arm 2 with subsequent positive ctDNA results will be enrolled in cohort B for a second randomization to receive either FOLFOX6/CAPEOX (Arm 3) or 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan (FOLFIRINOX; Arm 4) for 6 months. Patients with positive postoperative ctDNA results will be directly enrolled in cohort B and randomized to receive either FOLFOX6/CAPEOX (Arm 3) or FOLFIRINOX (Arm 4). Patients with stage II or stage IIIC colon cancer with positive ctDNA results (tested as standard of care with commercial testing) will be eligible for enrollment in cohort B. The primary end point for cohort A is time to positive ctDNA status for phase 2 and disease-free survival for phase 3 with a noninferiority design. The primary end point for cohort B is disease-free survival for both phase 2 and phase 3 with a superiority design.

DISCUSSION: CIRCULATE-US will aim to understand postoperative ctDNA dynamics in early-stage colon cancer and will investigate escalation and de-escalation approaches by using ctDNA status as a surrogate for MRD status.

Rationale

Management of early-stage colon cancer has evolved over the past decade, leading to improved survival outcomes particularly with evolution of adjuvant chemotherapy.[1,2] Historically, whether to use adjuvant therapy—and, if so, which type—was determined by using the tumor/node/metastasis (TNM) staging system and by considering high-risk clinical and pathological factors for recurrence, such as tumor grade, presence of lymphovascular or perineural invasion, tumor perforation, bowel obstruction, and positive margin. However, the TNM staging system and the prognostic factors used to determine adjuvant therapy regimens lack precision. Given that adjuvant chemotherapy is beneficial only for a subgroup of patients with colon cancer and because the long-term toxicities of chemotherapy agents, such as neuropathy, can significantly impact quality of life, a more precise identification of the patient population that would benefit from adjuvant chemotherapy is needed.

Minimal residual disease (MRD) is a well-defined risk factor for inferior outcomes for patients with several cancers. MRD can be detected with different methodologies; these include

molecular methods with the use of cell-free tumor DNA (molecular residual cancer) or immunological methods including flow cytometry (used in liquid tumors). Moreover, MRD has long been utilized to determine treatment stratification for patients with acute myeloid leukemia.[3] Research on circulating tumor DNA (ctDNA), a surrogate for MRD for patients with early-stage colon cancer, has rapidly evolved within the past decade. When investigating ctDNA in patients with stage II colon cancer, Jeanne Tie, MD, MBChB, and colleagues found that 79% of patients with positive postoperative ctDNA status, but only 9.8% of patients with negative ctDNA status, had recurrent disease (HR, 18; 95% CI, 7.9-40; $P < .001$).[4] In another study among patients with stage III colon cancer who underwent serial ctDNA testing, Tie and colleagues again showed a significantly increased risk of recurrence for patients with positive ctDNA status after R0 resection (HR, 3.8; 95% CI, 2.4-21.0; $P < .001$).[5] A study by Maximilian Diehn, MD, PhD, and colleagues investigated the role of ctDNA in R0 resected stage II and III colorectal cancer, and the 2-year relapse-free survival rate was 17% vs 88% for patients with positive and negative ctDNA status, respectively (HR, 10.3; 95% CI, 2.3-46.9; $P < .00001$).[6] In the same study, time to recurrence was shorter for patients with positive ctDNA status (HR, 20.6; 95% CI, 3.1-139.0; $P < .00001$).[6]

More recently, the CIRCULATE-Japan study (jRCT1031200006) investigated serial ctDNA testing using Signatera assays.[7] In this study, patients with positive ctDNA status 4 weeks after surgery had a significantly lower 1-year disease-free survival (DFS) rate compared with patients with negative ctDNA status (55.5% vs 95.2%, respectively; HR, 13.3; 95%, CI 8.0-22.2; $P < .001$). Notably, patients who remained ctDNA positive at 12 weeks after surgery and who had negative-to-positive seroconversion were found to be at further increased risk of recurrence at 6 months (HR, 15.8; 95% CI, 5.7-44.2; $P < .001$) compared with patients with negative ctDNA, indicating the greater importance of serial testing vs that of a single ctDNA test. The investigators also found that ctDNA clearance at 12 weeks was significantly higher for patients who received adjuvant chemotherapy for stage III disease (58% vs 11%; $P < .001$).[7] Cumulative incidence of ctDNA clearance was also significantly higher for patients who received adjuvant therapy than for those who did not (67% vs 7% by 24 weeks; HR, 17.1; 95% CI, 6.7-43.4; $P < .001$). How ctDNA clearance correlates with clinical outcomes for these patients will require longer follow-up.

Collectively, these data indicate that ctDNA status is a clinically meaningful surrogate for MRD status for patients with colon cancer who are undergoing adjuvant therapy and that serial ctDNA can be utilized to escalate and de-escalate adjuvant therapy and to deliver adjuvant therapy to the right patient population more precisely than TNM staging.

Hypothesis

The primary hypothesis of this phase 2/3 randomized study is that patients with negative postoperative ctDNA results (considered MRD negative) can undergo serial ctDNA testing in place of immediate adjuvant chemotherapy without significant detrimental effect on the 3-year DFS rate with the introduction of adjuvant therapy at the time of seroconversion to positive ctDNA: phase 3 H0 (null hypothesis): 3-year DFS, 85.0% vs 74.6%; HR, 1.8; and alternative hypothesis (HA): 3-year DFS, 85.0% vs 82.1% (HR, 1.21), with a 90% power at α of 0.025 one-sided. For patients with positive postoperative ctDNA results (considered MRD positive), we hypothesize that escalation of chemotherapy to FOLFIRINOX in place of CAPEOX and FOLFOX will result in an improved 3-year DFS rate with a 33.3% risk reduction (phase 3 HA: HR of 0.667 or a 3-year DFS rate of 40.0% vs 54.3%, with a 90% power at α of 0.025 one-sided). The primary objective for cohort A (ctDNA negative) is to compare time to ctDNA positivity (phase 2) and DFS (phase 3) between immediate and delayed adjuvant chemotherapy arms. The primary objective for Cohort B (ctDNA positive) is to compare DFS between patients in the FOLFOX/CAPEOX and FOLFIRINOX arms for both phase 2 and phase 3 cohorts.

Eligibility

The study will enroll patients with histologically/pathologically confirmed stage IIIA/IIIB mismatch repair–proficient colon adenocarcinoma (T1-3, N1/N1c) with R0 resection and an ECOG performance status of 0 or 1. Patients with mismatch repair–deficient colon cancer or distal tumor extension of 12 cm or less from the anal verge or below the peritoneal reflection will not be enrolled in this study. Patients will be required to undergo Signatera ctDNA testing no longer than 8 weeks after surgical date to allow ctDNA results to be available and to initiate adjuvant therapy within acceptable 12 weeks postoperative period of time. Time interval between surgery (defined as postoperative day 7) and study entry must be within 60 days (ie, 67 days from date of R0 resection). Due to the potential false-negative risk of ctDNA testing and the inherently increased risk of recurrence of T4 or N2 disease, cohort A will not enroll patients with T4 or N2 disease. Patients with pathologic stage II or IIIC colon adenocarcinoma with R0 resection and commercially obtained Signatera ctDNA assay with positive results are eligible for enrollment in cohort B. These patients will require confirmatory central ctDNA testing before randomization in cohort B. Patients should have negative CT or MRI

results for metastatic disease and adequate organ function within 28 days prior to enrollment. Patients with tumor perforation, history of prior colorectal cancer, previous systemic therapy or radiotherapy for colorectal cancer, or tumor histology other than adenocarcinoma will be excluded from the trial. Patients with a history of other active cancer within 5 years, bone marrow or solid organ transplant, or grade 2 or greater sensory or motor neuropathy will also be excluded. Patients with HIV who are on antiviral therapy and have a negative viral load are eligible for enrollment.

Interventions

In this randomized phase 2/3 trial, patients with negative ctDNA status will be included in cohort A and then will undergo randomization to either receive the standard of care with immediate adjuvant therapy for 3 to 6 months with FOLFOX6/CAPEOX (Arm 1) or undergo serial ctDNA testing without adjuvant therapy every 3 months (±21 days) over the first year and every 6 months throughout years 2 and 3 until ctDNA becomes positive (Arm 2). Patients randomized to Arm 1 will also undergo ctDNA testing at the same frequency. Patients in Arm 2 with subsequent positive ctDNA results will transition to cohort B and will undergo a second randomization to receive either 6 months of FOLFOX/CAPEOX (Arm 3) or FOLFIRINOX (Arm 4).

Patients with positive postoperative ctDNA status assessed no later than 8 weeks after R0 resection will be included in cohort B and randomized to either the standard-of-care arm with FOLFOX/CAPEOX (Arm 3) or the interventional arm with FOLFIRINOX for 6 months (Arm 4). All patients will undergo routine clinical and radiological surveillance with follow-up restaging scans every 6 months. Patients in cohort B will undergo the same serial ctDNA testing as those in Arm 2.

End Points and Statistical Plan

The primary end point of phase 2 for cohort A is time to ctDNA positivity, which is defined as the time from randomization to the first ctDNA-positive result after randomization to Arm 1 and the second ctDNA-positive result after randomization to Arm 2. The difference in definition of ctDNA positivity for Arm 1 and Arm 2 allows for the possibility that delayed chemotherapy on Arm 2 could seroconvert the patient back to negative ctDNA. Recurrence without a positive ctDNA result will be considered as an event for the primary end point for both arms (Arms 1 and 2). The last ctDNA test will be used to censor patients without any postrandomization positive ctDNA results. Patients with only 1 positive ctDNA result in Arm 2 will be censored at the last ctDNA test. The primary end point of phase 3 for cohort A and of phase 2/3 for cohort B is DFS, which is defined as time from randomization to recurrence or death from any cause.

The stratification factors for cohort A include disease stage (IIIA vs IIIB) and intended fluoropyrimidines chemotherapy (5-FU vs capecitabine). The stratification factors for Cohort B include intended fluoropyrimidines chemotherapy (5-FU vs capecitabine) and the initial postoperative ctDNA status (positive vs negative). The statistical design for cohort A is powered to prove the noninferiority of delayed adjuvant therapy with serial ctDNA testing compared with immediate adjuvant therapy (no more than a small detriment with delayed adjuvant chemotherapy under HA; phase 2: 1-year event-free rate for immediate and delayed adjuvant arms, 88.0% vs 85.7%, respectively [HR, 1.21]; phase 3: 3-year DFS rate, 85.0% vs 82.1%, respectively [HR, 1.21]).[5,8] The statistical design for cohort B is powered to prove the superiority of treatment intensification with FOLFIRINOX compared with standard arm with regard to 3-year DFS rate (HA for phases 2 and 3: 54.3% vs 40.0%, respectively [HR, 0.667]).[5] The 1-sided type I errors of the noninferiority tests (Cohort A) are set to be 0.05 and 0.025 for phases 2 and 3, respectively. The type I errors of the superiority tests (Cohort B) are set to be 0.15 (1-sided) and 2.5% (1-sided) for phases 2 and 3, respectively.

Study Status

The study was activated on March 1, 2022, through the National Cancer Institute's National Clinical Trials Network and is actively recruiting across the United States. All United States cooperative groups (ALLIANCE, ECOG-ACRIN, SWOG, and NRG) through their network members are actively participating in the trial to enhance study recruitment. The study is expected to open at both community and academic institutions to maximize race, gender, and age diversity in the study cohorts. ■

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For references visit
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Residual disease test (MRD)

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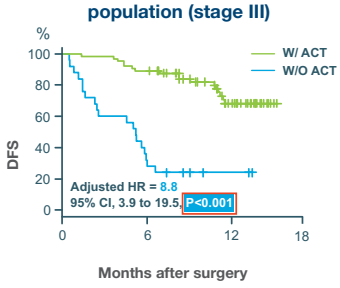
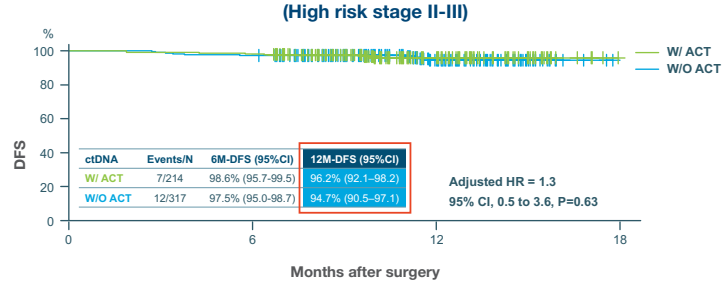
Signatera is prognostic and predictive of treatment benefit in early-stage CRC[1]

Data presented at ASCO Gastrointestinal Cancers Symposia in January 2022 included an interim analysis from the largest MRD-guided trial indicating that personalized MRD testing can guide adjuvant treatment decisions.

DFS in post-op-4w MRD-positive population (stage III)



DFS in post-op-4w MRD-negative population (High risk stage II-III)



Key takeaways

- MRD-positive CRC patients at 4w post-op benefit significantly from chemo (HR 8.8-9.4)
- MRD-negative CRC patients at 4w post-op do NOT benefit significantly from chemo

Scan or visit www.natera.com/events/asco-gi-2022 to learn how a tumor informed approach optimizes patient management

References

1 Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.

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CLINICAL TRIALS IN PROGRESS

CIRCULATE-US

TITLE

Colon Adjuvant Chemotherapy Based on Evaluation of Residual Disease: CIRCULATE-US (NRG-GI008) (NCT05174169)

BACKGROUND

Currently, determination of whether adjuvant chemotherapy is required for colon cancer is based on tumor/node/metastasis staging and clinical and pathological factors. However, the absolute benefit of adjuvant therapy for stage II and III colon cancer is ~5% and ~25% to 30%, respectively, indicating that the benefit is limited to a subgroup of patients with colon cancer. Therefore, more precise approaches to defining patients at risk for recurrence are required.

The detection of circulating tumor DNA (ctDNA) in blood samples has evolved significantly over the past decade, and studies have investigated the clinical and prognostic value of ctDNA in early-stage colon cancer. Recent studies identified ctDNA status as one of the most powerful prognostic factors and a surrogate for minimal residual disease (MRD) for patients with early-stage colon cancer. However, at this time, the clinical use of ctDNA for the determination of adjuvant therapy is not well established and represents an unmet need for research. CIRCULATE-US, a prospective phase 2/3 trial, will be investigating MRD-based adjuvant therapy for patients with early-stage colon cancer with intensified and deintensified adjuvant therapy approaches by using ctDNA status as a surrogate for MRD status. This trial will use Signatera ctDNA testing to determine the ctDNA status of patients entering the study.

INCLUSION CRITERIA

Patients with confirmed stage IIIA or stage IIIB mismatch repair–proficient colon adenocarcinoma (T1-3, N1/N1c) will be included in this study. Patients with T4 or N2 disease will be excluded from cohort A to exclude the potential negative impact of a possible false-negative result of ctDNA testing on the survival of patients. Patients who have positive ctDNA results from commercially obtained Signatera testing and stage II and IIIC colon adenocarcinoma and who otherwise meet the rest of the eligibility criteria can be enrolled in cohort B. Eligible patients will have adequate organ function and a baseline radiologic exam within 28 days before enrollment without evidence of metastatic disease. Patients with mismatch repair–deficient colon cancer, tumor-related bowel perforation, or distal tumor extension of 12 cm or less will be excluded from this study.

PATIENT ACCRUAL INFORMATION

- **Open date:** The study was activated on March 10, 2022, and is currently actively recruiting across the United States.
- **Accrual goal:** The study is powered to enroll 1912 patients with resected stage III A, B, and patients with positive ctDNA and stage II or IIIC colon adenocarcinoma.
- **Percent accrued:** In progress.

STUDY SITES

The study is activated across the National Cancer Institute's National Clinical Trials Network. Please find more details at: https://clinicaltrials.gov/ct2/show/results/NCT05174169?view=results

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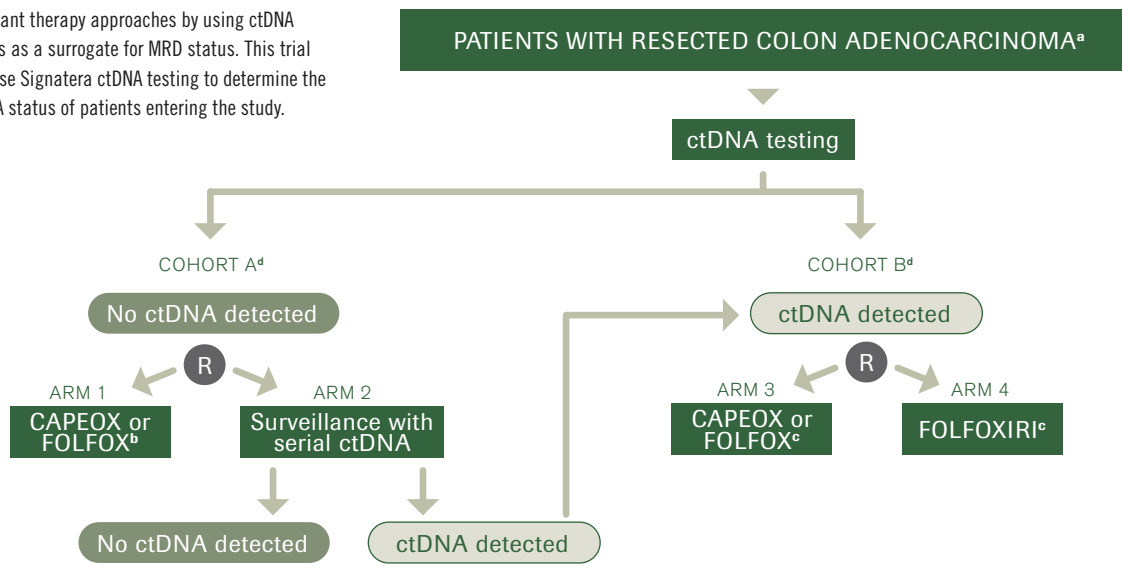

CAPEOX, capecitabine plus oxaliplatin; ctDNA, circulating tumor DNA; FOLFOX, fluorouracil, folinic acid, and oxaliplatin; FOLFOXIRI, fluorouracil, folinic acid, oxaliplatin, and irinotecan.
[a]Stage III (T1-3, N1/N1c) or ctDNA+ stage II or IIIC post-R0 resection. Patients in Arm 2 who subsequently have positive ctDNA results will cross over to Cohort B.
[b]Duration and regimen at physician discretion.
[c]Duration of therapy = 6 months.
[d]Stratification factors: intended fluoropyrimidine (5-FU vs capecitabine, both cohorts), disease stage (IIIA vs IIIB, Cohort A), initial postoperative ctDNA status (positive vs negative, Cohort B).

CLINICAL TRIALS IN PROGRESS

COBRA

TITLE

Phase 2/3 Study of Circulating Tumor DNA as a Predictive Biomarker in Adjuvant Chemotherapy in Patients With Stage IIA Colon Cancer (COBRA)

BACKGROUND

In 2022, approximately 25% of all new cases of colon cancer will be diagnosed as stage II. Although adjuvant chemotherapy is recommended for patients with high-risk stage II colon cancer, its overall benefit is marginal (<5%) in an unselected population and exposes many to excessive toxicity. This trial addresses the need for more objective criteria for patients with risk-stratifying stage II colon cancer who may (or may not) benefit from adjuvant chemotherapy.

Identification of circulating tumor DNA (ctDNA), which is shed into the bloodstream following cancer cell apoptosis, represents a highly sensitive approach to detecting minimal residual disease after surgery. Across all stages of colon cancer, the presence of ctDNA postoperatively is strongly associated with eventual recurrence. Conversely, those with undetectable ctDNA are likely to remain disease free.

Despite clear prognostic utility for ctDNA methodologies, observational series thus far have reported mixed outcomes regarding the ability of chemotherapy to clear ctDNA and improve survival for patients with resected locoregional colon cancer. NRG GI-005 (NCT04068103), a first-in-kind trial supported by the National Cancer Institute for any solid tumor to evaluate ctDNA as an integral biomarker, seeks to provide level 1 evidence in evaluating the role of ctDNA as a guide for clinicians in the decision to administer adjuvant chemotherapy to patients with stage IIA colon cancer.

The Guardant Health REVEAL assay will evaluate ctDNA status in this study. This assay is a next-generation sequencing diagnostic test that can detect ctDNA in cell-free DNA that is isolated from whole blood by identifying somatic variations and colorectal cancer–specific epigenetic signatures. No accompanying tumor tissue is required for analysis of ctDNA in a CLIA-certified central laboratory, and estimated turnaround time for results is less than 3 weeks.

The primary end points are ctDNA clearance (phase 2) and recurrence-free survival (phase 3) among ctDNA-detected participants. The phase 2 analysis will be performed after 16 ctDNA-detected patients have been on study for 6 months (ie, the time to complete adjuvant chemotherapy). If $P > .35$ for ctDNA clearance between the 2 arms of patients with detectable ctDNA who do or do not receive adjuvant chemotherapy on study, then the trial will be stopped for futility. If $P \leq .35$, then enrollment will continue to the phase 3 portion. For the phase 3 primary analysis, using a 1-sided $\alpha = .025$ and a power of 92%, we hypothesize that, among the "ctDNA detected" group, adjuvant chemotherapy will improve recurrence-free survival by 60%. Secondary end points will evaluate overall survival, recurrence-free survival, and time to recurrence according to ctDNA status and treatment arm.

ELIGIBILITY CRITERIA

Participants with low-risk pT3N0M0 stage IIA colon (nonrectal) cancer who would be deemed suitable for observation (and no adjuvant chemotherapy) according to current practice patterns by their evaluating provider are eligible. Participants are not allowed to have had prior testing for ctDNA status prior to study entry, and prior systemic therapy or radiotherapy for colon cancer is not permitted. At least 12 lymph nodes must have been resected, and there must be no evidence for micro- or macroperforation of the primary colon cancer. Study registration must occur within 60 days of resection.

PATIENT ACCRUAL INFORMATION

NRG GI-005 (NCT04068103) is currently enrolling at sites across the United States and Canada. This trial opened in December 2019. As of September 16, 2022, 416 of 1408 planned participants (30%) have been enrolled.

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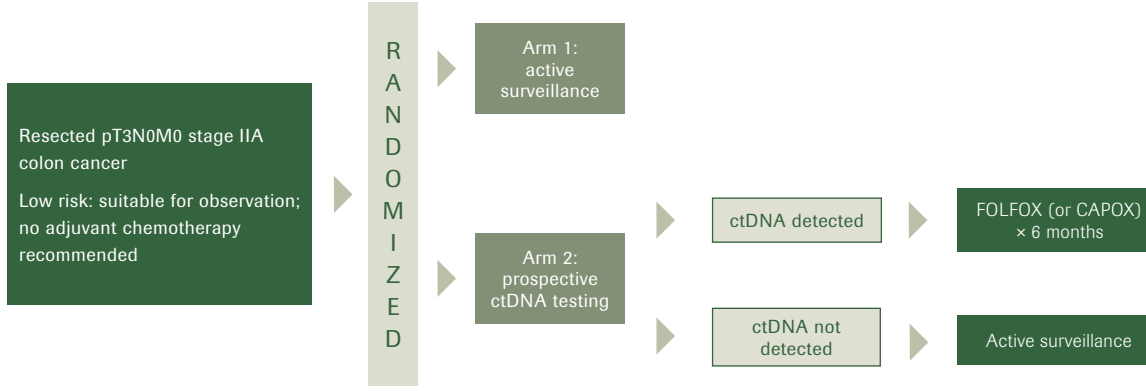

CAPOX, capecitabine and oxaliplatin; ctDNA, circulating tumor DNA; FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

DARZALEX® (daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARZALEX Faspro® (daratumumab and hyaluronidase-fihj)
Injection for subcutaneous use | 1,800mg/30,000units

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma[1]:

ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

- **70.6% of patients had not progressed** with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)†

44% **reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.56; 95% CI, 0.43–0.73; *P*<0.0001)

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

- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.[1]

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

*Range: 0.0-41.4 months.[4]

†Kaplan-Meier estimate.

‡Range: 0.03-69.52 months.[3]

§TEAEs are defined as any adverse event (AE) that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered drug related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

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

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

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

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

47% **reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

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

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

- Most frequent TEAEs§ ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms
- Grade 3/4 infections were 41% for DRd vs 29% for Rd
- Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5-year analyses are not included in the current Prescribing Information.

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

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

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX *FASPRO*®: Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX *FASPRO*®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX *FASPRO*® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX *FASPRO*® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX® and DARZALEX *FASPRO*®.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX *FASPRO*®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX *FASPRO*® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX *FASPRO*®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX *FASPRO*® on adjacent pages.

cp-248517v3

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

Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported *[see Adverse Reactions]*.

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision *[see Adverse Reactions]*.

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4:<1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX can cause fetal harm when administered to a pregnant woman. DARZALEX may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

The combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

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

- Infusion-related reactions *[see Warning and Precautions]*.
- Neutropenia *[see Warning and Precautions]*.
- Thrombocytopenia *[see Warning and Precautions]*.

Clinical Trials Experience

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA *[see Clinical Studies (14.1) in Full Prescribing Information]*. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).

Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

Body System Adverse Reaction	DRd (N=364)			Rd (N=365)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders						
Diarrhea	57	7	0	46	4	0
Constipation	41	1	<1	36	<1	0
Nausea	32	1	0	23	1	0
Vomiting	17	1	0	12	<1	0
Infections						
Upper respiratory tract infection[a]	52	2	<1	36	2	<1
Bronchitis[b]	29	3	0	21	1	0
Pneumonia[c]	26	14	1	14	7	1
Urinary tract infection	18	2	0	10	2	0
General disorders and administration site conditions						
Infusion-related reactions[d]	41	2	<1	0	0	0
Peripheral edema[e]	41	2	0	33	1	0
Fatigue	40	8	0	28	4	0
Asthenia	32	4	0	25	3	<1
Pyrexia	23	2	0	18	2	0
Chills	13	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Back pain	34	3	<1	26	3	<1
Muscle spasms	29	1	0	22	1	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[f]	32	3	<1	20	1	0
Cough[g]	30	<1	0	18	0	0
Nervous system disorders						
Peripheral sensory neuropathy	24	1	0	15	0	0
Headache	19	1	0	11	0	0
Paresthesia	16	0	0	8	0	0
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	15	<1	<1
Hyperglycemia	14	6	1	8	3	1
Hypocalcemia	14	1	<1	9	1	1
Vascular disorders						
Hypertension[h]	13	6	<1	7	4	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[b] Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

[c] Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

[d] Infusion-related reaction includes terms determined by investigators to be related to infusion

[e] Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

	DRd (N=364)			Rd (N=365)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	90	30	5	82	20	4
Neutropenia	91	39	17	77	28	11
Lymphopenia	84	41	11	75	36	6
Thrombocytopenia	67	6	3	58	7	4
Anemia	47	13	0	57	24	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX *[see Clinical Studies (14.2) in Full Prescribing Information]*. Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 3: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

Adverse Reaction	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Infections						
Upper respiratory tract infection[a]	65	6	< 1	51	4	0
General disorders and administration site conditions						
Infusion-related reactions[b]	48	5	0	0	0	0
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[b] Infusion-related reaction includes terms determined by investigators to be related to infusion

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Lymphopenia	95	42	10	87	32	6
Neutropenia	92	36	17	87	32	8
Thrombocytopenia	73	7	6	67	10	5
Anemia	52	13	0	57	19	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

Immunogenicity

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

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

Postmarketing Experience

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

Immune System disorders: Anaphylactic reaction, IRR (including deaths)
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

Risk Summary

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

Females and Males of Reproductive Potential

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

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use

Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients *[see Adverse Reactions]*. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing, itching, and blurred vision *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding *[see Warnings and Precautions]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions]*.

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

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

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, pomalidomide, or thalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Hereditary Fructose Intolerance (HFI)

DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol *[see Description (11) in Full Prescribing Information]*.

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

cp-271933v2

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation *[see Warnings and Precautions* and *Adverse Reactions].*

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Dosage and Administration (2.5) in Full Prescribing Information].* Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions *[see Dosage and Administration (2.5) in Full Prescribing Information].*

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone *[see Adverse Reactions].* Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations].*

The combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO *[see Dosage and Administration (2.1) in Full Prescribing Information].*

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions].* This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

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

- Hypersensitivity and Other Administration Reactions *[see Warnings and Precautions].*
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis *[see Warnings and Precautions].*
- Neutropenia *[see Warnings and Precautions].*
- Thrombocytopenia *[see Warnings and Precautions].*

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (14.2) in Full Prescribing Information].* Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Adverse Reaction	DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)	
	All Grades (%)	Grades ≥3 (%)
General disorders and administration site conditions		
Fatigue[a]	52	5#
Pyrexia	23	2#
Edema peripheral	18	3#
Gastrointestinal disorders		
Diarrhea	45	5#
Constipation	26	2#
Nausea	12	0
Vomiting	11	0
Infections		
Upper respiratory tract infection[b]	43	3#
Pneumonia[c]	23	17
Bronchitis[d]	14	2#
Urinary tract infection	11	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	31	2#
Back pain	14	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	22	3
Cough[f]	14	0
Nervous system disorders		
Peripheral sensory neuropathy	17	2#
Psychiatric disorders		
Insomnia	17	5#
Metabolism and nutrition disorders		
Hyperglycemia	12	9#
Hypocalcemia	11	0

[a] Fatigue includes asthenia, and fatigue.
[b] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c] Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
[d] Bronchitis includes bronchitis, and bronchitis viral.
[e] Dyspnea includes dyspnea, and dyspnea exertional.
[f] Cough includes cough, and productive cough.
[#] Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Lenalidomide and Dexamethasone[a]	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	94	34
Decreased lymphocytes	82	58
Decreased platelets	86	9
Decreased neutrophils	89	52
Decreased hemoglobin	45	8

[a] Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

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

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 812 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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

The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision *[see Warnings and Precautions]*.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

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

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion *[see Warnings and Precautions]*.

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

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Investigating the Use of Circulating Tumor DNA in Early-Stage Colon Cancer

Ardaman Shergill, MD[1], and Aparna Raj Parikh, MD[2,3]

ABSTRACT

Historically, presence or absence of clinicopathologic features like T stage, N stage, perineural invasion, lymphovascular invasion, tumor deposits, obstruction, etc, are used to select those patients who may benefit from adjuvant chemotherapy. However, emerging data suggest that risk stratification based on clinicopathologic criteria alone may be imprecise. Circulating tumor DNA (ctDNA) is an emerging novel tool in the management of early-stage colon cancer. ctDNA can be used in patients who have had resection of their primary cancer to measure minimal residual disease (MRD) and serve as a biomarker to help refine patient selection for adjuvant therapy. Prospective cohort studies have provided compelling data to suggest that ctDNA outperforms existing clinicopathologic criteria. Several clinical trials are currently underway to examine the role of ctDNA-guided MRD assessment and its role in recurrence risk stratification as well as in selection of adjuvant therapy. In this article, we review the current literature evaluating the role of ctDNA in the management of early-stage colon cancer.

Introduction

Colorectal cancer (CRC) represents about 7.9% of all new cancer cases and is the second leading cause of cancer death in the United States. In 2022, about 150,000 new cases will occur and the 5-year survival is projected to be 65.1%.[1] Likely due to screening efforts via colonoscopy, approximately 80% of patients with CRC present with early-stage disease;1 however, about 25% to 40% of patients with early-stage disease treated with curative intent have recurrence of their cancer despite definitive treatmen.[2] Hence, therapies that improve upon current treatments, as well as strategies that improve earlier detection of recurrences, have the potential to significantly influence patient outcomes. In this article we discuss the role of circulating tumor DNA (ctDNA) in management and surveillance of early-stage colon cancer.

Currently, staging of nonmetastatic colon cancer is done pathologically. Clinical or pathologic risk factors such as obstruction or perforation on presentation, presence of lymphovascular or perineural invasion, presence of T4 disease, presence of lymph node involvement, or presence of tumor deposits predict for high risk of recurrence in stage I, II, or III disease. Historically, these factors have been used to determine the need for adjuvant chemotherapy to decrease the risk of disease recurrence.[3,4] However, these factors have been identified only through retrospective analysis, limiting their real prognostic impact. Carcinoembryonic antigen (CEA) is the most commonly used prognostic and predictive blood-based biomarker in the management of CRC.

Recent studies have examined the role of circulating tumor DNA (ctDNA) as a measure of minimal residual disease (MRD). MRD detection refers to the least amounts of cancer that may be present in a patient after completion of definitive therapy but are not yet detectable radiographically.[5] Stratification for risk of recurrence based on the clinicopathologic criteria is imprecise, and it does not accurately identify patients with MRD, which may result in over- or undertreatment of patients.[6-8] Results of recent studies have shown that ctDNA is a promising biomarker for MRD for colon cancer because in colon cancer, compared with other types of cancers, there are overall higher rates of "shedding" of tumor fragments in circulation.[9-11]

Management of Early-Stage Colon Cancer

Primary therapy for nonmetastatic colon cancer is with resection of the primary tumor along with the removal of regional lymph nodes. Surgery alone is

TABLE 1. **Tumor-Informed and Tumor-Agnostic ctDNA Assays for MRD Detection in Colon Cancer**

ctDNA assay	Test characteristics	Tumor-informed	Considerations
Signatera	WES of tumor tissue used to identify 16 patient-specific somatic variants. Detection of at least 2 tumor-specific variants in plasma constitute positive ctDNA results	Yes	▪ Requires tumor tissue to be sent to the lab ▪ Allows quantification of ctDNA ▪ Turnaround time: ▫ First test: 4-6 weeks ▫ Subsequent: 7-10 days
Guardant REVEAL	Plasma-only test that integrates genomic and epigenomic cancer signatures to identify presence of methylation signatures associated with normal vs cancer DNA	No	▪ Tumor tissue not required ▪ Positive or negative test results; no quantification ▪ Turnaround time: ▫ 7-10 days
Safe-SeqS	Tumor-specific mutations detected by sequencing tissue and deep sequencing of plasma DNA	Yes	▪ Tumor tissue required ▪ Positive or negative test results ▪ Turnaround time: ▫ First test: 4-6 weeks ▫ Subsequent: 7-10 days
ddPCR [28]	Targeted sequencing of the primary tumor to detect 29 prespecified genes, followed by evaluation of plasma cfDNA to detect tumor-specific mutations (1-2 mutations)	Yes	▪ Tumor tissue required ▪ Turnaround time: ▫ First test: 4-6 weeks ▫ Subsequent: 2-5 days

cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; ddPCR, digital droplet polymerase chain reaction; WES, whole exome sequencing.

curative in about 50% of patients, even those with stage III disease.[6,8] Based on traditional clinicopathologic criteria, however, adjuvant chemotherapy is recommended for all patients with stage III colon cancer even if they have had curative resection because these criteria do not take residual disease into consideration; this leads to possible overtreatment of some patients.

Oxaliplatin-based adjuvant chemotherapy has improved 5-year disease-free survival (DFS) to about 67% to 70% in patients with resected stage III disease. The benefit of the addition of oxaliplatin in elderly patients has been questioned.[12,13] In many cancer registries, patients with stage I or II colon cancer have 5-year survival rates of greater than 90% and about 80%, respectively.[13,14] But based on current clinicopathologic stratification criteria alone, the questions of who benefits most from adjuvant chemotherapy and which patients have the highest risk of disease recurrence are still unanswered. For example, no adjuvant chemotherapy is currently recommended for patients with stage I disease; however, about 5% of such patients will have recurrence, and about 10% to 20% of patients with stage II disease who do not get chemotherapy will have recurrence.[15] Approximately 15% and 30% of patients with stage II and III disease, respectively, experience recurrence despite completing appropriate treatment.[12] These data highlight the limitations of current standards and underscore the need for improved patient selection for adjuvant therapy and better monitoring.

ctDNA is proving to be a promising biomarker in this setting. Many studies now have reported a correlation between the presence of ctDNA in plasma after the completion of definitive treatment and cancer recurrence.[11,16-23] In general, 95% to 100% of patients with persistently detectable ctDNA recur if no systemic therapy is offered.[11,17,20,24,25]

ctDNA Assays

Cell-free DNA (cfDNA) refers to extracellular DNA fragments detectable in various body fluids, including plasma, urine, cerebrospinal fluid, and saliva. DNA is released due to necrosis, apoptosis, active secretion, and autophagy as well as other forms of cell death (such as phagocytosis). In healthy individuals, the majority of cfDNA in plasma is released from hematopoietic cells. Cancer cells also release detectable cfDNA fragments, and these fragments have the genetic and epigenetic alterations that are unique to the tumor from which they originated.

ctDNA refers to short tumor-derived DNA fragments detectable in plasma. Factors including tumor burden, anatomic site of tumors, shedding characteristics of the tumor, and recent trauma or surgery can all influence the detection of ctDNA.[26-28] Several ctDNA assays are currently in practice and trials (**Table 1**). These can be divided into tumor-agnostic and tumor-informed assays. Tumor-agnostic assays (eg, Guardant REVEAL) are broad panel–based assays that look for genomic alterations and aberrant DNA methylation patterns known to occur in a given tumor. Advantages of tumor-agnostic assays can include logistical simplicity

TABLE 2. **Select Recent Studies Evaluating the Role of ctDNA in Early-Stage Colon Cancer**

Study	Design	Key findings
DYNAMIC II Tie et al, 2022[23]	Tumor-informed, ctDNA-guided management vs standard management for adjuvant chemotherapy for patients with stage II resected CC (SafeSeqS)	▪ ctDNA-guided management was noninferior to standard management for 2-year RFS ▪ 3-year RFS rate was 92.5% among ctDNA-negative patients and 86.4% among ctDNA-positive patients ▪ 3-year RFS rate in untreated ctDNA-negative patients was 92.5% vs 96.7% in patients with low-risk disease who underwent standard management (per standard histopathologic criteria), suggesting that low-risk patients with negative ctDNA may not benefit from adjuvant chemotherapy
GALAXY Kotaka et al, 2022[34]	Serial ctDNA measurement in patients with stage II-IV resectable CRC using tumor-informed assay (Signatera)	▪ 4-week postop ctDNA positivity was associated with inferior DFS ▪ For patients with positive ctDNA, DFS rates at 6 and 12 months were worse in patients who had positive ctDNA postop and remained positive, compared with those whose ctDNA became negative ▪ Adjuvant chemotherapy cleared ctDNA in 68% of the patients ▪ Two of the 3 patients with stage I or low-risk stage II disease and positive 4-week postop ctDNA had recurrence ▪ Patients with high-risk stage II and III disease and negative 4-week postop ctDNA did not seem to derive significant benefit from adjuvant chemotherapy
Henriksen et al, 2022[35]	Serial ctDNA measurement in patients with stage III CC using tumor-informed assay (Signatera)	▪ ctDNA was the strongest prognostic marker among conventionally used risk markers ▪ ctDNA was a strong prognostic marker even immediately after adjuvant chemotherapy ▪ Serial ctDNA analysis detected recurrence with 9.8 months lead time ▪ Serial assessment allowed escalation of ctDNA to be evaluated regularly ▪ ctDNA escalating relatively quickly was associated with worse clinical outcomes
Parikh et al, 2021[17]	Prospective evaluation of MRD detection using plasma-only (tumor-agnostic) ctDNA assay in patients with stage I-IV CRC (Guardant REVEAL)	▪ Recurrence sensitivity and specificity were reported to be 55.6% and 100%, respectively ▪ Longitudinal specimens increased sensitivity from 55.6% to 69.0%, with specificity remaining 100% ▪ Integrated epigenomic and genomic results increased MRD detection sensitivity by 25%-36%, relative to genomic results alone

CC, colon cancer; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DFS, disease-free survival; MRD, minimal residual disease; postop, postoperative; RFS, recurrence-free survival.

(because of occasional limited availability of tumor tissue) and faster turnaround time. Tumor-informed assays (eg, Signatera, SafeSeqS) utilize whole-exome sequencing (WES) or targeted sequencing of the tumor. The assay is designed specifically for a given patient's tumor, and it detects genomic alterations unique to that tumor. Tumor-informed assays have high sensitivity and low rates of false positivity. However, tumor-informed assays have a longer turnaround time, which can mean results are not available in time to influence clinical decision-making if the assays were ordered post surgery.

The fraction of ctDNA in plasma varies widely in patients with cancer, from less than 0.1% to greater than 10%, depending on burden of tumor, tumor DNA shedding, and anatomic site of the tumors.[28-31] Notably, recent trauma, including surgery, can cause elevated cfDNA levels for up to 4 weeks post event, and thus it can influence ctDNA results. The currently available techniques cannot distinguish trauma-induced cfDNA from ctDNA that would indicate MRD. Hence, the optimal time to check ctDNA may be at least about 4 weeks post surgery. ctDNA results checked sooner than 4 to 6 weeks post surgery may need to be repeated to ensure accuracy.[32]

ctDNA-Guided MRD Detection and Recurrence Risk Assessment

ctDNA presence has been studied in several adjuvant studies to predict risk of recurrence as well as to guide adjuvant therapy management (**Table 2**). Most recently, the DYNAMIC-II study results showed that analysis of ctDNA in resected stage II colon cancer may reduce the use of adjuvant chemotherapy in low-risk patients by 50%, without affecting the risk of disease recurrence.[23] Using the tumor-informed Safe-SeqS assay, patients were randomized 2:1 to have treatment decisions guided by

ctDNA or standard clinicopathologic features. The 2-year recurrence-free survival (RFS) rates were statistically equivalent in the ctDNA-guided adjuvant therapy group compared with the standard management group: 93.5% vs 92.4%; absolute difference, 1.1%; 95% CI, –4.1 to 6.2; noninferiority margin, –8.5%. The 3-year RFS rate was 92.5% in ctDNA-negative patients and 86.4% in ctDNA-positive patients (HR, 1.83; 95% CI, 0.79-4.27). The risk of recurrence in stage II, low-risk disease by historic clinicopathologic features was 96.7%, indicating that chemotherapy may be avoided in these patients with low-risk disease. These study results suggest that there may be low-risk, ctDNA-negative patients with resected stage II colon cancer in whom chemotherapy may be avoided.

Furthermore, in this study, those patients who had ctDNA-positive disease and then received chemotherapy seemed to derive a benefit from treatment based on the low rate of disease recurrence that they experienced. It should be noted that among all patients who received adjuvant chemotherapy, a higher percentage of patients in the ctDNA-guided group received an oxaliplatin-based doublet compared with those in the standard-management group (62% vs 10%) per treating physician's choice. This may reflect a bias based on known prior knowledge of prognostic significance of ctDNA positivity, and historical data suggesting benefit of adding oxaliplatin to adjuvant fluorouracil (5-FU) alone for patients with high-risk disease. Among patients with ctDNA positivity, the 3-year RFS rate was 92.6% among those who received an oxaliplatin-based regimen and 76% among those who received 5-FU alone. Overall, this study shows that in stage II colon cancer that has been resected, ctDNA may be used to choose to de-escalate or even avoid therapy in lower-risk patients with postsurgery ctDNA-negative disease, but we have not yet answered all questions regarding de-escalation of adjuvant therapy in patients with high-risk stage II colon cancer. Furthermore, while numerically better RFS was seen in ctDNA-positive patients who were treated with an oxaliplatin-based regimen compared with 5-FU alone, large studies are needed to define the relative effect of adding oxaliplatin to adjuvant treatment in this setting.[23]

In prior stage II and III observational studies and pooled analyses, inferior 5-year RFS (38.6% vs 85.5%; P <.001) and overall survival (64.6% vs 89.4%; P < .001) rates in patients with detectable ctDNA after the completion of definitive therapy have been seen, which hints at the prognostic impact of ctDNA in the management of early-stage colon cancer.[19,20,24] In a study of patients with stage II colon cancer who were treated with chemotherapy and were ctDNA positive immediately after completing adjuvant chemotherapy, inferior RFS was noted compared with those having ctDNA negativity following adjuvant chemotherapy (HR, 11; 95% CI, 1.8-68, P = .001). Additionally, ctDNA also outperformed CEA in predicting radiographic recurrence; 85% of patients with positive ctDNA had radiographic recurrence vs only 41% of the patients with CEA elevation (P = .0003).[19,20,24]

Similar studies evaluating the role of ctDNA in postoperative settings showed that patients with ctDNA-positive disease had a higher risk of recurrence compared with patients with ctDNA-negative disease (HR, 7.2; P <.001). Similarly, positive ctDNA immediately after adjuvant chemotherapy and during surveillance was associated with 17 times (HR, 17.5; 95% CI, 5.4-56.5; P <.001) and 40 times (HR, 43.5; 95% CI, 9.8-193.5; P <.001) increased risk of cancer relapse, respectively, compared with negative ctDNA. A single test obtained postoperatively had sensitivity of about 41%; serial testing improved sensitivity to 88%. Specificity was 98% serially. In multivariable analyses, ctDNA was independently associated with the risk of cancer recurrence after adjusting for known clinicopathologic risk factors.[11,28]

In addition, tumor-agnostic assays, such as Guardant Health's REVEAL assay, have emerged as important prognostic tools for the management of early-stage colon cancer. The REVEAL assay detects genomic changes and epigenomic signatures related to aberrant DNA methylation; this helps in detecting ctDNA but does not require any sequencing of tumor tissue, and so may be a valuable option especially in cases where tumor cellularity may be low. Aparna Raj Parikh, MD, and colleagues, tested feasibility of using a tumor-uninformed, plasma-only MRD ctDNA assay in 103 patients with stage I to IV colon cancer undergoing curative-intent surgery. Samples were collected 4 weeks after surgery and 4 weeks after completion of adjuvant therapy. The "landmark" time point was defined as when samples were collected approximately 1 month after completion of definitive therapy (surgery alone or surgery and chemotherapy in those who needed adjuvant therapy). Overall, 84 patients were evaluable, of whom 70 were evaluable for "landmark" analysis. Seventeen out of 70 patients (24%) had detectable ctDNA after definitive therapy. Two of the 17 patients had less than 1 year of follow up. Fifteen out of 15 patients with positive ctDNA and at least 1 year of clinical follow up had cancer recurrence (positive predictive value, 100%; HR, 11.28; P <.0001). The single time point sensitivity of this assay was 55.6% and single time point specificity was 100.0%. Longitudinal specimens improved sensitivity from 55.6% to 69.0% (n = 20/29 patients with positive ctDNA; HR, 12.26, P <.0001). In patients who had positive surveillance ctDNA results in a test obtained within 4 months of clinical recurrence, the observed sensitivity improved to 90.9% (n = 20/22). Notably,

in this study, serum CEA levels did not predict recurrence well (positive predictive value, 53.9%; HR, 1.84; *P* = .18). Hence, plasma-based tumor-agnostic assays may have very promising clinical utility in MRD detection.[17]

The prospective CIRCULATE-Japan trial (jRCT1031200006) is an adaptive platform study that has 3 complementary clinical trials encompassing both de-escalation and escalation treatment strategies for patients with CRC, with selection (or enrollment) into each trial based on their ctDNA results. More than 3000 patients with CRC with stage I to IV disease will enroll. The tumor-informed Signatera assay is used for MRD detection.[33] The 3 studies are:

- GALAXY, the observational arm for stage II to IV CRC. Blood samples are collected before surgery, 1 month after surgery, and every 3 months for 2 years.
- VEGA, a randomized phase 3 study designed to test the benefit of 3 months of adjuvant capecitabine plus oxaliplatin therapy compared with surgery alone in patients with high-risk stage II or low-risk stage III colon cancer who have negative ctDNA 4 weeks after curative surgery, per the GALAXY study. VEGA is designed to test the role of de-escalating adjuvant therapy in patients in whom resection alone may be curative based on their postoperative ctDNA results at 4 weeks.
- ALTAIR, a double-blind, phase 3 study designed to establish the superiority of trifluridine/tipiracil (TAS-102) compared with placebo in patients who have ctDNA-positive disease, per the GALAXY study. ALTAIR is designed to test the role of therapy escalation if ctDNA clearance is not achieved after standard adjuvant chemotherapy.

Preliminary results from the GALAXY observational cohort study showed that ctDNA positivity after surgery was predictive of benefit from adjuvant chemotherapy and that changes in the ctDNA in response to adjuvant chemotherapy predicted improved outcomes. Further, those patients who were ctDNA negative did not seem to benefit from adjuvant chemotherapy. The risk of disease relapse in patients with resected stage II and III colon cancer correlated well with ctDNA positivity at 1 month after surgery (HR, 13.3; P <.001). ctDNA clearance was observed in 68% of the patients, and in those patients the survival outcomes were similar to the outcomes of those who were ctDNA negative post surgery (HR, 0.8; *P* = .60). On the other hand, patients who were ctDNA positive despite adjuvant chemotherapy had 15.8 times increased risk of cancer recurrence than those who were ctDNA negative (*P* ≤.001). Patients with negative ctDNA 4 weeks after surgery had good survival outcomes regardless of adjuvant chemotherapy administration, with a DFS of approximately 95% at 12 months. The results were reported after a median follow-up of only 11.4 months. These data indicate the potential of ctDNA technologies in guiding patient selection for adjuvant therapy; however, longer follow-up, especially at completion of study accrual, is needed.[34]

Similarly, in a study of Danish and Spanish patients who had stage III CRC, ctDNA detection postoperatively and after adjuvant chemotherapy was strongly predictive of recurrence (HR, 7.0; 95% CI, 3.7-13.5; *P* <.001; and HR, 50.76; 95% CI, 15.4-167; *P* <.001, respectively). Recurrence rate was 80% in those who had positive ctDNA postoperatively and after adjuvant chemotherapy. Only those patients who cleared their ctDNA permanently did not relapse. This study also evaluated the correlation between the rate of rise of ctDNA and survival prognosis (HR, 2.7; 95% CI, 1.1-6.7; *P* = .039). There were 2 growth patterns: slow (25% mean ctDNA increase per month) and fast (143% mean ctDNA increase per month). The median lead time of detection of recurrence using every-3-month ctDNA detection in addition to standard imaging techniques was 9.8 months. However, importantly, standard imaging recommendations outside of the United States incorporate less-frequent images than those commonly used in this country, which may have influenced the lead time reported in this study.[35]

Role of ctDNA in Surveillance

The goal of monitoring patients who have achieved what is, clinically, "no evidence of disease," is to detect early recurrence and enable intervention early enough to improve their outcomes. Currently, the follow-up for patients who have completed definitive therapy for colon cancer incorporates clinical exams, serial serum CEA levels, periodic CT scans, and periodic colonoscopy evaluations.[4] As noted above, studies using serial ctDNA monitoring seem to outperform those involving traditional CEA or radiographic surveillance. In one such study, serial ctDNA testing predicted cancer recurrence up to 16.5 months before radiologic imaging (mean, 8.7 months earlier; range, 0.8-16.5).[10] Several studies have compared the sensitivity and specificity of ctDNA vs CEA in predicting cancer relapse, and the outcomes indicated that ctDNA significantly outperformed CEA and imaging.[11,20,35] However, whether ctDNA-based early detection of colon cancer recurrence improved overall survival in patients is unclear and is a subject of future studies.

ctDNA-Guided Clinical Trials and Future Directions

Several clinical trials are underway to further investigate the clinical utility of ctDNA (**Table 3**). These include testing risk of recurrence in various cohorts of patients with CRC, adjuvant therapy modification based on ctDNA levels, and overall impact of these ctDNA-based modifications on survival of patients.

TABLE 3. **Ongoing ctDNA-Based MRD Detection Clinical Trials in Early-Stage Colon Cancer**

Study title	Stage	Assay	Brief study design
CIRCULATE-US (NCT05174169)	II, III	Signatera	▪ Postop ctDNA negative: observation vs SOC ▪ Postop ctDNA positive: SOC vs FOLFIRINOX
DYNAMIC III (ACTRN-12615000381583)	III	Safe-SeqS	▪ Randomization to SOC management vs ctDNA-guided management in adjuvant setting (therapy escalation for ctDNA positive; therapy de-escalation for ctDNA negative)
VEGA (jRCT1031200006)	High-risk stage II or low-risk stage III colon cancer	Signatera	▪ ctDNA negative 4 weeks postop: 3 months of adjuvant CAPOX vs observation
ALTAIR (NCT04457297)	II, III, IV	—	▪ Therapy escalation to TAS-102 vs placebo if ctDNA positive after intended adjuvant chemotherapy
GALAXY (UMIN000039205)	II, III, IV	Signatera	▪ Prospective observational study; patients enroll to VEGA or ALTAIR depending on results
PEGASUS (NCT04259944)	High-risk stage II or stage III	Guardant REVEAL	▪ Postop ctDNA-guided adjuvant chemotherapy. ▪ ctDNA positive: CAPOX, 3 months ▪ ctDNA negative: capecitabine, 6 months. Retest after 1 cycle and if ctDNA positive, change to CAPOX ▪ Additional chemotherapy if ctDNA positive after intended chemotherapy
TRACC (NCT04050345)	I, II, III	ddPCR	▪ Prospective observational study
COBRA (NCT04068103)	Low-risk stage II	Guardant REVEAL	▪ SOC observation vs ctDNA-guided management ▪ ctDNA positive: adjuvant chemotherapy for 6 months ▪ ctDNA negative: observation]
ACT 3 (NCT03803553)	III	Guardant REVEAL	▪ Postadjuvant therapy ctDNA evaluation. If ctDNA positive, then biomarker-based additional therapy (or second-line FOLFIRI if no biomarker) vs observation
CIRCULATE-PRODIGE 70 (NCT04120701)	II (excluding T4b)	ddPCR	▪ Postop ctDNA negative: observation ▪ Postop ctDNA positive: randomized to adjuvant chemotherapy vs observation
MEDOCC-CrEATE (NL6281/NTR6455)	II	PGDx elio	▪ Postop ctDNA negative: observation ▪ Postop ctDNA positive: randomized to adjuvant chemotherapy vs observation
IMPROVE-IT (NCT03748680)	I, II	ddPCR	▪ Postop ctDNA positive: randomized to observation vs adjuvant chemotherapy
BESPOKE (NCT04264702)	II, III	Signatera	▪ Prospective observational study

CAPOX, capecitabine and oxaliplatin; ctDNA, circulating tumor DNA; ddPCR, digital droplet polymerase chain reaction; FOLFIRI, leucovorin, fluorouracil, and irinotecan; FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; postop, postoperative; SOC, standard of care; TAS-102, trifluridine/tipiracil.

Some of these trials are PEGASUS (NCT04259944), IMPROVE-IT (NCT03748680), CIRCULATE-US (NRG-GI008; NCT05174169), VEGA (jRCT1031200006), COBRA (NCT04068103), DYNAMIC-III (ACTRN-12615000381583), TRACC (NCT04050345), MEDOCC-CrEATE (NL6281/NTR6455), and CIRCULATE-PRODIGE 70 (NCT04120701) to name several.

CIRCULATE-US is a large cooperative-group clinical trial, which will use the Signatera assay for MRD detection in patients with stage II and III colon cancer who have undergone resection. Since adjuvant chemotherapy does not cure all patients with colon cancer, this is an effort to improve outcomes by modifying therapy based on ctDNA detection postoperatively. Patients with ctDNA-negative disease will be randomized to standard-of-care (SOC) adjuvant chemotherapy or observation with standard close serial evaluations including clinical examinations, imaging, and CEA as well as ctDNA monitoring. Those with ctDNA-positive disease will be randomized to SOC chemotherapy or intensified chemotherapy with leucovorin, fluorouracil, irinotecan, and oxaliplatin (ie, FOLFIRINOX).

The BESPOKE (NCT04264702), ACT3 (NCT03803553), and COBRA studies were among the first ctDNA/colon cancer trials in the United States to open at a national level. BESPOKE is a prospective observational study in patients with stage I to IV CRC who undergo curative surgery and are followed for up to 2 years to examine the impact of tumor-informed ctDNA testing on adjuvant treatment decisions. COBRA is a phase 2/3 NRG Cooperative Group trial evaluating a plasma-only ctDNA detection approach to select high-risk patients with stage IIA colon cancer to receive chemotherapy following resection. ACT3 is evaluating the escalation of a different treatment—either chemotherapy with leucovorin, fluorouracil, and irinotecan (ie, FOLFIRI) or molecularly driven therapy—in patients who are ctDNA positive after chemotherapy for stage III disease. ACT3 is also evaluating how to modify therapy for those who continue to be ctDNA positive despite completing standard adjuvant therapies. However, additional questions remain to be answered in ongoing and future studies, including determining the best agents for treatment if ctDNA positivity persists and the impact of treating molecularly detected disease vs reinitiating therapy only when there is radiographic or other evidence of recurrent disease.

It is important to note that our outcomes are only as good as our tests, all of which must be used in the appropriate disease settings. We must be cautious about the possibility of false-negative ctDNA results, because if testing is done only immediately after surgery, or prior to 4 weeks post surgery, it may be impossible to say whether or not there is MRD: A patient could have truly negative MRD status or, alternatively, ctDNA titers might not high enough for detection or they could have low-shedding disease. If ctDNA is used for clinical decision-making or prediction, we recommend baseline testing prior to surgery in early-stage disease. In addition, consider repeating tests that indicate undetectable ctDNA post-op, 2 to 4 weeks later, to avoid false-negative results. When a decision is being made to escalate or de-escalate therapy, we want to be confident with the specificity of any given test.

As discussed here, a significant body of literature suggests that ctDNA-guided risk stratification in patients with resected early-stage colon cancer outperforms the current clinicopathologic criteria–based risk stratification. Hence, ctDNA monitoring in early-stage colon cancer is a novel emerging strategy that is likely to change current clinical practice with regard to monitoring, early detection of recurrence, and, potentially, adjuvant therapy selection. ■

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

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In HER2+ MBC following 1L progression and beyond*

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TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine

- **Median PFS:** 7.8 months (95% CI: 7.5-9.6) vs 5.6 months (95% CI: 4.2-7.1); HR = 0.54 (95% CI: 0.42-0.71); *P* <0.00001 **(primary endpoint)**[1†]

More than 2 years median overall survival at follow-up analysis[2]

- **Primary analysis[‡]:** 21.9 months (95% CI: 18.3-31.0) vs 17.4 months (95% CI: 13.6-19.9); HR = 0.66 (95% CI: 0.50-0.87); *P* = 0.0048 **(secondary endpoint)**[1]
- **Follow-up analysis[§]:** 24.7 months (95% CI: 21.6-28.9) vs 19.2 months (95% CI: 16.4-21.4); HR = 0.73 (95% CI: 0.59-0.90); median follow-up: 29.6 months[2]

Follow-up OS analysis: Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution.

Safe and well tolerated[1,3]

- The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash[1]
- 6% of patients discontinued TUKYSA due to adverse reactions vs 3% with placebo[3]

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TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

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- **The Prescribing Information for TUKYSA contains warnings and precautions** for diarrhea, hepatotoxicity, and embryo-fetal toxicity, some of which may be severe
- **The most common serious adverse reactions** in ≥2% of patients who received TUKYSA were diarrhea, vomiting, nausea, abdominal pain, and seizure

Study design: HER2CLIMB was a randomized (2:1) trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints included OS. A prespecified exploratory analysis was included to evaluate OS at ~2 years. Please see additional study design on the following page.

*≥1 anti-HER2-based regimen in the metastatic setting.[1]
†Data from the first 480 patients.[1]
‡Primary analysis (data cutoff: September 4, 2019).[3]
§Prespecified exploratory analysis (data cutoff: February 8, 2021).[2]
‖Based on brand prescriptions from 10/20 to 05/21.[4]

1L = first-line; 2L = second-line; BICR = blinded independent central review; CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; PPE = palmar-plantar erythrodysesthesia; T-DM1 = ado-trastuzumab emtansine.

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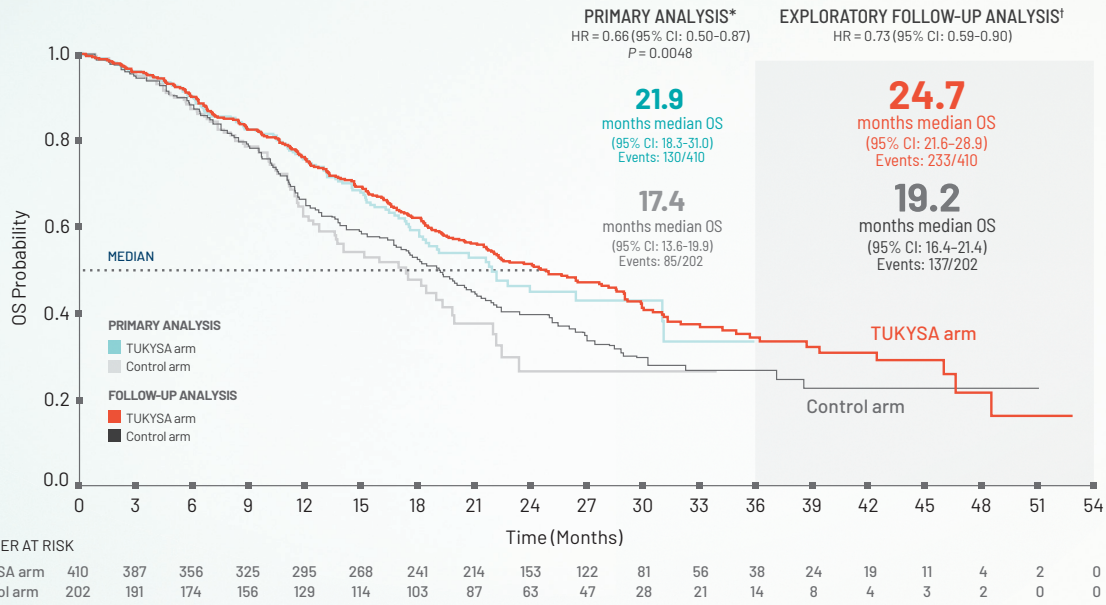
OS in the total population (N = 612)[1,2]



Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution. Data cutoff for follow-up analysis was February 8, 2021.[2]

Important Safety Information

Warnings and Precautions

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

  If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients.

  Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Lab Abnormalities

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.

CONSISTENT SAFETY PROFILE AT FOLLOW-UP ANALYSIS[2†]

At the 2-year follow-up analysis[2]

The most common adverse reactions (≥20%) were diarrhea, PPE, nausea, fatigue, vomiting, decreased appetite, stomatitis, headache, AST increased, anemia, ALT increased, and blood bilirubin increased

TEAEs Grade ≥3
61% (245/404) in the TUKYSA arm vs
51% (101/197) in the control arm

TEAEs leading to death
2% (8/404) in the TUKYSA arm vs
3% (6/197) in the control arm

The rate of discontinuation due to adverse reactions for the TUKYSA arm remained consistent with the primary analysis[2,3†]

	TUKYSA		PLACEBO
PRIMARY ANALYSIS[3]	6%	vs	3%
FOLLOW-UP ANALYSIS[2]	6%	vs	4%

*Study design: HER2CLIMB was a randomized (2:1), double-blind trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints assessed in the full study population included OS, PFS in patients with brain metastases, confirmed ORR, and safety.

The protocol included a prespecified exploratory analysis to evaluate OS, PFS (by investigator assessment), and safety in the total study population (N = 612) at ~2 years from the last patient randomized. After the primary analysis, 12.9% of patients in the placebo arm (26/202) crossed over to receive TUKYSA in combination with trastuzumab and capecitabine, with the first patient crossover in February 2020. Median overall study follow-up: 29.6 months (data cutoff: February 8, 2021). Because formal testing of all alpha-controlled endpoints was considered final at the primary analysis, data from this prespecified updated analysis are for descriptive purposes only.[1-3]

†Follow-up safety analysis was done as part of a prespecified exploratory analysis. Results are presented as descriptive data that are not intended to provide conclusions about safety and should be interpreted with caution.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ORR = objective response rate; TEAE = treatment-emergent adverse event.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

Drug Interactions

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. TUKYSA [Prescribing Information]. Bothell, WA: Seagen Inc. April 2020. **2.** Curigliano G, Mueller V, Borges V, et al. Updated results of tucatinib vs placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB). Poster presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021. **3.** Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609. **4.** Data on file. Seagen Inc.

TUKYSAhcp.com

Seagen®

TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA® (tucatinib) tablets, for oral use

Brief summary of Prescribing Information (PI). See full PI. Rx Only

INDICATIONS AND USAGE

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time.

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m^2 orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions

The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

Dose Reduction	Recommended TUKYSA Dosage
First	250 mg orally twice daily
Second	200 mg orally twice daily
Third	150 mg orally twice daily

Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

Severity	TUKYSA Dosage Modification
Diarrhea[1]	
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.
Hepatotoxicity[1,2]	
Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> 3 to 10 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)	Permanently discontinue TUKYSA.
ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN	Permanently discontinue TUKYSA.
Other adverse reactions[1]	
Grade 3	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Dosage Modifications for Severe Hepatic Impairment: For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors: Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. 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 TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy and contraception information.

ADVERSE REACTIONS

Clinical Trials Experience

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

HER2-Positive Metastatic Breast Cancer *(HER2CLIMB)*

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm.

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

Adverse Reaction	TUKYSA + Trastuzumab + Capecitabine (N = 404)			Placebo + Trastuzumab + Capecitabine (N = 197)		
	Grade (%)			Grade (%)		
	All	3	4	All	3	4
Gastrointestinal disorders						
Diarrhea	81	12	0.5	53	9	0
Nausea	58	3.7	0	44	3	0
Vomiting	36	3	0	25	3.6	0
Stomatitis[1]	32	2.5	0	21	0.5	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia syndrome	63	13	0	53	9	0
Rash[2]	20	0.7	0	15	0.5	0
Hepatobiliary disorders						
Hepatotoxicity[3]	42	9	0.2	24	3.6	0
Metabolism and nutrition disorders						
Decreased appetite	25	0.5	0	20	0	0

Adverse Reaction	TUKYSA + Trastuzumab + Capecitabine (N = 404)			Placebo + Trastuzumab + Capecitabine (N = 197)		
	Grade (%)			Grade (%)		
	All	3	4	All	3	4
Blood and lymphatic system disorders						
Anemia[4]	21	3.7	0	13	2.5	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	0.5	0	4.6	0.5	0
Investigations						
Creatinine increased[5]	14	0	0	1.5	0	0
Weight decreased	13	1	0	6	0.5	0
Nervous System Disorders						
Peripheral neuropathy[6]	13	0.5	0	7	1	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	12	0	0	5	0	0

1. Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, and aphthous ulcer
2. Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis
3. Hepatotoxicity includes hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury
4. Anemia includes anemia, hemoglobin decreased, and normocytic anemia
5. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function
6. Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

	TUKYSA + Trastuzumab + Capecitabine[1]		Placebo + Trastuzumab + Capecitabine[1]	
	All Grades %	Grades ≥3 %	All Grades %	Grades ≥3 %
Hematology				
Decreased hemoglobin	59	3.3	51	1.5
Chemistry				
Decreased phosphate	57	8	45	7
Increased bilirubin	47	1.5	30	3.1
Increased ALT	46	8	27	0.5
Increased AST	43	6	25	1
Decreased magnesium	40	0.8	25	0.5
Decreased potassium[2]	36	6	31	5
Increased creatinine[3]	33	0	6	0
Decreased sodium[4]	28	2.5	23	2
Increased alkaline phosphatase	26	0.5	17	0

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v.4.03.

Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

Strong CYP3A Inducers or Moderate CYP2C8 Inducers: Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Lactation

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

Contraception:

Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Infertility: Based on findings from animal studies, TUKYSA may impair male and female fertility.

Pediatric Use: The safety and effectiveness of TUKYSA in pediatric patients have not been established.

Geriatric Use: In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

Renal Impairment: The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Seagen®

CONTINUING MEDICAL EDUCATION (CME)

Antibody-Drug Conjugates in Gynecological Cancer: Setting the Stage

FACULTY

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

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LEARNING OBJECTIVES

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

- Review the structure of an antibody-drug conjugate (ADC) agent, and how this structure impacts the ADC's function
- Outline how the development of ADC agents is driving discovery of targets on cancer cell
- Discuss ongoing clinical trials of ADC therapy in patients with gynecologic cancers

RELEASE DATE: October 1, 2022
EXPIRATION DATE: October 1, 2023

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Treatment options for most cancers have expanded rapidly in the past few decades, leading to an improvement in survival for many cancers.[1] Unfortunately, this has not been the case in endometrial and cervical cancers.[2,3] However, recent advances in treatment for gynecological cancer as a whole have cast a glimmer of hope into this space.

One class of therapeutics being investigated across a broad spectrum of cancer types is antibody-drug conjugates [ADCs]. These agents consist of 3 parts: an antibody targeted to a cell surface molecule, a cytotoxic payload, and a linker to join the two. Ideally, the antibody target would be a marker that is highly expressed on cancer cells but not found on normal tissue throughout the body. Such a marker would limit off-target toxicities due to the action of the payload. The cytotoxic molecule typically attacks microtubules—making them either too stable or too unstable—or topoisomerases, leading to DNA damage. If the linker is cleavable under intracellular conditions, the cytotoxic payload is free to migrate to neighboring cells, increasing the drug's potency through the bystander effect. If the linker is uncleavable, the conjugate is more stable in circulation, thereby reducing off-target toxicity.[4]

For some ADCs, immunohistochemistry [IHC] testing is required to determine whether the level of the antibody target is sufficiently high on the cancer cell membrane. For others, the marker is known to be ubiquitously expressed, and the ADC can be administered without waiting for test results. In this first of a 2-part series, Kathleen Moore, MD, reviews current treatment options in gynecologic cancers and circumstances in which ADCs might fit into treatment protocols.

Q: What are the limitations of current chemotherapy for ovarian cancer, and what is driving research in targeted therapies?

MOORE: When we think about treatment for epithelial ovarian cancer, we have evolved a great deal over the past few decades. Physicians who've been in practice for many years will remember that every patient with epithelial ovarian cancer was treated with paclitaxel or carboplatin. There was no use of maintenance, there was no widespread testing for *BRCA*, and there was certainly not somatic testing for any sort of targeted therapy, because it really didn't exist, and there wasn't an understanding of what could potentially be targetable in ovarian cancer.

When we think about treatment for epithelial ovarian cancer, we have evolved a great deal over the past few decades.

This led to a lumping of different subtypes into just the term epithelial ovarian cancer, which prevented us from seeing significant differences. And now we look at epithelial ovarian cancer as having different sorts of categories. We look primarily at high-grade serous and high-grade endometrioid carcinoma for those tumors that have *TP53* alterations as one group of tumors. We're looking differently now at clear cell tumors as a different molecular subtype and what may be targetable there. We look at the low-grade serous carcinoma as an entirely different disease than high-grade epithelial ovarian cancer in general. It has completely different origins and molecular drivers, and it should be really considered a distinct disease, in my opinion. And then mucinous ovarian cancer is just so rare, and very difficult to treat and is a completely different disease in and of itself.

With that kind of separation of histologies, we've gotten a little bit better with standard chemotherapies, because those tumors that are *TP53*-altered do respond better to chemotherapy, especially in the front line.[5] Carboplatin, which is a DNA damaging agent, is going to work better in tumors that are driven by loss of *TP53*.[6] These have lost checkpoint 1 and are relying on checkpoint 2, which can also be altered to repair DNA damage. We see responses to frontline therapy being very robust and sometimes of good duration, whereas, in the other histologic subtypes [eg, clear cell, low-grade serous, mucinous], those responses are far less because they're different molecular drivers.[6-9]

Once tumors recur—and, unfortunately, the expectation for a good majority of our patients is that these tumors will recur— we'll reuse platinum-based therapies, and it may work again or it may not.[10] Ultimately, all these tumors develop resistances to platinum. And then we are left with these nontherapeutic cytotoxic agents, such as weekly paclitaxel, which does retain a pretty good response rate in the platinum-resistance setting of about 30%, so it's not a bad option.[11] After that, though, pegylated liposomal doxorubicin, gemcitabine, topotecan, and oral etoposide, all of these have really pretty dismal expectations for response, and the clinical benefit is relatively low.[12-16] So the constant development of resistances to these agents is a challenge and we start to run through things quickly.

That's been the state of affairs for a long time, but with increased understanding of targets we now know are present in ovarian cancer, this is changing. The biggest example is universal testing for germline mutations and *BRCA1* and *BRCA2*, and other high-penetrance genes. *BRCA1* and *BRCA2* are not only prognostic for how a tumor will respond to chemotherapy and how a patient will do over time, but they're

also predictive of response to DNA damage therapies, such as carboplatin, pegylated liposomal doxorubicin, and—most importantly— PARP inhibitors, which have been moved into frontline maintenance in this setting.[17]

Another example is the emergence of somatic testing. Among patients with no *BRCA1* or *BRCA2* germline mutation, 7% of patients will have tumors that harbor these mutations. While the prognostic implication of that isn't as understood, because it's a relatively recent discovery, the predictive significance of finding that in terms of response to PARP inhibition is as strong as that of a germline mutation.[18] So somatic testing for *BRCA* and other high-penetrance genes, has become an expectation. Assays that are testing for vulnerability as to how a tumor fixes its DNA—we call these homologous recombination deficiency assays—have given us additional information on patients who don't have a *BRCA* mutation, either germline or somatic, but who have other alterations in the tumor that render it vulnerable to DNA-damaging therapies, such as PARP inhibitors.

Some patients are going to be cured with PARP inhibitors in the front line, and we're starting to see that data emerge in 2022, and we'll see more of it in 2023.[19] And many patients benefit, but we're still seeing recurrences. And so there's still this drive for identifying other targets—either mutational targets, epigenetic targets, or cell-surface antigens—that can be targeted by a new class of drugs called antibody-drug conjugates (ADCs) to try and individualize the therapies we select for our patients in a more precision-medicine way so that we are delivering appropriate therapies in the right sequence over time.

And so this is really being just driven continuously by understanding molecular drivers, and, also, the importance and function of these cell-surface antigens and ways we can best exploit them to therapeutic benefit and, hopefully, less toxicity.

Q: What kinds of testing do you recommend to identify ADC targets on tumor cells?

MOORE: At the current time, for ovarian cancer, we don't have any approved ADCs. It hopefully will change in 2022, as we await the FDA decision on the ADC mirvetuximab.[20] Currently, for ovarian cancer, there's no established testing for an approved drug. However, there are things that we can do. If mirvetuximab is approved, we will start testing archival tissue via IHC for its target, which is folate receptor alpha.

For a lot of these ADCs, the testing is going to be relatively simple. These are mainly going to be IHC tests looking for antigens that are overexpressed or exclusively expressed on the tumor cell as related to normal cells. In the case of mirvetuximab, we're looking for FOLR1, which is almost ubiquitously expressed on high-grade serous ovarian cancer. About 80% of tumors will have some expression, and in 40% of tumors, it will be high.[21]

There are other ADCs that have different markers, such as the sodium-gated phosphate channel NaPi2b. It's a lineage marker for ovarian cancer, and it is almost ubiquitously expressed on ovarian cancer. It also has degrees of positivity. The up-and-coming trials in the ADC [upifitamab rilsodotin] will also be looking at a certain level of NaPi2b expression.[22]

Other markers haven't required testing up front (eg, TROP2). In cervical cancer, tissue factor hasn't required testing, because the target is so ubiquitously expressed. The one exception to IHC testing may be for ADCs that are targeting HER2. Now, the IHC tests apply here—and I'll come back to that point—but when we send next-generation sequencing tests, we'll find these ERBB2 or HER2 amplifications, which may also identify tumors that would be susceptible to treatment with ADCs targeting HER2.[23]

Types of testing will evolve over time as agents are approved. I think once mirvetuximab is approved, most tumors will be tested for FOLR1 at the time of diagnosis. That's what we do in colon cancer; that's what we do in lung cancer.[24,25] We don't wait to do all the testing for targeted therapies until someone with advanced stage disease recurs. From the start, you know your panel of biomarkers that you could potentially target. And there are enough data in those disease sites to know how to sequence targeted agents to the best therapeutic benefit.

Types of testing will evolve over time as agents are approved.

We're just getting to the point where we can start having those conversations for ovarian cancer, but I do believe it will move up. When you have a diagnosis of epithelial ovarian cancer, there'll be this panel of IHC that you do. You're going to know your *BRCA* status, both either germline or somatic. You're going to know your homologous recombination deficiency test status. And now you're going to know your FOLR1 status.

And then we're going to have to figure out when there's overlapping positivity. For example, what if you're FOLR1-high and NaPi2b-high? How do you sequence those drugs? We're going to have to figure that out over time. But I think there'll be a panel of tests that are sent so that we know what is and is not on a patient's option list moving forward.

I think the other thing that will change, and is already changing, is specific to the HER2 story. One of the big stories for 2022 was the advocacy of ADCs in targeting breast cancer

tumors that were previously considered to be HER2-low. They didn't fall into that HER2-positive, either HER 3+ or 2+ with fluorescence in situ hybridization [FISH]. And so we weren't accessing traditional HER2-targeted agents, such as trastuzumab and pertuzumab. However, trastuzumab deruxtecan has a phenomenal benefit in breast cancer tumors that are HER2-low.[26] So that's IHC 1+ or IHC 2+, and FISH-negative. This is going to be very important in endometrial cancer.[27] It may be important in ovarian cancer, as well, where we've never tested for HER2, because HER2 positivity by traditional diagnostics was very low.[23] But we don't really know what HER2-low is in ovarian cancer. And so identifying these markers in tumors may be important—to have that knowledge so you can offer these exciting agents to patients.

It's not just the incorporation of these IHC tests into the diagnostics for ovarian cancer, but it's also evolving over time, what we call "positive." It's a continuous change in how you interpret pathology, which can be quite challenging not only for a provider, but also for pathologists. Now we're changing the rules on an uncommon subset of tumors so we can identify our best therapeutic options for patients. This is really a moving target right now, but it's worth the work that's going into it, because it's going to be practice-changing for women with ovarian cancer.

Q: Should testing be repeated when a patient relapses after chemotherapy? Do the results change over time in individual patients?

MOORE: We don't really know yet what temporal heterogeneity does to the expression of any of these IHC markers, with the exception of mirvetuximab and FOLR1. There was a specific study done where the patients could enroll in the trial based on our archival tissue positivity, but then, before they got their first dose, they had another biopsy.[28] So there was a proximal biopsy done, and it was restained. The concordance was actually quite high. There were some on the edges that were not concordant, but the concordance was quite high, over 80%.[28] And so at least for FOLR1, it was not believed that a new biopsy needed to be obtained. And these were all done in a phase 1 setting, so very heavily pretreated and quite temporally distant from the archival specimen. And we still showed that concordance.

For FOLR1, based on current knowledge, I would say, "No." My sense with NaPi2b is the same in that it is a lineage marker. HER2 may be another story, especially if you're looking at HER2-low—there may be temporal and spatial heterogeneity that we don't understand yet in gynecologic cancers, because it hasn't been as widely studied as it has been in breast cancer. And the others—TROP2, tissue factor, and cadherin-6—are all very new.

At this point, all the studies are based on archival tissue positivity. Many of the studies that are in phase 1, like the cadherin study, are doing a pretissue biopsy.[29] If we see signals that the proximal biopsy is more selective, that may prompt us to change our behavior with how we assess a patient's eligibility for these drugs over time, but right now we're just using archival. The only time I would use a proximal biopsy is if I didn't have enough archival to test, and then I would get another biopsy to look. ■

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