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PRACTICAL, PEER-REVIEWED PERSPECTIVES

APRIL 2021 | Vol 35 • No 4

BREAST CANCER

SARA A. HURVITZ, MD, ON

Advancing the Paradigm of Breast Cancer

“It’s a time for great hope with breast cancer.”

Prostate Cancer Focus on Transitional Disease: A Critical Interval to Delay Progression of Prostate Cancer

Lung Cancer Strategies for Optimizing Molecular Testing in Non-Small Cell Lung Cancer

Multiple Myeloma Treatment Considerations for Transplant-Ineligible Multiple Myeloma

Hepatocellular Carcinoma How to Radiologically Assess and Follow Response After Treatment of Hepatocellular Carcinoma

Immunotherapy Messenger RNA Vaccines: Beckoning of a New Era in Cancer Immunotherapy

Ovarian Cancer: CME in Ovarian Cancer

WHAT

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ONCOLOGY® (ISSN 0890-9091) is published monthly by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. Annual subscription rates: US, \$237 and Canada, \$261; students and nurses, \$96; international, \$296. Single copies: \$20 each. Institutional US, \$299; Canada, \$329; international, \$375. Periodicals postage paid at Trenton, NJ and at additional mailing offices. POSTMASTER: Please send address changes to Oncology PO Box 457, Cranbury NJ 08512-0457, USA. Publications Mail Agreement No 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542 London ON N6C 6B2. Canadian G.S.T number: R-124213133RT001. Printed in U.S.A.

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A NEW APPROACH IN 1L aRCC TREATMENT...

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Use your phone QR Reader to gain instant access. No app needed for iOS users—
just aim your cell phone camera at the QR Code to get connected.

INDICATIONS

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

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1L=first-line; aRCC=advanced renal cell carcinoma.

LEARN MORE ON NEXT PAGE ➔

The first and only 1L aRCC combination treatment to double PFS and ORR while delivering superior OS¹

More than 16 months median PFS^{1*}

CheckMate-9ER was a randomized (1:1), open-label, phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.[†]

*PFS and ORR were assessed by BICR.[†]

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2

patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and

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More than double ORR^{1†}

► 5.6% of patients had progressive disease with CABOMETYX + OPDIVO vs 13.7% of patients with sunitinib²

[†]PFS and ORR were assessed by BICR¹.

Superior OS outcomes¹

► 40% reduction in risk of death with CABOMETYX + OPDIVO (HR=0.60; 98.89% CI: 0.40-0.89; P=0.0010)¹
— Median OS not reached in either treatment arm

New CABOMETYX combination starting dose

CABOMETYX 40 mg starting dose—
optimized for combination treatment
with OPDIVO¹

CABOMETYX 40 mg once daily	+	OPDIVO 240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (30-minute IV infusion)
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Tablet shown is not actual size.

1L=first-line; AR=adverse reaction; aRCC=advanced renal cell carcinoma; BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; IMDC= International Metastatic RCC Database Consortium; IV=intravenous; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PO=by mouth; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS

periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome

(RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:
CABOMETYX as a single agent: diarrhea, fatigue, decreased

appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

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

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc. 2021. 2. Data on file. Exelixis, Inc.

CABOMETYX® (cabozantinib) TABLETS
BRIEF SUMMARY OF PRESCRIBING INFORMATION.
PLEASE SEE THE CABOMETYX PACKAGE
INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX-treated patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 63% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt

CABOMETYX and nivolumab and consider administering corticosteroids. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

5.8 Adrenal insufficiency
CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC. Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 Proteinuria
Proteinuria was observed in 7% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

5.11 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications h.060t been established.

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.13 Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR) and 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), and in combination with nivolumab 240 mg/m² every 2 weeks in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

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.

Renal Cell Carcinoma

METEOR
The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331) ¹		Everolimus (n=322)	
	All Grades ²	Grade 3-4	All Grades ²	Grade 3-4
Percentage (%) of Patients				
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain ³	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2

Adverse Reaction	CABOMETYX (n=331) ¹		Everolimus (n=322)	
	All Grades ²	Grade 3-4	All Grades ²	Grade 3-4
Percentage (%) of Patients				
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash ⁴	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension ⁵	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

¹One subject randomized to everolimus received cabozantinib.
²National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
³Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
⁴Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
⁵Includes the following terms: hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥25% Patients Who Received CABOMETYX in METEOR

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Percentage (%) of Patients				
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Percentage (%) of Patients				
Chemistry				
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia ¹	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase. NCI CTCAE, Version 4.0				
¹ Based on laboratory abnormalities				

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥1% Patients Who Received CABOMETYX in CABOSUN

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4 ¹	Grade 3-4 ¹
Percentage (%) of Patients		
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia ²	9	8
Hypophosphatemia ²	9	7

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4 ¹	Grade 3-4 ¹
Percentage (%) of Patients		
Metabolism and Nutrition		
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia ²	3	0
Hypomagnesemia ²	3	0
Hyperkalemia ²	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension ³	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT ²	5	0
Weight decreased	4	0
Increased AST ²	3	3
Increased blood creatinine ²	3	3
Lymphopenia ²	1	6
Thrombocytopenia ²	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1
ALT, alanine aminotransferase; AST, aspartate aminotransferase		
¹ NCI CTCAE Version 4.0		
² Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values		
³ Includes the following term: hypertension		

CHECKMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab.

The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 6% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either CABOMETYX or nivolumab occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥15% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Percentage (%) of Patients				
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain ^a	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia ^b	15	0	22	0.3
General				
Fatigue ^c	51	8	50	8
Hepatobiliary				
Hepatotoxicity ^d	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis ^e	37	3.4	46	4.4
Rash ^f	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension ^g	36	13	39	14
Endocrine				
Hypothyroidism ^h	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain ⁱ	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic and Mediastinal				
Cough ^j	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
Infections and Infestations				
Upper respiratory tract infection ^k	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.
^aIncludes abdominal discomfort, abdominal pain lower, abdominal pain upper.
^bIncludes gastroesophageal reflux disease.
^cIncludes asthenia.
^dIncludes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.
^eIncludes mucosal inflammation, aphthous ulcer, mouth ulceration.
^fIncludes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.
^gIncludes blood pressure increased, blood pressure systolic increased.
^hIncludes primary hypothyroidism.
ⁱIncludes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.
^jIncludes productive cough.
^kIncludes nasopharyngitis, pharyngitis, rhinitis

Table 5. Laboratory Values Worsening from Baseline^a Occurring in ≥20% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Percentage (%) of Patients				
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.3	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

^aEach test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: CABOMETYX and nivolumab group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 33% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 6. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL¹

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades ²	Grade 3-4	All Grades ²	Grade 3-4
Percentage (%) of Patients				
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash ³	21	2	9	<1
Vascular				
Hypertension ⁴	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

¹Includes terms with a between-arm difference of ≥ 5% (grades) or ≥ 2% (Grade 3-4)
²NCI CTCAE Version 4.0
³Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected
⁴Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL¹

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Percentage of Patients				
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

¹Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX
Strong CYP3A4 Inhibitors
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.
Strong CYP3A4 Inducers
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended 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 2-4% and 15-20%, respectively.

Data
Animal Data
In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).
In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).
In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation
Risk Summary
There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception
CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility
Females and Males
Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use
The safety and effectiveness of CABOMETYX in pediatric patients have not been established.

Juvenile Animal Toxicity Data
Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypercellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use
In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.
Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment
Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment
No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE
One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving CABOMETYX with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Embryo-fetal toxicity:
• Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

• Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information
Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information
Revision 01/2021

Distributed by Exelixis, Inc. Alameda, CA 94502

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Printed in USA 01/21 CA-1121-3

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Treatment Targeting Is Key to Success in Oncology

With precision-guided approaches to care establishing themselves across tumor types, newer systemic therapy regimens are almost exclusively developed for the treatment of histological or biomarker subtypes within a larger disease state. One of the most prevalent examples of this is breast cancer, which has seen significant and consistent progress in terms of advancing overall survival in the treatment of HER2-positive tumors.

"HER2-positive breast cancer is unique and it's relatively rare for a particular type of cancer to be defined by one genetic alteration that is driving the tumor biology," said Sara A. Huvitz, MD, who is featured in this issue of *ONCOLOGY*® (see pages 162-165). "The success of that is absolutely outstanding, but that type of story is not going to be possible in a number of other tumor subtypes."

Huvitz, who is director of the Breast Cancer Clinical Research Program at the David Geffen School of Medicine at University of California, Los Angeles, and co-chair of the *20th Annual International Congress on the Future of Breast Cancer*® West, hosted by Physicians' Education Resource®, LLC (PER®), also discussed underwhelming responses noted with the use of immunotherapy in triple-negative breast cancer and the future of these agents. "I do think that there needs to be more work done to define biomarkers, subsets, and settings where these agents are going to have the best therapeutic index, the highest efficacy, and the lowest chance of causing significant toxicity," she said.

Also in this issue, *ONCOLOGY*® editorial board member E. David Crawford, MD, and colleagues, propose a new model for guiding the treatment of prostate cancer that focuses on a "transitional state," which occurs during the interval of progression to metastatic castration-resistant prostate cancer (see pages 166-168).

"Recognizing the transition state, the period before these events, is crucial to extending survival and improving quality of life," they wrote, adding that nonmetastatic castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, and oligometastatic disease represent essential moments in the progression of disease that warrant intervention in the hopes of delaying metastasis.

A thought-provoking Clinical Quandaries is presented by Alejandro Gabutti, MD; and Tommaso Cascella, MD, of a 36-year-old patient with a diagnosis of hepatocellular carcinoma (see pages 199-204).

As always, the articles within these pages and more on breakthroughs in oncology across multidisciplinary specialties can be found at CancerNetwork.com, home of the journal *ONCOLOGY*®.

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Messenger RNA: A Technology of the Moment

Howard S. Hochster, MD

We have all learned the *central dogma* of molecular biology: the DNA code is translated to messenger RNA which, in turn, is transcribed to proteins. To date, cancer therapeutics have focused on DNA by causing damage in replication or on proteins by targeting the molecule of interest with signal transduction inhibitors or antibodies. The excellent review in this article by ONCOLOGY® editorial board member Mehmet Sitki Copur, MD, FACP, explains the basis for progress in the area of exploiting the middle step using mRNA and reviews a number of new trials using this technology.

The use of artificial mRNAs provides a real opportunity to make any protein of interest, or even multiple proteins, which may induce therapeutic immune reaction. The story of mRNA from underappreciated lab curiosity to therapeutic entity is one of skepticism, appreciation of its potential, extensive investment by public and private entities, and entrepreneurship leading to the current vaccines for SARS-CoV2 from Moderna and Pfizer-BioNTech. I refer readers to an excellent article from STAT by Damian Garde and Jonathan Saltzman.¹ The field of mRNA therapeutics, despite validation in murine models, was treated with great skepticism regarding human application in the 1990s. Some of the major discoveries in the field were made by Katalin Karikó, PhD, and Drew Weissman, MD, PhD, at University of Pennsylvania, including

incorporation of “pseudo-bases” to reduce immune reaction to the message itself and immediate degradation. Karikó was eventually demoted in rank at UPenn for lack of grants, but is now a senior vice president at BioNTech, a German biotechnology company that was co-founded by a pair of Turkish married physicians at Mainz University. BioNTech has become a major source of mRNA research publishing more than 150 papers in the field. Their partnership with Pfizer has brought us 1 of the mRNA SARS-CoV2 vaccines. In the United States, a Harvard professor, Derrick J. Rossi, PhD, found these mRNA congeners could reprogram stem cells, and this led to founding of Moderna (“Modified RNA”), in conjunction with the Massachusetts Institute of Technology investigators and entrepreneurial funding.

It should be noted that Moderna has been a major recipient of United States’ government funding as well as private capital. Even prior to the current pandemic, it has been funded to the tune of hundreds of millions of dollars by the Defense Advanced Research Projects Agency (DARPA) to produce mRNA vaccines against diseases including Ebola, chikungunya, and Zika. In particular, a recent letter to the government has asserted the importance of National Institute of Allergy and Infectious Diseases’ mRNA-1273 as a critical part of the invention and the contributors to numerous other patents which may have been funded by taxpayers. The

Public Citizen website maintains taxpayers in the United States are paying twice for these vaccines given the degree of public funding. Moderna has never published its technologies, so funding sources for particular patents are not transparent.

In any case, key findings leading to effective mRNA-based therapy include use of pseudo-bases, proper construct including the poly-A tail, and lipo-nanoparticle encapsulation. These are all critical components and detailed by Copur. The key to this approach is translocation of the artificial mRNA coding for proteins of interest to the cytoplasm, transcription by the ribosome, and protein overproduction (as in the anti-spike protein antibodies). Also, the other arm of the immune system is involved in an alternate process involving protein degradation by proteasomes; and finally, presentation of neoantigens to dendritic and T cells induce cellular immunity. These may be augmented with use of anti-PD-(L)1 antibodies as being investigated in a number of ongoing trials listed in the table in the accompanying paper.

Most important, mRNA technology has been validated and is now subject to multibillion-dollar efforts. We hope and expect to see these important advances extend from vaccination to cancer therapies in the near future. ■

REFERENCE

1. Garde D, Saltzman J. The story of mRNA: How a once-dismissed idea became a leading technology in the Covid vaccine race. *STAT*. November 10, 2020. Accessed March 22, 2021. <https://bit.ly/3caFHwj>

MEET OUR EXPERT

Hurvitz is director of the Breast Cancer Clinical Research Program, co-director of the Santa Monica–UCLA Outpatient Hematology/Oncology Practice, and an associate professor of medicine in the Division of Hematology/Oncology at the David Geffen School of Medicine at UCLA in Santa Monica, California, as well as co-chair of the *20th Annual International Congress on the Future of Breast Cancer® West*, hosted by Physicians' Education Resource®, LLC (PER®).

Advancing the Paradigm of Breast Cancer Therapies by Critically Gauging Success Across Histologies

“It’s a time for great hope with breast cancer, given the number of agents being evaluated now.”

In recent years, the field of breast cancer management—specifically tumors in the metastatic setting—has experienced numerous breakthroughs, with novel therapies on the horizon across histologies and treatment settings. Of late, substantial interest has been focused on the use of immunotherapies, which have finally emerged in the breast cancer setting after notable success in other tumor types such as lung cancer and melanoma. Despite apparent early promise, these therapies are being reconsidered by the FDA based on indeterminable benefits of therapy in patients without PD-L1–expressing tumors or those progressing past the first-line setting.

In addition, matching the success achieved in HER2-driven tumors across all histologies in breast cancer has been a challenge, with overall survival times holding steady in many settings. To address these concerns, *ONCOLOGY®* sat down with Sara A. Hurvitz, MD, director of the Breast Cancer Clinical Research Program, co-director of the Santa Monica–UCLA Outpatient Hematology/Oncology Practice, and associate professor of medicine in the Division of Hematology/Oncology at the

David Geffen School of Medicine at UCLA in Santa Monica, California, to discuss issues of interest in the treatment of breast cancer.

Hurvitz is a program co-chair of the *20th Annual International Congress on the Future of Breast Cancer® West*, hosted by Physicians' Education Resource®, LLC (PER®), to be held July 30–31, 2021. The meeting will cover topics discussed by Hurvitz, with the hopes of demystifying some pressing questions in the field of oncology and facilitating thoughtful conversations about next steps in advancing care.

Q: What are the most exciting studies involving targeted therapies you're looking forward to seeing data from in the coming year?

HURVITZ: There are a number of therapies outside of the HER2-positive realm that are being tested in phase 1 through phase 3 trials right now. Just looking at the hormone receptor [HR]-positive subtype, I'm really excited to see data forthcoming related to one of the many oral SERDs, or [selective] estrogen receptor downregulators, that are being evaluated.

The furthest along is Elaces-

trant [RAD1901], which is being evaluated in a phase 3 randomized trial called EMERALD [NCT03778931]. That study should be reporting out in the next year or so, as the enrollment, I believe, completed this past year. So that'll be interesting to see if we have an oral SERD available for patients. There are at least 7 or 8 other ones that are very promising being evaluated in neoadjuvant, adjuvant, and metastatic settings, so I'm excited to see those data come out.

There are some interesting studies looking at PI3K inhibitors—for example, alpelisib [Piqray]—and triple-negative, PI3K-activated breast cancers. I don't know that we'll have data in the next year, but I do know those studies are ongoing as well in the HER2-positive breast cancer setting. I'm also very excited to see data relating to sacituzumab govitecan [TropEly], the TROP-2 antibody-drug conjugate that was FDA-approved last year for triple-negative breast cancer.¹ It's being looked at now in HR-positive breast cancer in the TROPICS-02 study [NCT03901339]. That is a study that also completed enrollment in HR-positive, metastatic disease. TROP-2 expression isn't just

limited to triple-negative breast cancer, so it makes sense to look at it in HR-positive breast cancer.

With T-DXd, or trastuzumab deruxtecan [Enhertu], which is FDA-approved for HER2-positive metastatic breast cancer, I'm excited to see data relating to the evaluation of this drug in HER2-low-expressing breast cancer, which comprises about two-thirds of HR-positive, HER2-negative breast cancer and about a third of triple-negative breast cancers. This is being evaluated in a randomized phase 3 trial called DESTINY-Breast04 [NCT03734029]. That study also completed enrollment this last year, so we should have data in the next year or so validating whether or not this agent really does look better than chemotherapy in HER2-low-expressing breast cancer that's more heavily pretreated.

There are early studies looking at other antibody-drug conjugates. For example, there is ladiratuzumab vedotin, a targeted antibody-drug conjugate being looked at in triple-negative breast cancer. Phase 1 data are emerging relating to that. There are a lot of exciting, ongoing clinical trials that should have results in the next year or 2.

Q: The FDA has been reconsidering the use of certain immune checkpoint inhibitors for many diseases, including atezolizumab (Tecentriq) for triple-negative breast cancer. What does that mean for its use in women with breast cancer?

HURVITZ: Immunotherapy is very exciting for certain tumor types, but it's not had the easiest path forward in breast cancer. Breast cancer was [one of] the last tumor histologies to show that it may be beneficial, and the benefits are restricted right now to those tumors that are PD-L1-positive in the metastatic setting. The benefits appear to be fairly restricted to the front-line setting rather than later-line settings. It hasn't been the blockbuster that it was in other tumor histologies.

The data surrounding atezolizumab from the IMpassion130 trial [NCT02425891] are certainly very promising in terms of pro-

gression-free survival and possibly overall survival.² But it's restricted to patients with PD-L1-positive tumor immune cells, as tested by [the VENTANA PD-L1 (SP142) assay]. The use of pembrolizumab [Keytruda] in the metastatic setting is restricted to those patients with a CPS [combined positive score] of 10 or greater, which is not the majority of triple-negative breast cancers.

We have some negative studies...and then we have very inconsistent data in the neoadjuvant setting where we're seeing promising pathologic complete response rates by adding immune checkpoint inhibitors to chemotherapy, but it doesn't appear to be restricted to PD-L1-positive cancers. It's hard to sort through the different clinical trial designs, the different antibodies that we're asked to use to test for PD-L1 expression, the different outcome results, and the lack of overall survival benefit thus far.

Although [these agents are] well-tolerated, there are severe, irreversible, and even life-threatening toxicities that can occur in patients receiving these drugs. Although this is more acceptable in the metastatic setting, where you are facing a life-threatening disease, it's incurable. As we move these drugs forward into the curative setting, we have to take that toxicity seriously before endorsing the use of these agents with no long-term data suggesting long-term benefit.

Q: Do you think the hope of immune checkpoint inhibitors exceeded the science and now we're going back and doing some of the research that probably should have been done ahead of time?

HURVITZ: There was a lot of hope surrounding these agents, especially since we are focusing the use of the drugs on triple-negative disease, where our therapies have been unsuccessful. For the most part, we haven't budged the median overall survival [for this disease] in the past several decades. Patients just aren't doing better with this disease. When we see an agent that may be well-tolerated and benefit patients, there's a lot of excitement, especially when we see the enormous advances that immune checkpoint

inhibitors have [achieved] in diseases like melanoma and lung cancer. I do think that there needs to be more work done to define biomarkers, subsets, and settings where these agents are going to have the best therapeutic index, the highest efficacy, and the lowest chance of causing significant toxicity. Work needs to be done. I'm somebody who has been a little more skeptical along the way about immunotherapy, and I do think that these therapies, for the most part, still should belong in the research realm. We should be doing more clinical trials and more biomarker studies to define the role of these agents in this disease.

Q: Why has treatment been so successful in the HER2-positive setting, but hasn't translated to other breast cancers?

HURVITZ: HER2-positive breast cancer is unique, and it's relatively rare for a particular type of cancer to be defined by 1 genetic alteration that is driving the tumor biology. The tumor is addicted to its [HER2-expression]. That unique addiction of tumor cells in HER2-positive disease makes it simple relative to other tumor types where there's a lot of things going on driving biology. It's fairly homogeneous. The fact that this is the gene that is driving biology [allows you to] develop drugs to target that and go after it. The success of that is absolutely outstanding, but that type of story is not going to be possible in a number of other tumor subtypes.

For example, targeting CDK4/6 in HR-positive breast cancers has been incredibly successful both in terms of progression-free survival and overall survival benefits. But resistance to this pathway develops, and we haven't demonstrated that the pathway remains important after the disease has become resistant to inhibitors of that pathway. In fact, it appears that once resistance develops to CDK4/6 inhibitors, its upregulation of other pathways, like PI3K, become the important drivers of tumor biology. [Therefore,] developing other inhibitors of CDK4/6 isn't necessarily going to benefit patients whose disease is

resistant to it. I think the heterogeneity of other tumor types and the number of other signaling pathways that are involved in the development of resistance makes it much more complicated.

I do think that we have made major strides in the treatment of HR-positive breast cancer. When CDK4/6 inhibitors were approved and available to patients, we start seeing median overall survival data come out for patients who were diagnosed with disease in 2018 through 2020. We will start to see that the length of median survival is improving for HR-positive breast cancer because of these agents, and my hope is that in the future we're going to have better agents for triple-negative disease and that we'll see an improvement in survival with that disease subtype as well.

Q: Are there potential targets that you're seeing that might be targets for therapeutics in the future, but aren't quite there yet?

HURVITZ: I think there are a lot of exciting targets being explored. I'm involved in a number of phase 1 clinical trials of agents that are targeting novel areas that relate to, for example, homologous recombination deficiencies—or different mechanisms of DNA repair—[trying to determine if] we can target that and prevent resistance to PARP inhibitors or if we can expand the use of agents beyond *BRCA* mutations. There are a lot of therapies that are looking at unique antigens expressed on tumor cells that can be targeted with antibody-drug conjugates. That is very promising. It's a time for great hope with breast cancer, given the number of agents being evaluated now.

Q: Is there one change you would make to the current treatment paradigm that would make the most difference for your patients?

HURVITZ: I think if we knew that, what would stop us from doing it? Clinical trial enrollment is key to moving the science forward. If there was a way to augment the percentage of patients who enroll in at least 1 clinical trial in their lifetime, that would allow the

advance of science (and in breast cancer) at a much faster pace. Getting more people involved in clinical trials and reaching a more diverse patient population is an unmet need. That's something that we should be all charged with addressing.

Q: How do you get more patients from minority populations to participate in clinical trials?

HURVITZ: There are a number of factors that lead to this. A lot of it has to do with access to centers that have clinical trials and the type of insurance that patients have. Clinical trials don't cover 100% of care; when a patient is on a clinical trial, you need to have insurance that's going to be able to cover the standard of care, exams, imaging, and therapies that are involved in the clinical trial. It's not as though if you go on a clinical trial, 100% of your care is covered. If you have somebody who has a very limited insurance plan, their access to clinical trials is going to be limited. Moreover, a lot of our centers that do clinical trials—phase 1, 2, and 3—are placed in more economically wealthy areas, so I think the NCI [National Cancer Institute] is asking Comprehensive Cancer Centers to demonstrate that they're enrolling a diverse patient population. [Thereby,] in order to get NCI backing and be a part of the NCCN [National Comprehensive Cancer Network], you have to open centers or collaborate with centers that are in low-income areas, county facilities, and the like. That motivation helps access for these patients.

Then you've got the other side of it—the patient side. Science has not been completely ethical in the past century if you look at how there have been some wrongs done to vulnerable patient populations, including African Americans. There are some real injustices that occurred, so gaining trust about going on a clinical trial is something that is a challenge that needs to be addressed. Engaging with advocates who have access to communities is useful as well.

I think you have to address it from financial aspects by motivating the centers to put resources and funding into it, motivating

[the pharmaceutical industry] to put resources and funding into it, and then providing a level of reassurance on the patient side where trust is earned and deserved.

Q: It appears as though cancer care has moved away from multimodality therapy and has moved toward combining agents and sequencing. Are we heading that way?

HURVITZ: In the metastatic setting, that is certainly the case. In the early-stage setting, it remains multimodality. You approach cancer with your surgery or radiation and your systemic therapy. But in the metastatic setting, the results from the ECOG-ACRIN [2108 (NCT01242800)] trial, looking at whether removal of the primary tumor in a person with de novo metastatic breast cancer improves survival, were negative; it did not demonstrate an improvement in overall survival.³ It's data like that that indicate, when you have systemic disease throughout the body, even if you can only see it in 1 or 2 spots on scan, the best way of addressing it is with systemic therapy that goes everywhere. "Cherry picking" by using surgery here and radiation there and ablation there, how much is that going to add to a patient's survival and quality of life compared with just getting systemic therapy and focusing on the safety and efficacy of that? We still utilize radio-ablation and radiation and surgery for palliation, but the goal is on survival. I personally want to see that adding those therapies to effective systemic therapy improves survival for a patient compared with just doing systemic therapy, because you can only use locoregional therapies so many times.

Q: Is there a study that you would like to conduct or you'd like to lead that you haven't? Or a topic you'd like to study that you haven't been able to get into yet?

HURVITZ: I think there are so many, it's hard to focus. I would love to see a clinical trial dovetailing off the topic of looking at a molecularly defined patient population—meaning triple-negative, HR-positive, or

HER2-positive—[instead of] an all-comer population, which all of these multimodality studies do. They take all tumor subtypes, and then you have to do your subset analyses retrospectively and see whether we benefit patients by radiating oligometastatic disease or removing the tumor at the time of surgery.

My suspicion is that doing all of that extra locoregional therapy and spot radiation is not improving survival in a disease that already has such good survival as HER2-positive breast cancer. There are a lot of unanswered questions out there. One of the big ones that came out from the 2020

San Antonio Breast Cancer Symposium that's generated a lot of discussion is relating to early-stage HR-positive breast cancer with a few lymph nodes involved from the RxPONDER study [NCT01272037]. In that study, they showed that, you know, if your OncotypeDx [Recurrence Score] is less than 26, you don't need chemotherapy if you have 1 to 3 positive nodes, and that's with HR-positive, HER2-negative breast cancer.⁴ But premenopausal women do appear to benefit from chemotherapy, regardless of how low the score is. The question that has been asked from that trial that everybody

wants to see [answered] is if chemotherapy is really necessary.

I think we all suspect that chemotherapy probably isn't benefiting these patients with 1 to 3 nodes with [high] OncotypeDx Recurrence Scores as long as you suppress the ovaries. That's one of those huge questions, I would love to see that [studied]. ■

FINANCIAL 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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FROM THE PUBLISHERS OF:

**Medical
Economics®**

How Physicians Can Earn Money, Expand Their Careers With Moonlighting

Chris Mazzolini

In the annual *Medical Economics*® Physician Report, nearly 1 out of 3 physicians said that they earn secondary income by moonlighting. The most popular forms of secondary work include consulting, teaching, and even work that does not involve a medical degree. The average income earned from these jobs is about \$40,000 per year.

Medical Economics® sat down with Suneel Dhand, MD, an internist who moonlights and co-founded a company called DocsDox that helps physicians find secondary income opportunities, to discuss ways physicians can find opportunities for themselves.

***Medical Economics*®: How many physicians are taking on secondary income? Is this common? And is there a growing interest in this kind of career diversification?**

DHAND: Yes, we are seeing a vast expansion in the number of doctors who are going down this route. It used to be an absolute minority of physicians, especially when we were in the era of physicians basically owning their own practices. Where was there ever time for secondary income? ... Some estimates suggest it's now the majority of physicians who in some ways are pulling in secondary income.

How do you find secondary work as a physician?

DHAND: I did it all ... I tried to maintain a larger professional network, which I [achieved] through previous jobs, at conferences, and so forth.

What factors should physicians consider, broadly speaking, as they're evaluating different opportunities?

DHAND: It's important to be clear about what you would enjoy. It's important for a doctor to really be honest with themselves and ask, "What do you enjoy about being a doctor?" If they don't really enjoy clinical medicine ... [they should] go down a nonclinical route. Don't just go for something because it sounds like a cushy opportunity. These opportunities will come physicians' way. But they'll realize very quickly if they do that, if it's not for them, they're not going to be happy.

It may sound counterintuitive to some to say that taking on more work may help your burnout. Can you talk a little bit about the relationship there?

DHAND: Physicians have to realize everything doesn't have to be a set career path; they can cut back on their regular clinical work. It doesn't mean that your secondary income is necessarily

adding to it, and I actually wouldn't advise doing that if you already work 80 hours a week. Using my own example, I was practicing internal medicine, doing the same thing week in, week out, and then decided to pull back on that. I thought, "What can I do that will be satisfying but also avoid that sense of monotony?" If you can reach that kind of balance, it can really add a lot of variety to your career.

Is there anything you think is important for physicians to keep in mind as they look for secondary work?

DHAND: If you have that itch to try something different [and] you feel that your job is not where you want it to be, whether that's because you're burned out or you just feel a general sense of drudgery, go ahead and try secondary work as soon as possible. I wish I had years before I did because there are so many opportunities out there for doctors. We historically undersell ourselves and don't market and understand our value even in other arenas. If you feel the urge to do that, go ahead and do it as soon as possible. Don't wait, and you will surprise yourself.

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A version of this article was originally published by Medical Economics®.

Focus on Transitional Disease: A Critical Interval to Delay Progression of Prostate Cancer

E. David Crawford, MD; Christopher J. Kane, MD; Richard G. Harris, MD; Alan H. Bryce, MD; and Daniel P. Petrylak, MD

Models of prostate cancer (PCa) progression guide the clinician in decisions about patient care. The prevailing categorization of PCa, however, does not take into account next-generation imaging (NGI), molecular and biologic markers of disease progression, or the impact of genetic alterations, either prognostically or in response to therapy. In addition, the current model of clinical states characterizes PCa as a stepwise continuum, obscuring the important interval when transitions occur from one clinical state to another. The transitions from nonmetastatic castration-resistant PCa (nmCRPC) or metastatic castration-sensitive PCa (mCSPC) to metastatic castration-resistant PCa (mCRPC) are seminal events in disease progression and are associated with significantly decreased survival if left unrecognized and untreated.

The RADAR (Radiographic Assessments for Detection of Advanced Recurrence) Group originally convened in 2013 to complement current PCa guidelines with practical decision-making. In 2020, RADAR IV convened to evaluate the use of NGI for assessing patients with mCSPC and nmCRPC and to review results from studies evaluating newer agents, primarily next-generation androgen receptor antagonists (antiandrogens), for delaying progression to mCRPC. Recommendations were also made regarding PCa

PERSPECTIVE

Rana R. McKay considers this proposal in prostate cancer on [page 169](#)

nomenclature to accurately represent transitional disease and guide treatment decisions.¹

This article is a follow-up to RADAR IV and represents a call to action for earlier intervention in the disease state. We need to implement clinical trials that evaluate early and therapeutic layering of agents to delay progression to mCRPC. Clinicians are encouraged to consider shifting their strategy from waiting for men to develop mCRPC to actively preventing its onset. NGI, biomarkers, and antiandrogens are tools to allow earlier initiation of therapy and prolong survival.

Overwhelming evidence has shown that metastasis and castration resistance (and shorter times to reach them) drastically lower overall survival (OS). Recognizing the transition state—the period before these events—is crucial to extending survival and improving quality of life. Thus nmCRPC, mCSPC, and oligometastatic disease are not just steps along a continuum, but critical points for intervention and clinical studies to delay mCRPC (**Figure 1**). We propose to further distinguish oligometastatic mCSPC from high-volume mCSPC, with the former being a transitional state and the

latter being an advanced state. This proposal also recognizes the dramatically inferior outcomes for men presenting with de novo mCSPC, which is thus classified as an advanced state downstream of the transitional state.

Next-Generation Imaging

Distinguishing between hormone-sensitive biochemical recurrence and mCSPC depends in part on current imaging modalities (CT and bone scans), which are limited in their ability to accurately detect low-volume PCa dissemination to lymph nodes and bone. More-sensitive molecular and functional imaging technologies are emerging, such as ¹⁸F-fluciclovine PET, PET imaging based on prostate-specific membrane antigen (PSMA), and multiparametric MRI. Earlier intervention via evaluation with these NGI modalities will reduce the time to discovering metastatic disease and will provide a potential increase in OS. RADAR IV suggests that a single PET imaging (either fluciclovine or PSMA) may be sufficient to determine treatment options in most cases.

Regarding oligometastasis, both fluciclovine and PSMA PET offer the potential to detect disease both within and outside

FIGURE 1. **Prevailing Maps of Prostate Cancer**

Arrows lead from diagnosis to death, suggesting an unbroken continuum

FIGURE 2. **Proposed Maps and Terminology**

The emergence of nmCRPC or mCSPC signals a transitional state, during which the primary focus is delaying progression.

CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer; mCRPC, metastatic CRPC; mCSPC, metastatic CSPC; nmCRPC, nonmetastatic CRPC; nmCSPC, nonmetastatic CSPC; PSA, prostate-specific antigen.

the prostate bed early in its development (eg, within the anastomosis or the pelvic lymph nodes). Disease in these disparate locations has differing treatment implications.

The advancement of imaging technology is intertwined with the advancement of biomarkers and pharmaceuticals. Well-designed clinical trials that lead to the approval and use of NGI are necessary in part because studies of newer treatments depend on the acceptance and availability of NGI.

Biomarkers

Molecular and genomic biomarkers may indicate disease that is aggressive or at high risk for metastasis. PTEN deficiency, TP53 mutation or loss, and aberrations

in PI3K signaling are just a few of the markers emerging as promising predictors from large studies. Results of a recent larger registration trial in patients with nmCRPC, SPARTAN (NCT01946204), suggest that patients with higher DECI-PHER scores have greater treatment effects with apalutamide plus androgen deprivation therapy (ADT) than those with low scores.² Biomarkers related to immunologic interventions have also received attention in mCRPC, and epigenetic markers, such as genetic hypermethylation patterns, can convey information about prognosis.

Preventing Progression

In 3 recent large registrational trials, the addition of third-generation antiandrogens—eg, apalutamide (Erleada), enzalutamide

(Xtandi), and darolutamide (Nubeqa)—to ADT in men with nmCRPC, based on conventional imaging and PSADT of 10 months or less, significantly prolonged metastasis-free survival. In other words, this strategy delayed progression to mCRPC, and it subsequently demonstrated a statistically significant benefit in median OS compared with placebo plus ADT (73.9 vs 59.9 months with apalutamide; 67.0 vs 56.3 months with enzalutamide; medians for OS not reached with darolutamide).¹ Based on these findings and a tolerable adverse effect (AE) profile compared with ADT alone, all 3 agents are now approved by the FDA to treat patients with nmCRPC.

Similarly, in 2 recent large phase 3 registrational trials, the addition of apalutamide (TITAN; NCT02489318)³ or

enzalutamide (ARCHES; NCT02489318)⁴ to ADT in men diagnosed with mCSPC by conventional imaging showed a statistically significant improvement in progression-free survival (PFS)—in other words, delayed progression to mCRPC—and in the case of apalutamide, also showed a statistically significant improvement in median OS. Both of these agents are now also approved to treat men with mCSPC.

Strong evidence from these large trials as well as observational studies confirm that the earlier results of improved PFS with modern therapeutic agents have indeed translated into longer OS, with tolerable AEs and quality of life comparable with that of ADT alone. Although patients may be on therapy longer, which risks AEs and higher costs, these potential drawbacks are more than balanced by improved OS. Good outcomes represent a good value proposition despite the potential for increased expense.

Conclusions

We now have new tools and novel therapeutic regimens that effectively identify appropriate patients, delay progression to mCRPC, and afford OS benefits. These advances prompt reconsideration of how we categorize and describe PCa. It is imperative that accurate imaging be used

to identify the proper matches between situation and therapy.

A model to describe the continuum of PCa should fill 4 needs.⁵ It should (1) describe the progression of PCa from diagnosis to death; (2) represent both the natural and treated history of the disease and allow iterative reassessment of prognosis over time; (3) have clearly defined, mutually exclusive disease states; and (4) support clinical decision-making based on the risk of disease progression. An additional issue is how the increased understanding of disease progression that is emerging from NGI should be incorporated—in other words, how to go forward with an “imaging state.”

We suggest dividing PCa into 4 stages: localized disease, biochemically recurrent disease, transitional disease, and advanced disease (**Figure 2**). Definition of a transitional disease state is meaningful not only because of differences in biology and prognosis vs advanced PCa, but also because newer therapies can significantly prolong transitional disease and delay progression to advanced disease. Also, defining this state provides a framework for considering future clinical trial design using common nomenclature.

Delaying progression is an important and achievable goal for patients with transitional PCa, and NGI can permit earlier

identification of these patients and refine risk stratification. It is important to achieve consensus on more easily understood terminology to communicate with health care professionals, as well as to clearly and effectively talk to patients. A map of disease states should make clear the need to initiate appropriate treatment—particularly for transitional disease. Earlier identification of specific disease states and interventions will translate to improved outcomes. ■

FINANCIAL DISCLOSURE: EDC is a speaker for Janssen, Bayer and Pfizer. CJK declares that he declares stock ownership in Stratify Genomics. RGH and AHB report no conflicts of interest that might be relevant to the contents of this manuscript. DPP reports consultant fees from Advanced Accelerator Applications, Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Incyte, Janssen, Mirati, Monopteros, Pfizer, Pharmacyclics, Roche, Seattle Genetics, Urogen and grant support from Advanced Accelerator Applications), Agensys Inc, *Astellas, AstraZeneca, *Bayer, BioXcel Therapeutics, Bristol Myers Squibb, Clovis Oncology, Eisai, *Eli Lilly, *Endocyte, Genentech, *Innocrin, MedImmune, Medivation, Merck, Mirati, *Novartis, Pfizer, *Progenics, Replimune, Roche, *Sanofi Aventis, Seattle Genetics

*Denotes study trials that have terminated

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PERSPECTIVE BY

Rana R. McKay, MD

Redefining the Clinical States of Prostate Cancer in the Modern Era

The authors of the accompanying article present a call to action to redefine historically characterized prostate cancer disease states to a contemporary model that emphasizes earlier interventions to prevent disease progression. They propose recategorization of prostate cancer into 4 states: localized, biochemically recurrent, transitional, and advanced disease. In the proposed model, biochemically recurrent disease would encompass castration-sensitive prostate cancer, including both states of rising prostate-specific antigen alone and oligometastatic disease. Transitional disease would include patients with de novo oligometastatic disease, metastatic castration-sensitive, nonmetastatic castration-resistant, and advanced disease representing the former lethal state of metastatic castration-resistant prostate cancer. The model emphasizes the integration of next-generation imaging, biomarkers, and earlier interventions to prevent the progression to advanced disease.

Accurate staging and disease detection of localized, biochemically recurrent, and metastatic prostate cancer is of critical importance to optimizing local and systemic treatment. Next-generation imaging, including positron emission tomography (PET) and multiparametric magnetic resonance imaging (mpMRI), have emerged as more advanced techniques for prostate cancer localization. The FDA approval of Ga 68 PSMA-11 PET in December 2020 in the United States is a landmark event for the widespread availability of this imaging modality for men with prostate cancer. While this is an overall advancement for patients with prostate cancer, many questions exist regarding the management of oligometastatic disease detected on next-generation

imaging and the role of local treatment, metastasis-directed therapy, and systemic therapy in this context. Ultimately, we need robust data derived from well-designed, prospective clinical trials to optimize the utilization of next-generation imaging techniques and validate whether the augmentation of clinical practice based on imaging improves patient outcomes. Furthermore, newer imaging modalities are not yet widely accessible. Pending further validation to clarify usage in routine practice, steps need to be taken to ensure broad and equal access among men with prostate cancer.

Advances in molecular technologies have enabled large-scale genomic analyses of metastatic prostate cancer. These advancements have revealed a high frequency of alterations in cancer-specific genes that are actionable or being investigated as candidate predictive biomarkers to guide therapy selection for patients with advanced disease. The approval of PARP inhibitors for patients with metastatic castration-resistant prostate cancer has launched us into the era of precision medicine.^{1,2} The identification of numerous potentially actionable alterations have fueled biomarker-based clinical trials of novel therapeutics, as well as standard therapies. As we move forward, it is critical that such studies are designed across the spectrum of the disease's natural history to prevent the emergence of castration resistance and disease progression.

Lastly, the authors emphasize the early intervention of antiandrogens in the management of prostate cancer, based on a series of phase 3 studies in men with nonmetastatic castration-resistant prostate cancer and metastatic hormone-sensitive prostate cancer. In addition to the early use of antiandrogens, several large phase 3 studies

have demonstrated the utility of early chemotherapy with docetaxel^{3,4} and abiraterone.^{5,6} Currently, there are no prospective studies comparing choice of agent among docetaxel, abiraterone, and next-generation antiandrogens. Biomarker-based strategies will be critical to optimize therapy intensification and de-escalation strategies. Additionally, defining early intermediary end points such as metastasis-free survival, a robust surrogate for overall survival in prostate cancer, will enable the earlier integration of therapeutic interventions for men with localized or biochemically recurrent disease.

The authors should be commended for proposing a change in the former categorization of prostate cancer disease states to better reflect current advancements in imaging and genomics. However, in its current form, the taxonomy is somewhat ambiguous and does not reflect the underlying biology or a regulatory framework for drug development and approval. There is a need to build on the existing framework established by the Prostate Cancer Working Groups 2 and 3, which links disease biology to drug development and common clinical practice.^{7,8} Subsequent guidelines addressing the full spectrum of the natural history of prostate cancer and integrating advancements in imaging and biomarkers will be warranted, to optimize future clinical trial design and the clinical care of patients with prostate cancer. ■

FINANCIAL DISCLOSURE: McKay reports research funding from Bayer, Pfizer, Tempus; serves on Advisory Board for AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Merck, Novartis, Pfizer, Sanofi, Tempus; is a consultant for Dendreon, Vividion; and serves on the molecular tumor board at Caris.

➔ For full reference list, visit cancernetwork.com/McKay_4.21

Treatment Considerations for Transplant-Ineligible Multiple Myeloma

Radowan A. Elnair, MD; and Sarah A. Holstein, MD, PhD

ABSTRACT: While significant advances have been made in the treatment of multiple myeloma, the management of the transplant-ineligible (TI) patient population remains challenging. The individuals enrolled in clinical trials for newly diagnosed TI patients, or those with no planned transplant, may not always be reflective of real-world patients, with respect to age, comorbidities, or frailty status. Likewise, results obtained from randomized relapsed/refractory studies also may not be applicable to this generally older and frailer patient population. In this review, we discuss assessment of frailty and focus on treatment options in both the newly diagnosed and relapsed/refractory settings for TI patients. We describe the patient-specific considerations that factor into treatment decisions as well as provide some guidance about management.

Introduction

The significant developments in medicine have contributed to a globally aging population. Between 1959 and 2016, US life expectancy increased from 69.9 to 78.9 years.¹ With the multitude of treatment options available for many diseases, this makes it more important than ever for physicians to make treatment decisions that take into account the nature of the disease, the treatment toxicity, and a patient's fitness and comorbidity profile.

Multiple myeloma (MM) is an embodiment of this challenge. The median age at diagnosis is 69 years,² and despite

the many strides made in the treatment of MM and discovery of agents with novel mechanisms, MM is still considered an incurable disease.³ Nonetheless, the depth of response to treatment—as assessed by minimal residual disease (MRD)—has been shown to correlate with survival, even in TI patients.⁴ Whether achievement of MRD negativity translates to being able to safely discontinue therapy without increasing risk of relapse remains to be determined. The goal is to give each patient the best chance of achieving the best possible response, while not conferring excessive toxicity with treatment that is not

curative. When making those treatment decisions, there is no one-size-fits-all approach; therefore, the patient's fitness can play a significant role in determining the appropriate therapy. In this review, we discuss treatment options for newly diagnosed (ND) and relapsed/refractory (R/R) MM in the context of the generally older and/or frail transplant-ineligible (TI) patient population. It is important to note that transplant eligibility can be in the eye of the beholder; there is no strict age cut-off. Multiple groups have documented the safety and efficacy of transplant in the older population.⁵⁻⁷ However, with advancing age and/or increasing comorbidities, the benefit-to-risk ratio may change, and thus a multidisciplinary approach, including geriatric evaluation, is recommended to optimally determine transplant candidacy.^{8,9} As discussed in greater detail below, there is increasing overlap between induction regimens in transplant-eligible (TE) and TI groups. However, identifying those patients who are TE remains important, given the progression-free survival (PFS) benefit obtained from an upfront autologous stem cell transplant (ASCT) approach.^{10,11}

Assessment of Frailty in MM

Association of a patient's ECOG performance status (PS) with survival and outcomes has been documented in patients with cancer.¹²⁻¹⁴ However, in an older can-

cer population, methods such as Karnofsky PS (KPS) or ECOG PS have limitations in reflecting a patient's frailty or comorbidities.¹⁵ Therefore, objectively assessing a patient's fitness for treatment is important, and a number of tools have been developed to provide this objective insight. One such tool is the International Myeloma Working Group (IMWG) frailty score. The score was developed from a cohort of 869 ND TI patients from 3 prospective multicenter trials.¹⁶ The median age in this cohort was 74 years, with 46% of patients aged more than 75 years. The score encompasses patient age, the Katz Activity of Daily Living score, the Lawton Instrumental Activities of Daily Living score, and the Charlson Comorbidity Index (CCI) score; it then stratifies patients into 3 groups: fit, intermediate-fit, and frail. The score predicted overall survival (OS) as well as risk of toxicity in this population. While patients aged more than 80 years made up 47% of the frail group, only 19% of patients in this category were frail due to age alone, reflecting the limitation of age as a single data point in defining frailty. The scoring system has been externally validated.¹⁷

Another tool that was shown to be predictive of OS is the Revised Myeloma Comorbidity Index (R-MCI), which categorizes patients into fit, intermediate-fit, and frail.¹⁸ This model incorporates age, renal function, lung function, KPS, frailty (as determined by the Fried definition),¹⁹ and disease cytogenetics. Calculating the IMWG frailty score requires a time-consuming evaluation, so the R-MCI was proposed as a more clinically applicable scoring system.¹⁸ The R-MCI was subsequently validated in a multicenter MM trial conducted by a German study group.²⁰ Of note, there has not been systematic utilization of these scoring systems in prospective clinical trials, making it difficult to gauge frailty of enrolled patients.

After assessing a patient's fitness, other factors that should be taken into account include the route of administration of

FIGURE 1. Evolution of Induction Regimens for Transplant-Ineligible (TI) Multiple Myeloma Tested in Phase 2 or 3 Clinical Trials

There have been 2 major paths forward: one based on adding novel agents to the backbone of melphalan/prednisone and the other based on adding novel agents to the backbone of lenalidomide/dexamethasone. Most recent efforts have focused on incorporating anti-CD38 monoclonal antibody therapy (eg, daratumumab) into the newly diagnosed TI setting. To provide a sense of the timing of the development of these regimens, the dates of the key publications are shown in parentheses.

C, cyclophosphamide; D, daratumumab; d, dexamethasone; I, ixazomib; K, carfilzomib; M, melphalan; P, prednisone; R, lenalidomide; T, thalidomide; V, bortezomib.

the drugs included in a regimen; the frequency of infusion visits; the adverse effect (AE) profile of each medication in a particular regimen and its potential for that to overlap with the patient's baseline comorbidities; and financial toxicity.^{21,22}

Historical Perspective of Evolution of Induction Therapy for TI MM

Induction regimens for TI patients over the past 20 years have evolved, primarily because of the incorporation (or replacement) of immunomodulatory drugs (IMiDs)²³⁻²⁵ or proteasome inhibitors (PIs)^{26,27} into the alkylating regimen of melphalan/prednisone.²⁸ In addition, the field has not only moved away from alkylator-based therapy to lenalidomide/dexamethasone (Rd)-based therapy,²⁹⁻³² but also away from a fixed number of

cycles to continuous therapy. More recently, monoclonal antibody (mAb) therapy has been incorporated into the upfront setting.³³⁻³⁵ This evolution is summarized in **Figure 1**. In this article, we review some of these key studies and discuss how the choice of initial therapy affects subsequent sequencing of therapies in the R/R setting.

Several points must be made about this patient population:

- The TI designation encompasses an inherently heterogeneous group of patients, because reasons for their transplant ineligibility vary. The reason for transplant ineligibility is typically an irreversible factor that plays into treatment decisions along the patient's journey.
- Several of the studies investigating treatment of ND TI MM used an

age cut-off of 65 years as a criterion. This differs significantly from the real-life practice in the United States, in which the age cut-off differs by center. Further, evidence suggests that even patients aged more than 70 years derive similar antimyeloma benefit from transplant as younger patients.⁵⁻⁷ We thus recommend that all ND patients be evaluated by a MM specialist at the nearest referral transplant center.

- As we highlight below, a limited number of patients with high-risk cytogenetics—primarily defined as deletion (del) (17p), translocation (t)(4;14), or t(14;16)—were included in many of these studies. The definition of high risk is evolving, however.³⁶

Agents under development and phase 1 studies are beyond the scope of this review.

Induction Regimens for Patients With TI ND MM:

Lenalidomide/PI combinations: Evidence for bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRd) as an induction regimen comes from the SWOG S0777 study, which enrolled patients with ND MM who were not necessarily TI but rather had no intent to proceed with upfront ASCT.³⁰ Patients were randomized to 6 months of induction with either VRd (eight 21-day cycles) or lenalidomide and dexamethasone (Rd; six 28-day cycles), followed by Rd maintenance. Patients 65 years or older comprised 43% of the study population. The study showed significant PFS and OS advantages for the triplet arm, with median PFS of 41 months vs 29 months for Rd (HR, 0.74; 96% Wald CI, 0.594-0.928; $P = .003$) and median OS not yet reached (> 84 months) versus 69 months for Rd (HR, 0.7; 96% Wald CI, 0.543-0.926).³⁷ The high-risk cytogenetic subgroup (~33%) did have a trend toward better outcomes with the triplet, but this was not statistically significant.

The open-label, phase 3 ENDUR-

ANCE trial compared VRd with carfilzomib (Kyprolis), lenalidomide, and dexamethasone (KRd) in patients who had no intention for immediate transplant.³¹

This study, then, enrolled a mixed population of patients, including fit TI patients as well as TE patients choosing not to undergo upfront ASCT. The median age of the study population was 65 years, with roughly 31% of patients in both arms 70 years or older. This study did not enroll patients with high-risk disease defined as t(14;16), t(14;20), or del (17p), but it did not exclude t(4;14). Enrolled patients received 36 weeks of induction followed by a second randomization to lenalidomide maintenance (2 years fixed duration vs until progression). At an interim analysis with a median follow-up of 9 months (interquartile range [IQR], 5-23), treatment with KRd did not improve PFS (34.6 months vs 34.4 months in the VRd arm) but did result in more toxicity as assessed by a composite of grade 3 to 5 cardiac, pulmonary, and renal treatment-emergent AEs (TEAEs) (16%, KRd, vs 5%, VRd; $P < .0001$).³¹ Not surprisingly, higher rates of peripheral neuropathy were observed in the VRd arm (8% grade ≥ 3 for VRd vs <1% for KRd). Results from the second randomization have not yet been reported. Given the caveats of primarily standard risk and mixed population of TE/TI patients, it is difficult to extrapolate these results to a frail TI patient population; however, the observed AE profiles of the 2 arms could be used to guide treatment decisions.

The phase 3 TOURMALINE-MM2 study enrolled TI MM patients to treatment with either ixazomib (Ninlaro), lenalidomide, and dexamethasone (IRd) or placebo plus Rd. Patients 75 years or older made up roughly 43% of both treatment arms, and approximately 40% of the study population had high-risk cytogenetics. The median PFS was 35.3 months for IRd vs 21.8 months for Rd (HR, 0.83; 95% CI, 0.676-1.018; $P = .73$).³² The most common AEs in the triplet arm (vs doublet) were diarrhea

(61.0% vs 46.1%, respectively), rash (56.2% vs 37.2%) and peripheral edema (48.6% vs 33.5%).³² This study may serve as an example of a result that is clinically significant (ie, improvement in median PFS of 13.5 months) but not statistically significant. As such, the IRD regimen could be an option for frail/unfit patients who are unable to travel for infusion appointments.

The “conventional” VRd regimen with twice-weekly bortezomib has a range of AEs, including thrombocytopenia and neutropenia, constitutional symptoms, infection, and neurologic effects.^{31,37} In real-world practice, dose adjustments are often needed in TI patients. The RVd-lite regimen was proposed to mitigate the toxicity seen with the conventional VRd regimen; it consists of 35-day cycles with lenalidomide (15 mg on days 1-21), weekly subcutaneous bortezomib, and dexamethasone. A phase 2 study of RVd-lite, in which TI ND patients received 9 cycles of RVd followed by 6 cycles of Rd, showed an overall response rate (ORR) of 86%. The median PFS was 41.9 months, and the median OS was not reached at 61 months follow-up.^{38,39} Although peripheral neuropathy was common (reported in 62% of patients), only 1 of 31 patients (3.2%) reported grade 3 symptoms. As comparators, the rates of grade 3 or greater neuropathy in the SWOG S0777 and ENDURANCE studies in the VRd arms were 33% and 8%, respectively.^{30,31} Patients with high-risk cytogenetics constituted a minority of the patients enrolled (12%).

In our practice, VRd is one of our preferred induction regimens for TI patients, with the caveat that once-weekly bortezomib/dexamethasone dosing is used. In addition, lenalidomide dosing is commonly reduced as well. With these modifications, we have found that even frail patients can tolerate this triplet therapy. We reserve KRd for fit patients who have significant baseline neuropathy without significant cardiovascular

Continued on page 178

WHEN HER2+ MBC PROGRESSES

PURSUE UNPRECEDENTED SURVIVAL

**TUKYSA + trastuzumab + capecitabine vs
placebo + trastuzumab + capecitabine¹**

Reduced risk of disease progression or death by 46%

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); $P < 0.00001$

Extended median OS by 4.5 months

Median OS: 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); $P = 0.0048$

The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.¹

TUKYSAhcp.com

Indication

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.

Select 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.

CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio;
MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival;
T-DM1 = ado-trastuzumab emtansine.

Please see full Important Safety Information on the following pages.

TUKYSA[®]
tucatinib
50 mg | 150 mg tablets

RAISING THE STANDARD FOR SURVIVAL

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*1

4.5 MONTH IMPROVEMENT IN MEDIAN OS

The most common adverse reactions in patients who received TUKYSA ($\geq 20\%$) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash¹

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 $>5 \times$ ULN, 6% had an AST increase $>5 \times$ ULN, and 1.5% had a bilirubin increase $>3 \times$ 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 $\geq 2\%$ 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 $\geq 1\%$ 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 $\geq 2\%$ of patients were hepatotoxicity (8%) and diarrhea (6%).

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

In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

PRIMARY ENDPOINT*

PFS

46% reduction in the risk of disease progression or death[†]

- HR = 0.54 (95% CI: 0.42-0.71); $P < 0.00001$
- Median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.6 months (95% CI: 4.2-7.1) in the control arm

EXPLORATORY ANALYSIS*†

PFS AT 12 MONTHS

~3x as many patients were progression-free²

TUKYSA ARM	vs	CONTROL ARM
33%		12%
(33.1%; 95% CI: 26.6-39.7)		(12.3%; 95% CI: 6.0-20.9)

*Study design: HER2CLIMB was a randomized (2:1), double-blind, placebo-controlled trial of 612 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm; n = 410) or placebo + trastuzumab + capecitabine (control arm; n = 202). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause). PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.¹

†This exploratory analysis is descriptive only. These are estimates and not exact numbers. HER2CLIMB was not powered to assess a statistical difference between treatment groups at this time point.

BICR = blind 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; RECIST = Response Evaluation Criteria in Solid Tumors.

Lab Abnormalities

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

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 (CL_{cr} < 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. Murthy RK, Loi S, O'Kines A, et al. Supplemental appendix for: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382:597-609.

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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/m² 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
Diarrhea¹	
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 reactions¹	
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.

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Treatment Considerations for Transplant-Ineligible Multiple Myeloma

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comorbidities. IRd may be a reasonable option for select patients, particularly those with transportation issues. As noted above, the various studies have included disparate numbers of cycles of induction therapy. Our approach is to have the goal of continuous therapy (ie, treatment until progression), with dose reductions or drug discontinuations based on patient- and disease-specific factors, including toxicity, cytogenetic risk, and disease response.

PI/Alkylator combinations: The phase 3 CLARION study randomized 955 patients with ND MM who were TI to carfilzomib, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP; 9 cycles).²⁷ The median age in both treatment arms was 72 years, with more than 30% of patients in both arms 75 years or older. Patients with higher-risk cytogenetics constituted a minority in both the KMP (11.3%) and VMP arms (14.0%). No statistically significant difference was observed in median PFS (22.3 vs 22.1 months for KMP and VMP, respectively; HR, 0.9; 95% CI, 0.746-1.101; $P = .159$). This trial highlighted the differences in the toxicity profiles of bortezomib vs carfilzomib, with peripheral neuropathy of any grade more common with bortezomib (13.6% vs 1.7%, respectively), while both cardiovascular complications (hypertension, cardiac failure) of any grade and acute kidney injury (AKI) were more common in the KMP arm (hypertension, 21.9% vs 6.8%; cardiac failure, 6.5% vs 2.1%; AKI, 6.3% vs 2.8%). In the United States, the use of oral melphalan remains uncommon, thus this study was not practice-changing. However, this study, in conjunction with the ENDURANCE study, provides evidence that carfilzomib is not superior to bortezomib, at least in the

ND nontransplant setting, and that the 2 agents have a notably different AE profile, which could impact the decision to recommend one regimen over the other for specific patients.

As noted, oral melphalan is rarely used in the United States, in part due to concerns related to stem cell toxicity.⁴⁰ VCD—bortezomib, cyclophosphamide, dexamethasone—substitutes cyclophosphamide for melphalan; however, evidence for the use of this combination in the TI setting is limited to retrospective reports and phase 2 studies. The phase 2 EVOLUTION study showed an ORR of 63% for VCD and 82% for VCD-modified (mod; in which an additional dose of cyclophosphamide was added at day 15).⁴¹ The corresponding 1-year PFS was 93% and 100%, respectively. The major grade 3 or greater AE was neutropenia (30%, VCD; 24%, VCD-mod); however, AEs leading to discontinuation of treatment were 12% for the VCD arm and 6% for the VCD-mod arm. Patients were enrolled in this study regardless of their transplant eligibility.⁴¹ Similarly high response rates were seen in a retrospective multicenter analysis⁴² and in a smaller phase 2 study of patients who proceeded to transplant.⁴³ This regimen can be a reasonable option in frail patients with unstable renal dysfunction or in patients who have an absolute contraindication to anticoagulation and therefore cannot receive lenalidomide.

Daratumumab-containing induction regimens: The anti-CD38 mAb daratumumab has found widespread use in the R/R setting; subsequently, investigators have begun to incorporate this agent into the ND setting. In the phase 3 ALCYONE trial, TI patients were randomized to VMP with daratumumab (Darzalex; D-VMP) or without.^{35,44} The median age was 71 years; 38% were aged at least 75

years. Patients received 9 cycles of induction followed by either observation (VMP arm) or single-agent daratumumab (D-VMP). The quadruplet resulted in a significant PFS advantage (HR, 0.42; 95% CI, 0.34-0.51; $P = .0001$) and OS advantage (HR, 0.6; 95% CI, 0.46-0.80; $P = .003$).⁴⁴ The high-risk cytogenetics subgroup comprised 14% of the study population. While an ORR benefit was observed in the quadruplet arm in this subgroup (odds ratio, 4.45; 95% CI, 1.32-15.01; $P = .0111$), there was not an OS advantage (HR, 0.91 95% CI, 0.5-1.65). Pneumonia was the most common grade 3 or 4 AE (11%, D-VMP vs 4.2%, VMP). Given the uncommon use of melphalan as part of an induction regimen in the United States, the results of this study were not practice-changing. However, this study is noteworthy as it provides some insight into the potential benefit of single-agent daratumumab maintenance post induction in the non-transplant setting.

The phase 3 MAIA trial randomized ND TI patients (based on age ≥ 65 years) or presence of comorbidities) to daratumumab, lenalidomide, and dexamethasone (DRd) vs Rd.³³ Treatment was continued until disease progression or unacceptable toxicity. With a median follow-up of 28 months, the triplet arm vs the doublet had a significantly longer PFS (median PFS, not reached vs 31.9 months, respectively; HR, 0.56; 95% CI, 0.43-0.73; $P < .001$), a higher ORR (92.9% vs 81.3%; $P < .001$), and a higher depth of response based on MRD negativity (24.2% vs 7.3% [10^{-5} using next-generation sequencing]; $P < .001$). The most common AE of any grade was infection (86.3% vs 73.4%, respectively), and grade 3 or 4 neutropenia was seen in 50.0% of patients in the triplet arm vs 35.3% in the doublet arm. Approximately 15% of patients had high-risk cytogenetics and the PFS benefit in the triplet arm was not statistically significant in this subgroup (HR, 0.85; 95% CI, 0.44-1.65). Of note, intra-

venous daratumumab was used in this study. In real-world practice, subcutaneous daratumumab has now become the default option given the similar efficacy, shorter administration time, and lower incidence of infusion reactions when compared with the intravenous formulation (13% vs 34%, respectively).⁴⁵

We find the DRd regimen useful in patients with preexisting neuropathy where the use of bortezomib is of concern. The use of the DRd regimen in patients who are at a significantly higher risk of pneumonia or infections (eg, due to underlying chronic lung disease) should be coupled with caution, given the higher incidence of pneumonia and neutropenia. When compared with the SWOG S0777 trial, the MAIA trial had a significantly older population, with 99% of patients aged more than 65 years and 44% 75 years or older. Furthermore, a recent report⁴⁶ of patient-reported outcomes (PROs) for patients in the MAIA trial from enrollment through cycle 12 showed that DRd resulted in faster and clinically meaningful improvements in PROs regardless of age or depth of treatment response, with a greater proportion of patients showing improvement in fatigue and physical functioning, and greater reductions in pain, compared with Rd. We thus consider this an appropriate option even in patients who are frail. The other daratumumab combinations (daratumumab plus bortezomib, thalidomide, and dexamethasone [dara-VTD]⁴⁷ and dara-VRd⁴⁸) were studied in the TE population, and we thus restrict the use of daratumumab in the upfront treatment of TI population to the DRd regimen.

Very few studies have specifically focused on the unfit or frail patient population. The phase 2 HOVON 143 study evaluated the combination of daratumumab, ixazomib, and dexamethasone in patients with ND MM who were unfit or frail per the IMWG frailty index.³⁴ Patients received 9 cycles of therapy followed by maintenance with daratu-

mumab-ixazomib for up to 2 years. The combination showed an ORR of 87% in unfit patients and 78% in frail patients, with a 9-month PFS rate of 78% and 61%, respectively, based on the data reported from the first 23 patients enrolled to each group.⁴⁹ Hematologic toxicity was mainly in the form of neutropenia (grade 4, 4% in unfit and 13% in frail) and thrombocytopenia (grade 4, 0% in unfit and 4% in frail). The main nonhematologic toxicity reported was grade 3 infections occurring in 9% of both unfit and frail patients. Early death rate (in 3 months or less) was 0% in the unfit arm and 12% in the frail arm. As the data for this combination come only from a phase 2 study, this regimen should be considered for treatment of ND TI MM patients only in scenarios where DRd or VRd are contraindicated.

Maintenance Post Induction

Lenalidomide: While maintenance therapy has been shown to prolong PFS and OS in the posttransplant setting,⁵⁰ only a PFS benefit has thus far been shown in the TI setting.⁵¹ The randomized phase 3 Myeloma XI trial had an adaptive design with 3 potential randomizations: induction treatment with allocation by transplant eligibility; intensification treatment with allocation by response to induction; and maintenance treatment.⁵¹ Maintenance was continued until progressive disease or development of unacceptable toxicity. In the TI patients, lenalidomide maintenance significantly improved PFS vs observation (median, 26 vs 11 months; HR, 0.44; 95% CI, 0.37-0.53; $P < .0001$) but not OS (3-year OS, 66.8% vs 69.8%; HR, 1.02; 95% CI, 0.80-1.29; $P = .88$). For the entire study population, the median duration of lenalidomide maintenance therapy was 18 cycles (IQR, 6-30) and 69% of patients required dose modifications. Overall in the study, the most common grade 3/4 hematological AEs associated with lenalidomide maintenance were neutropenia (33%) and

thrombocytopenia (7%), but information was not provided for the TI subgroup specifically.

The SWOG S0777 study incorporated maintenance Rd; however, the study population was not truly TI—as reviewed above—and the same limitation applies to the ENDURANCE trial, in which lenalidomide maintenance is being evaluated for 2 years vs indefinitely. In patients who start VRd and later develop neuropathy, it is reasonable to continue lenalidomide (with or without dexamethasone) for as long as it is tolerated or effective. The above-mentioned studies do not address the scenario of initiating lenalidomide maintenance following induction that lacks an IMiD, and we would not recommend that approach. Instead, for patients who did not receive lenalidomide with induction, we would recommend a lenalidomide-containing regimen at the time of relapse (as discussed in greater detail below).

Ixazomib: The phase 3 Tourmaline MM4 study randomized TI patients who had achieved a partial response or better, after standard induction therapy lasting 6 to 12 months, to receive either ixazomib or placebo for a total of 24 months. Approximately 60% of patients had received an induction regimen containing bortezomib (VMP, VCD, or VTd). The median age was 72 years; more than 37% of patients in the ixazomib arm were 75 years or older. Ixazomib maintenance resulted in a 34% reduced risk of progression or death compared with placebo (median PFS, 17.8 vs 9.8 months; HR, 0.659; 95% CI, 0.54-0.80; $P < .001$). A PFS benefit was also observed in a prespecified subgroup analysis of patients 75 years or older. Approximately 30% of patients in the ixazomib arm developed a TEAE requiring dose reduction.⁵² Ixazomib offers the advantage of an oral agent that can be given once weekly for defined period of 24 months, but whether maintenance beyond 24 months provides additional benefit is unknown.

Daratumumab: Data from the

FIGURE 2. First- and Second-Line Therapy Choices in the Newly Diagnosed Transplant-Ineligible Setting

Two of the most commonly used induction regimens are VRd and DRd. However, the decisions made after initiating either one of these triplet combinations affect the subsequent choice of therapy in the second-line setting. Common treatment decisions following initiation of induction therapy are shown, followed by some of the preferred second-line options.

C, cyclophosphamide; D, daratumumab; d, dexamethasone; elo, elotuzumab; I, ixazomib; isa, isatuximab; K, carfilzomib; M, melphalan; P, prednisone; R, lenalidomide; seli, selinexor; V, bortezomib.

ALCYONE trial showed the activity of single-agent daratumumab as a maintenance strategy post induction with VMP.^{35,44} Evaluation of the PFS curves from this study reveals that while there is separation of the curves (in favor of the daratumumab-containing arm) during induction (12-month PFS, 87% vs 76%),³⁵ the separation widened during the daratumumab-vs-observation portion of the study (36-month PFS, 51% vs 19%).⁴⁴ The most common grade 3/4 AEs reported during daratumumab maintenance included anemia (4%), pneumonia (4%), hypertension (3%), and neutropenia (2%).⁴⁴ However, extrapolation from that study to use of single-agent daratumumab maintenance following other daratumumab-containing regimens is not routinely recommended at this time. For patients who initiated DRd induction and subsequently become intolerant to lenalidomide, it may be reasonable to continue daratumumab (with or without dexamethasone) until time of progression.

Relapsed/Refractory Disease

More than a third of patients with MM

never receive a second-line therapy,⁵³ and even when they do, shorter durations of response are seen with subsequent lines of therapy.^{54,55} Factors that should be kept in mind when selecting a treatment strategy in the subsequent lines of therapy include the context of the relapse/progression, the patient’s fitness and comorbidities, tolerance to previous agents, and the potential for overlapping toxicities with agents in prior lines of therapy. For patients with an asymptomatic biochemical relapse and in the absence of extramedullary disease, a watch-and-wait approach can be reasonable and is in line with recommendations from the IMWG, provided that the rise in paraprotein level is slow.⁵⁶ While several phase 3 studies conducted over the past decade have established the superiority of (primarily) triplet combinations over doublets in the R/R setting, it is rare for studies to focus specifically on the TI population. Thus, modifications to dosing/schedule may be required to ensure tolerability of these multiagent regimens in unfit/frail patients; such modifications have unknown consequences on efficacy. Below, we discuss some general concepts

related to sequencing in the R/R setting as well as some of the recent studies that have reported outcomes based on frailty. In TI patients in the United States, similar to the TE population, it is becoming increasingly common for their disease to be lenalidomide-refractory at the time of first relapse. As noted above, the majority of the commonly used induction regimens include lenalidomide. Thus, while several randomized phase 3 studies have demonstrated the superiority of lenalidomide-containing triplets over Rd in early lines of relapse (summarized in the **Table**), these studies are not relevant for patients progressing on lenalidomide. In that context, regimens containing PIs or pomalidomide (Pomalyst) should be considered (**Figure 2**). However, multiple options exist, and aside from trying to perform cross-trial comparisons, it is not possible with the existing data to determine which option should be prioritized. Instead, we recommend an individualized approach which encompasses the induction (plus/minus maintenance) regimen previously received; the patient’s disease characteristics (eg, if rapid progression on lenalidomide, would favor

TABLE. Summary of Recent Phase 3 Studies in Relapsed/Refractory Multiple Myeloma

Study	Intervention arm (n)	Control arm (n)	Prior lines of the therapy	Age		Median PFS (mos)		PFS HR (95% CI)	PFS HR for older age group	Notable AEs of any grade more common in intervention arm (%)
				Median (years)	Older age (years) group (%)	Intervention	Control			
ASPIRE⁵⁸	KRd (396)	Rd (396)	1-3	64	≥ 65 (50%)	26.3	17.6	0.69 (0.57-0.83); <i>P</i> = .0001	0.85 (0.65-1.11)	Diarrhea (42.3%), hypokalemia (27.6%), hypertension (14.3%), cardiac failure (6.4%)
ELOQUENT-2⁶⁵	elo-Rd (321)	Rd (325)	1-3	66	≥ 65 (57%)	19.4	14.9	0.70 (0.57-0.85); <i>P</i> < .001	0.65 (0.50-0.85)	Thrombocytopenia (84%), infections (81%), diarrhea (47%), infusion reactions (10%)
TOURMALINE-MM1⁶⁶	IRd (360)	plac-Rd (362)	1-3	66	> 75 (15%)	20.6	14.7	0.74 (0.59-0.94); <i>P</i> = .01	0.87 (CI NA)	Thrombocytopenia (31%), diarrhea (45%), constipation (35%), nausea (29%), peripheral neuropathy (27%)
CANDOR⁶⁷	DKd (312)	Kd (154)	1-3	64	≥ 65 (49%)	Not reached	15.8	0.63 (0.46-0.85); <i>P</i> = .0027	0.76 (0.48-1.22)	Thrombocytopenia (37%), diarrhea (31%), peripheral neuropathy (17%), pneumonia (18%)
IKEMA⁶⁸	isa-Kd (179)	Kd (123)	1-3	64	≥ 65 (49%)	Not reached	19.15	0.531 (0.318-0.889); <i>P</i> = .0007	NA	Infusion reactions (45.8%), neutropenia (19.2% at grade ≥3), pneumonia (16.4% at grade ≥3)
PANORAMA1⁶⁹	pan-Vd (387)	plac-Vd (381)	1-3	63	≥ 65 (42%)	11.99	8.31	0.63 (0.52-0.76); <i>P</i> < .0001	0.72 (0.53-0.96)	Diarrhea (68%), asthenia or fatigue (57%), nausea (36%), decreased appetite (28%)
OPTIMISM⁷⁰	PVd (281)	Vd (278)	1-3	67	> 75 (17%)	11.2	7.1	0.61 (0.49-0.77); <i>P</i> < .0001	0.78 (0.46-1.32)	Neutropenia (46%), peripheral neuropathy (48%), peripheral edema (34%), constipation (37%)
BOSTON⁷¹	seli-Vd (195)	Vd (207)	1-3	67	≥ 65 (60%)	13.93	9.46	0.70 (0.53-0.93); <i>P</i> = .0075	0.55 (0.37-0.83)	Thrombocytopenia (60%), anemia (36%), nausea (50%), vomiting (21%)
ICARIA-MM⁶⁰	isa-Pd (154)	Pd (153)	> 2	67	≥ 75 (20%)	11.5	6.5	0.596 (0.44-0.81); <i>P</i> = .001	0.48 (0.24-0.95)	Infusion reactions (38%), upper respiratory tract infections (28%), bronchitis (24%), nausea (15%)
APOLLO⁷²	DPd (151)	Pd (153)	≥ 1	67	≥ 75 (18%)	12.4	6.9	0.63 (0.47-0.85); <i>P</i> = .0018	NA	Neutropenia (70%), infections (70%), infusion reactions (5%), diarrhea (22%)

D, daratumumab; d, dexamethasone; elo, elotuzumab; I, ixazomib; isa, isatuximab; K, carfilzomib; NA, not available; pan, panobinostat; R, lenalidomide; seli, selinexor; V, bortezomib.

a PI-based combination over pomalidomide-based); comorbidities (eg, if severe cardiac disease, would prefer not to use carfilzomib; if severe neuropathy, would prefer not to use a bortezomib-containing regimen); and other factors such as route/administration schedule. If a patient did not receive lenalidomide with induction, or has been off lenalidomide for an extended period of time prior to progression (eg, 6 months), then it would be reasonable to choose a lenalidomide-based combination. Likewise, the choice of third-line therapy will be dictated in large part by the decisions regarding first-line and second-line treatments. Further, in the older/unfit/frail patient population, comorbidities along with TEAEs may be more of an issue, preventing the consistent delivery of combination therapies.

Therefore, we cannot recommend a one-size-fits-all approach to this patient population, and that means that it is difficult to devise simple treatment algorithms. Figure 2 outlines several potential pathways from induction to second-line therapy, taking into account that while VRd and DRd may be 2 of the most common induction regimens for TI patients, one can take multiple paths after starting these triplet therapies. While the intent may be to continue all 3 agents until progression, in the real-world situation, this approach may not be possible, and dropping 1 (or 2) agent(s), or even stopping all therapy and monitoring, may be necessary because of toxicities or other emerging health problems. At all treatment decision points, referral to a MM specialist is encouraged; new treatment paradigms are

being rapidly developed and clinical trial options may be appropriate.

Analysis of frailty in the R/R setting: A post hoc analysis⁵⁷ of patients with R/R MM treated with carfilzomib in 3 phase 3 trials—ASPIRE (KRd vs Rd),⁵⁸ ENDEAVOR (Kd vs Vd),⁵⁹ and ARROW (once-weekly Kd vs twice-weekly Kd)⁵⁹—showed overall consistent efficacy and safety profiles across patient subgroups, regardless of frailty status. We thus consider a carfilzomib-containing regimen (such as dara-Kd) to be a reasonable second-line option in patients who are considered lenalidomide refractory (Figure 2). The phase 3 ICARIA-MM study⁶⁰ enrolled patients with R/R MM who had received 2 or more prior lines of therapy including lenalidomide and a PI. A regimen of isatuximab, pomalidomide, and dexamethasone (isa-Pd) was compared with a control arm of Pd, and treatment was continued until disease progression or unacceptable toxicity. The triplet arm had a superior PFS (median PFS, 11.5 vs 6.5 months for Pd; HR, 0.596; 95% CI, 0.44-0.81; $P = .001$).⁶⁰ A post hoc analysis was performed looking at differences in outcomes and toxicity based on patients' frailty scores according to the modified CCI stratified into fit, intermediate, and frail categories.⁶¹ This analysis revealed that patients in the frail group had similar outcomes and AE profiles to the overall study population. Finally, in a recent subgroup analysis of the phase 3 Boston study, which randomized patients to selinexor (Xpovio)/bortezomib/dexamethasone vs bortezomib/dexamethasone, an improvement in ORR and PFS was observed in those aged more than 65 years (60% of the study

population) as well as those considered frail (44% of the study population) who received triplet therapy.⁶²

Conclusions

Significant advances have been made in the treatment of MM. Currently, the 2 triplet combinations of choice for ND TI patients are VRd (using weekly bortezomib) and DRd. However, the optimal induction treatment for frail or unfit patients remains to be determined. Particularly in the R/R setting, the results of phase 3 randomized studies may not always be applicable to the TI population, necessitating extrapolation of data obtained from a predominantly younger/TE population, with possibly different disease biology and toxicity profiles.⁶³ In acknowledging our knowledge gaps in this territory, we highlight that the best answer for those patients—whenever available—is enrollment in a clinical trial and consultation with a MM specialist and geriatric oncologist. Furthermore, we advocate for more routine incorporation of geriatric assessment and frailty screening into both the clinical trial and nontrial settings (eg, as recently demonstrated by Nathwani et al⁶⁴), with the goal of optimizing treatment decisions. ■

FINANCIAL DISCLOSURE: RAE declares that he has no conflicts of interest that might be relevant to the contents of this manuscript. SAH has served as a consultant for Bristol Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Oncocept, Sanofi, Sorrento, and has received research funding from Oncocept.

➤ For full reference list, visit cancernetwork.com/Elnair_4.21

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Let **LENVIMA®** **change** the way you **view** treatment in **second-line advanced RCC**

- 14.6-month median PFS (95% CI: 5.9-20.1) with LENVIMA + everolimus vs 5.5 months (95% CI: 3.5-7.1) with everolimus alone (HR: 0.37 [95% CI: 0.22-0.62])¹
 - 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm

LENVIMA + everolimus is the only TKI-mTOR inhibitor combination following anti-angiogenic therapy in advanced RCC^{1,2}

INDICATION

LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

SELECTED SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC, hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC, hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥ 160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥ 100 mmHg. In HCC, hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

Cardiac Dysfunction. Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials. Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity. Across clinical studies enrolling 1,327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic

failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Renal Failure or Impairment. Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus-treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Proteinuria. In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria $\geq 2+$ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Diarrhea. Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus-treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

14.6-month median PFS: with LENVIMA + everolimus vs everolimus alone¹

- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm¹
 - 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus
 - Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus
- The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs with an observed HR of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm¹
- Study 205 randomized 153 patients with advanced or metastatic renal cell carcinoma who had previously received anti-angiogenic therapy 1:1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (≤ 13 g/dL vs >13 g/dL for males and ≤ 11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥ 10 mg/dL vs <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other efficacy outcome measures included overall survival and objective response rate¹

RCC=renal cell carcinoma; PFS=progression-free survival; TKI=tyrosine kinase inhibitor; mTOR=mammalian target of rapamycin; CI=confidence interval; HR=hazard ratio.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved

or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus-treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

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Please see all Selected Safety Information throughout and accompanying brief summary of full prescribing information.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

Across clinical studies of 1,823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus-treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤ 0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus-treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus-treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus, and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Adverse Reactions

In RCC, the most common adverse reactions ($\geq 30\%$) observed in LENVIMA + everolimus-treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions ($\geq 5\%$) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions ($\geq 5\%$) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with RCC or DTC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

No dose adjustment is recommended for patients with DTC or RCC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe hepatic impairment. Reduce the dose for patients with DTC or RCC and severe hepatic impairment.

Please see Brief Summary on the following pages.

References: 1. LENVIMA [package insert]. Woodcliff Lake, NJ: Eisai Inc. 2. AFINITOR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.

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LENVIMA® (lenvatinib) capsules BRIEF SUMMARY – See package insert for full prescribing information. INDICATIONS AND USAGE

Differentiated Thyroid Cancer LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

Renal Cell Carcinoma LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

Hepatocellular Carcinoma LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

DOSAGE AND ADMINISTRATION

Important Dosage Information

- Reduce the dose for certain patients with renal or hepatic impairment
- Take LENVIMA once daily, with or without food, at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration

Recommended Dosage for Differentiated Thyroid Cancer (DTC) The recommended dosage of LENVIMA is 24 mg orally once daily until disease progression or until unacceptable toxicity.

Recommended Dosage for Renal Cell Carcinoma (RCC) The recommended dosage of LENVIMA is 18 mg in combination with 5 mg everolimus orally once daily until disease progression or until unacceptable toxicity.

Refer to everolimus prescribing information for recommended everolimus dosing information.

Recommended Dosage for Hepatocellular Carcinoma (HCC) The recommended dosage of LENVIMA is based on actual body weight:

- 12 mg for patients greater than or equal to 60 kg or
- 8 mg for patients less than 60 kg

Take LENVIMA orally once daily until disease progression or until unacceptable toxicity.

Dosage Modifications for Adverse Reactions Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage reductions of LENVIMA for adverse reactions.

Table 1: Recommended Dosage Modifications for LENVIMA for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications for LENVIMA
Hypertension	Grade 3	<ul style="list-style-type: none">• Withhold for Grade 3 that persists despite optimal antihypertensive therapy.• Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	<ul style="list-style-type: none">• Permanently discontinue.
Cardiac Dysfunction	Grade 3	<ul style="list-style-type: none">• Withhold until improves to Grade 0 to 1 or baseline.• Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	<ul style="list-style-type: none">• Permanently discontinue.
Arterial Thromboembolic Event	Any Grade	<ul style="list-style-type: none">• Permanently discontinue.
Hepatotoxicity	Grade 3 or 4	<ul style="list-style-type: none">• Withhold until improves to Grade 0 to 1 or baseline.• Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity.• Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	<ul style="list-style-type: none">• Withhold until improves to Grade 0 to 1 or baseline.• Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria	2 g or greater proteinuria in 24 hours	<ul style="list-style-type: none">• Withhold until less than or equal to 2 grams of proteinuria per 24 hours.• Resume at a reduced dose.• Discontinue for nephrotic syndrome.
Gastrointestinal Perforation	Any Grade	<ul style="list-style-type: none">• Permanently discontinue.
Fistula Formation	Grade 3 or 4	<ul style="list-style-type: none">• Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	<ul style="list-style-type: none">• Withhold until improves to less than or equal to 480 ms or baseline.• Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	<ul style="list-style-type: none">• Withhold until fully resolved.• Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions	Persistent or intolerable Grade 2 or 3 adverse reaction	<ul style="list-style-type: none">• Withhold until improves to Grade 0 to 1 or baseline.• Resume at reduced dose.• Permanently discontinue.
	Grade 4 laboratory abnormality	
Other Adverse Reactions	Grade 4 adverse reaction	<ul style="list-style-type: none">• Permanently discontinue.

*National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Table 2: Recommended Dosage Reductions of LENVIMA for Adverse Reactions

Indication	First Dosage Reduction To	Second Dosage Reduction To	Third Dosage Reduction To
DTC	20 mg once daily	14 mg once daily	10 mg once daily
RCC	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
<ul style="list-style-type: none">• Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
<ul style="list-style-type: none">• Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue

When administering LENVIMA in combination with everolimus for the treatment of renal cell carcinoma, reduce the LENVIMA dose first and then the everolimus dose for adverse reactions of both LENVIMA and everolimus. Refer to the everolimus prescribing information for additional dose modification information.

Dosage Modifications for Severe Renal Impairment The recommended dosage of LENVIMA for patients with DTC and RCC and severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is:

- Differentiated thyroid cancer: 14 mg orally once daily
- Renal cell carcinoma: 10 mg orally once daily

Dosage Modifications for Severe Hepatic Impairment The recommended dosage of LENVIMA for patients with DTC or RCC and severe hepatic impairment (Child-Pugh C) is:

- Differentiated thyroid cancer: 14 mg taken orally once daily
- Renal cell carcinoma: 10 mg taken orally once daily

Preparation and Administration LENVIMA capsules can be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, put capsules into 1 tablespoon of water or apple juice without breaking or crushing the capsules. Leave the capsules in the water or apple juice for at least 10 minutes. Stir for at least 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swirl the contents a few times and swallow the water or apple juice.

DOSAGE FORMS AND STRENGTHS

Capsules:

- 4 mg: yellowish-red body and yellowish-red cap, marked in black ink with “E” on cap and “LENV 4 mg” on body.
- 10 mg: yellow body and yellowish-red cap, marked in black ink with “E” on cap and “LENV 10 mg” on body.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Hypertension Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 16 days in SELECT and 26 days in REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred <1% in SELECT and Grade 4 hypertension was not reported in REFLECT.

In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure ≥160 mmHg occurred in 29% of patients and diastolic blood pressure ≥100 mmHg occurred in 21%.

Serious complications of poorly controlled hypertension have been reported.

Control blood pressure prior to initiating LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity.

Cardiac Dysfunction Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC or HCC, Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypokinesia, or decrease in left or right ventricular ejection fraction of more than 20% from baseline) occurred in 3% of LENVIMA-treated patients.

Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Arterial Thromboembolic Events Among patients receiving LENVIMA or LENVIMA with everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in Study 205 (RCC), 2% of patients in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Permanently discontinue LENVIMA following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients.

In REFLECT (HCC), hepatic encephalopathy (including hepatic encephalopathy, encephalopathy, metabolic encephalopathy, and hepatic coma) occurred in 8% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of LENVIMA-treated patients and 2% of sorafenib-treated patients. Grade 3 to 5 hepatic failure occurred in 3% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Two percent of patients discontinued LENVIMA and 0.2% discontinued sorafenib due to hepatic encephalopathy and 1% of patients discontinued lenvatinib or sorafenib due to hepatic failure.

Monitor liver function prior to initiating LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Renal Failure or Impairment Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients receiving LENVIMA in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatality in each study.

In Study 205 (RCC), renal impairment or renal failure occurred in 18% of patients receiving LENVIMA with everolimus, including Grade 3 in 10% of patients.

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA for renal failure or impairment based on severity.

Proteinuria Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of LENVIMA-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus.

Monitor for proteinuria prior to initiating LENVIMA and periodically during treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24-hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Diarrhea Of the 737 patients treated with LENVIMA in SELECT (DTC) and REFLECT (HCC), diarrhea occurred in 49% of patients, including Grade 3 diarrhea in 6%.

In Study 205 (RCC), diarrhea occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 in 19%. Diarrhea was the most frequent cause of dose interruption/reduction and diarrhea recurred despite dose reduction.

Promptly initiate management of diarrhea. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Fistula Formation and Gastrointestinal Perforation Of 799 patients treated with LENVIMA or LENVIMA with everolimus in SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), fistula or gastrointestinal perforation occurred in 2%.

Permanently discontinue LENVIMA in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula.

QT Interval Prolongation In SELECT (DTC), QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In Study 205 (RCC), QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA with everolimus and QTc interval >500 ms occurred in 6%. In REFLECT (HCC), QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose of LENVIMA upon recovery based on severity.

Hypocalcemia In SELECT (DTC), Grade 3 to 4 hypocalcemia occurred in 9% of patients receiving LENVIMA. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation, with or without dose interruption or dose reduction.

In Study 205 (RCC), Grade 3 to 4 hypocalcemia occurred in 6% of patients treated with LENVIMA with everolimus. In REFLECT (HCC), Grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients.

Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome Across clinical studies of 1823 patients who received LENVIMA as a single agent, reversible posterior leukoencephalopathy syndrome (RPLS) occurred in 0.3%.

Confirm the diagnosis of RPLS with magnetic resonance imaging. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events Serious including fatal hemorrhagic events can occur with LENVIMA. Across SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), hemorrhagic events of any grade occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria.

In SELECT, Grade 3 to 5 hemorrhage occurred in 2% of patients receiving LENVIMA, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In Study 205, Grade 3 to 5 hemorrhage occurred in 8% of patients receiving LENVIMA with everolimus, including 1 fatal cerebral hemorrhage. In REFLECT, Grade 3 to 5 hemorrhage occurred in 5% of patients receiving LENVIMA, including 7 fatal hemorrhagic events.

Serious tumor related bleeds, including fatal hemorrhagic events, occurred in patients treated with LENVIMA in clinical trials and in the post-marketing setting. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g. carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA based on the severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction LENVIMA impairs exogenous thyroid suppression. In SELECT (DTC), 88% of all patients had a baseline thyroid stimulating hormone (TSH) level <0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients.

Grade 1 or 2 hypothyroidism occurred in 24% of patients receiving LENVIMA with everolimus in Study 205 (RCC) and in 21% of patients receiving LENVIMA in REFLECT (HCC). In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 70% of patients receiving LENVIMA in REFLECT and 60% of patients receiving LENVIMA with everolimus in Study 205.

Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing Impaired wound healing has been reported in patients who received LENVIMA.

Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment.

Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Hypertension
- Cardiac Dysfunction
- Arterial Thromboembolic Events
- Hepatotoxicity
- Renal Failure and Impairment
- Proteinuria
- Diarrhea
- Fistula Formation and Gastrointestinal Perforation
- QT Interval Prolongation
- Hypocalcemia
- Reversible Posterior Leukoencephalopathy Syndrome
- Hemorrhagic Events
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction
- Impaired Wound Healing
- Osteonecrosis of the Jaw (ONJ)

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

The data in the Warnings and Precautions reflect exposure to LENVIMA as a single agent in 261 patients with DTC (SELECT) and 476 patients with HCC (REFLECT), and to LENVIMA with everolimus in 62 patients with RCC (Study 205). Safety data obtained in 1823 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize the risks of serious adverse reactions. Among the 1823 patients who received LENVIMA as a single agent, the median age was 61 years (20 to 89 years), the dose range was 0.2 mg to 32 mg daily, and the median duration of exposure was 5.6 months.

The data below reflect exposure to LENVIMA in 799 patients enrolled in randomized, active-controlled trials (REFLECT; Study 205) or a randomized, placebo-controlled trial (SELECT). The median duration of exposure to LENVIMA across these three studies ranged from 6 to 16 months. The demographic and exposure data for each clinical trial population are described in the subsections below.

Differentiated Thyroid Cancer

The safety of LENVIMA was evaluated in SELECT, in which patients with radioactive iodine-refractory differentiated thyroid cancer were randomized (2:1) to LENVIMA (n=261) or placebo (n=131). The median treatment duration was 16.1 months for LENVIMA. Among 261 patients who received LENVIMA, median age was 64 years, 52% were females, 80% were White, 18% were Asian, and 2% were Black; and 4% were Hispanic/Latino.

The most common adverse reactions observed in LENVIMA-treated patients (≥30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA; 18% of patients discontinued LENVIMA for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 3 presents adverse reactions occurring at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the study.

Table 3. Adverse Reactions Occurring in Patients with a Between-Group Difference of ≥5% in All Grades or ≥2% in Grades 3 and 4 in SELECT (DTC)

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vascular				
Hypertension ^a	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis ^b	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain ^c	31	2	11	1
Constipation	29	0.4	15	1
Oral pain ^d	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General				
Fatigue ^e	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue				
Arthralgia/myalgia ^f	62	5	28	3
Metabolism and Nutrition				
Decreased appetite	54	7	18	1
Decreased weight	51	13	15	1
Dehydration	9	2	2	1
Nervous System				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash ^g	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric				
Insomnia	12	0	3	0
Infections				
Urinary tract infection	11	1	5	0
Dental and oral infections ^h	10	1	1	0
Cardiac				
Electrocardiogram QT prolonged	9	2	2	0

^a Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure

^b Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation

^c Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain

^d Includes oral pain, glossodynia, and oropharyngeal pain

^e Includes asthenia, fatigue, and malaise

^f Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia

^g Includes macular rash, maculo-papular rash, generalized rash, and rash

^h Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection

Clinically important adverse reactions occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of <5% were pulmonary embolism (3%, including fatal reports vs 2%, respectively) and osteonecrosis of the jaw (0.4% vs 0%, respectively).

Laboratory abnormalities with a difference of ≥2% in Grade 3-4 events and at a higher incidence in the LENVIMA arm are presented in Table 4.

Table 4: Laboratory Abnormalities with a Difference of ≥2% in Grade 3-4 Events and at a Higher Incidence in the LENVIMA Arm^{a,b} in SELECT (DTC)

Laboratory Abnormality	LENVIMA 24 mg	Placebo
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypocalcemia	9	2
Hypokalemia	6	1
Increased aspartate aminotransferase (AST)	5	0
Increased alanine aminotransferase (ALT)	4	0
Increased lipase	4	1
Increased creatinine	3	0
Hematology		
Thrombocytopenia	2	0

^a With at least 1 grade increase from baseline
^b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=253 to 258), Placebo (n=129 to 131)

The following laboratory abnormalities (all Grades) occurred in >5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

Renal Cell Carcinoma

The safety of LENVIMA was evaluated in Study 205, in which patients with unresectable advanced or metastatic renal cell carcinoma (RCC) were randomized (1:1:1) to LENVIMA 18 mg orally once daily with everolimus 5 mg orally once daily (n=51), LENVIMA 24 mg orally once daily (n=52), or everolimus 10 mg orally once daily (n=50). This data also includes patients on the dose escalation portion of the study who received LENVIMA with everolimus (n=11). The median treatment duration was 8.1 months for LENVIMA with everolimus. Among 62 patients who received LENVIMA with everolimus, the median age was 61 years, 71% were men, and 98% were White.

The most common adverse reactions observed in the LENVIMA with everolimus-treated group (≥30%) were, in order of decreasing frequency, diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria. The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA with everolimus. The most common adverse reactions (≥5%) resulting in dose reductions in the LENVIMA with everolimus-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA with everolimus-treated group.

Table 5 presents the adverse reactions in >15% of patients in the LENVIMA with everolimus arm. Study 205 was not designed to demonstrate a statistically significant difference in adverse reaction rates for LENVIMA in combination with everolimus, as compared to everolimus for any specific adverse reaction listed in Table 5.

Table 5: Adverse Reactions Occurring in >15% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)

Adverse Reactions	LENVIMA 18 mg with Everolimus 5 mg N=62		Everolimus 10 mg N=50	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism	24	0	2	0
Gastrointestinal				
Diarrhea	81	19	34	2
Vomiting	48	7	12	0
Nausea	45	5	16	0
Stomatitis/Oral inflammation ^a	44	2	50	4
Abdominal pain ^b	37	3	8	0
Oral pain ^c	23	2	4	0
Dyspepsia/Gastro-esophageal reflux	21	0	12	0
Constipation	16	0	18	0
General				
Fatigue ^d	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Metabolism and Nutrition				
Decreased appetite	53	5	18	0
Decreased weight	34	3	8	0
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia ^a	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System				
Headache	19	2	10	2
Psychiatric				
Insomnia	16	2	2	0
Renal and Urinary				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event ^f	18	10	12	2
Respiratory, Thoracic and Mediastinal				
Cough	37	0	30	0
Dyspnea/Exertional dyspnea	35	5	28	8
Dysphonia	18	0	4	0
Skin and Subcutaneous Tissue				
Rash ^h	35	0	40	0
Vascular				
Hypertension/Increased blood pressure	42	13	10	2
Hemorrhagic events ⁱ	32	6	26	2

^a Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration
^b Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
^c Includes gingival pain, glossodynia, and oropharyngeal pain
^d Includes asthenia, fatigue, lethargy and malaise
^e Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia
^f Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment
^g Includes erythema, erythematous rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, and septic rash
^h Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocoele

In Table 6, Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA with everolimus arm are presented.

Table 6: Grade 3-4 Laboratory Abnormalities Occurring in ≥3% of Patients in the LENVIMA with Everolimus Arm^{a,b} in Study 205 (RCC)

Laboratory Abnormality	LENVIMA 18 mg with Everolimus 5 mg	Everolimus 10 mg
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypertriglyceridemia	18	18
Increased lipase	13	12
Hypercholesterolemia	11	0
Hyponatremia	11	6
Hypophosphatemia	11	6
Hyperkalemia	6	2
Hypocalcemia	6	2
Hypokalemia	6	2
Increased aspartate aminotransferase (AST)	3	0
Increased alanine aminotransferase (ALT)	3	2
Increased alkaline phosphatase	3	0
Hyperglycemia	3	16
Increased creatine kinase	3	4
Hematology		
Lymphopenia	10	20
Anemia	8	16
Thrombocytopenia	5	0

^a With at least 1 grade increase from baseline
^b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA with Everolimus (n=62), Everolimus (n=50)

Hepatocellular Carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomized (1:1) patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=476) or sorafenib (n=475). The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight of ≥60 kg and 8 mg orally once daily for patients with a baseline body weight of <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was ≥6 months in 49% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 476 patients who received LENVIMA in REFLECT, the median age was 63 years, 85% were men, 28% were White and 70% were Asian.

The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.

The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%).

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

Table 7 summarizes the adverse reactions that occurred in ≥10% of patients receiving LENVIMA in REFLECT. REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 7.

Table 7: Adverse Reactions Occurring in ≥10% of Patients in the LENVIMA Arm in REFLECT (HCC)

Adverse Reaction	LENVIMA 8 mg/12 mg N=476		Sorafenib 800 mg N=475	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism ^a	21	0	3	0
Gastrointestinal				
Diarrhea	39	4	46	4
Abdominal pain ^b	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites ^c	15	4	11	3
Stomatitis ^d	11	0.4	14	1
General				
Fatigue ^e	44	7	36	6
Pyrexia ^f	15	0	14	0.2
Peripheral edema	14	1	7	0.2
Metabolism and Nutrition				
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia ^g	31	1	20	2
Nervous System				
Headache	10	1	8	0
Renal and Urinary				
Proteinuria ^h	26	6	12	2
Respiratory, Thoracic and Mediastinal				
Dysphonia	24	0.2	12	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	27	3	52	11
Rash ⁱ	14	0	24	2
Vascular				
Hypertension ^j	45	24	31	15
Hemorrhagic events ^k	23	4	15	4

^a Includes hypothyroidism, blood thyroid stimulating hormone increased
^b Includes abdominal discomfort, abdominal pain, abdominal tenderness, epigastric discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
^c Includes ascites and malignant ascites
^d Includes aphthous ulcer, gingival erosion, gingival ulceration, glossitis, mouth ulceration, oral mucosal blistering, and stomatitis
^e Includes asthenia, fatigue, lethargy and malaise
^f Includes increased body temperature, pyrexia
^g Includes arthralgia, back pain, extremity pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, and myalgia
^h Includes proteinuria, increased urine protein, protein urine present
ⁱ Includes erythema, erythematous rash, exfoliative rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash and rash
^j Includes increased diastolic blood pressure, increased blood pressure, hypertension and orthostatic hypertension
^k Includes all hemorrhage terms. Hemorrhage terms that occurred in 5 or more subjects in either treatment group include: epistaxis, hematuria, gingival bleeding, hemoptysis, esophageal varices hemorrhage, hemorrhoidal hemorrhage, mouth hemorrhage, rectal hemorrhage and upper gastrointestinal hemorrhage

In Table 8, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in ≥2% of Patients in the LENVIMA Arm^{a,b} in REFLECT (HCC)

Laboratory Abnormality	Lenvatinib (%)	Sorafenib (%)
Chemistry		
Increased GGT	17	20
Hyponatremia	15	9
Hyperbilirubinemia	13	10
Increased aspartate aminotransferase (AST)	12	18
Increased alanine aminotransferase (ALT)	8	9
Increased alkaline phosphatase	7	5
Increased lipase	6	17
Hypokalemia	3	4
Hyperkalemia	3	2
Decreased albumin	3	1
Increased creatinine	2	2
Hematology		
Thrombocytopenia	10	8
Lymphopenia	8	9
Neutropenia	7	3
Anemia	4	5
^a With at least 1 grade increase from baseline		
^b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=278 to 470) and sorafenib (n=260 to 473)		

Postmarketing Experience The following adverse reactions have been identified during post approval use of LENVIMA. 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.

Gastrointestinal: pancreatitis, increased amylase

General: impaired wound healing

Hepatobiliary: cholecystitis

Renal and Urinary: nephrotic syndrome

Vascular: arterial (including aortic) aneurysms, dissections, and rupture

DRUG INTERACTIONS

Drugs That Prolong the QT Interval LENVIMA has been reported to prolong the QT/QTc interval. Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. There are no available human data informing the drug-associated risk. 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 embryofetal development study, daily oral administration of lenvatinib mesylate at doses ≥0.3 mg/kg [approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retrosophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk; however, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma. Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment with LENVIMA and for at least 1 week after the last dose.

Data

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher [based on area under the curve (AUC)] in milk compared to maternal plasma.

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Infertility

LENVIMA may impair fertility in males and females of reproductive potential.

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

Juvenile Animal Data

Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption, and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the human exposure based on AUC at the recommended clinical dose of 24 mg). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities (including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level [attributed to primary duodenal lesions]) occurred at earlier treatment time-points in juvenile rats.

Geriatric Use Of the 261 patients with differentiated thyroid cancer (DTC) who received LENVIMA in SELECT, 45% were ≥65 years of age and 11% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 62 patients with renal cell carcinoma (RCC) who received LENVIMA with everolimus in Study 205, 36% were ≥65 years of age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between these subjects and younger subjects.

Of the 476 patients with hepatocellular carcinoma (HCC) who received LENVIMA in REFLECT, 44% were ≥65 years of age and 12% were ≥75 years of age. No overall differences in safety or effectiveness were observed between patients ≥65 and younger subjects. Patients ≥75 years of age showed reduced tolerability to LENVIMA.

Renal Impairment No dose adjustment is recommended for patients with mild (CL_{cr} 60-89 mL/min) or moderate (CL_{cr} 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with DTC or RCC and severe (CL_{cr} 15-29 mL/min) renal impairment. Reduce the dose for patients with RCC or DTC and severe renal impairment. There is no recommended dose of LENVIMA for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease.

Hepatic Impairment No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate or severe hepatic impairment.

No dose adjustment is recommended for patients with DTC or RCC and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC or RCC and severe hepatic impairment (Child-Pugh C). Reduce the dose for patients with DTC or RCC and severe hepatic impairment.

OVERDOSAGE

Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.

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Messenger RNA Vaccines: Beckoning of a New Era in Cancer Immunotherapy

Mehmet Sitki Copur, MD

ABSTRACT: Messenger RNA (mRNA) vaccines are a relatively new class of vaccines. They combine the potential of mRNA to encode for almost any protein with an excellent safety profile and a flexible production process. During the last decade, the mRNA vaccine approach has been increasingly recognized and viewed as a versatile tool for the development of new innovative therapeutics not only in infectious disease settings but also in cancer. mRNA vaccines traditionally consist of a messenger RNA synthesized by in vitro transcription using a bacteriophage RNA polymerase and a template DNA that encodes the antigen(s) of interest. Once administered and internalized by host cells, the mRNA transcripts are translated directly in the cytoplasm of the cell. The resulting antigens are presented to the immune system cells to stimulate an immune response. Dendritic cells (DCs) can be utilized as a carrier by delivering tumor-associated antigen mRNAs or total tumor RNA to their cytoplasm; then, the mRNA-loaded DCs can be delivered to the host to elicit a specific immune response. Recently, 2 mRNA vaccines were approved for the first time for human use—to prevent COVID-19 infection—bringing excitement for the future possibilities of this approach for cancer immunotherapy as well as for preventing other infectious diseases.

Introduction

Messenger RNA (mRNA) vaccines have generated significant excitement not only for their potential to complement or even replace traditional vaccines against infectious diseases, but also for their potential use in noninfectious diseases, including cancer. Nucleic acid therapeutics have emerged as promising alternatives to conventional vaccine approaches. Exploitation of mRNA, the intermediate step between the protein-encoding DNA and the protein manufactured by ribosomes, has proven to be a favorable alternative to conventional vaccines. In this approach, a linear DNA template and a T7, a T3, or

an Sp6 phage RNA polymerase are used in vitro to design the mRNA containing 5' and 3' untranslated regions (UTRs). The resulting product contains an open reading frame that encodes the protein of interest, flanking UTRs, a 5' cap, and a poly(A) tail; this tail resembles the fully processed mature mRNA molecule that naturally occurs in the cytoplasm of eukaryotic cells (**FIGURE 1**).¹ Successful cytosolic delivery of mRNA results in synthesis of the encoded protein, which undergoes posttranslational modifications and results in a properly folded, fully functional product that is delivered to the correct cellular compartments for

proper presentation or function.

In vitro transcribed mRNA is ultimately degraded by normal cellular physiological processes.²⁻⁴ Because the target for mRNA vaccines is the cytoplasm of the cell, they are easier to deliver, and cytosolic mRNA has no interaction with the genome.⁵ The small piece of genetic information mRNA vaccine carries is expressed only transiently, until it is degraded. mRNA can encode multiple proteins that possess very different chemical and physical properties without major changes in its physiochemical properties. mRNAs can theoretically be used to produce any protein, and doing so is a much

more simple and cost-effective way of manufacturing the proteins.

While the concept of possibly using mRNA vaccines against infectious diseases, genetic disorders, and cancer has been around for decades, until now no vaccines using this technology have received FDA approval for human use. Recently, 2 phase 3 trials led to the first FDA approvals of mRNA-based vaccines, and this marks the beginning of a new era not only for the infectious disease field but also for oncology.

Background

In an early proof-of-concept study, RNA and DNA expression vectors that contained genes for chloramphenicol acetyltransferase, luciferase, and beta-galactosidase were separately injected into mouse skeletal muscle; expression of all the proteins was later readily detected. The extent of expression from both the RNA and DNA constructs was comparable with that obtained from fibroblasts transfected in vitro under optimal conditions.⁶

Despite its revolutionary promise, though, mRNA work has been hampered by several challenges. These have included the instability of mRNA molecules, leading them to degrade quickly inside the cell; the inability of mRNAs to produce high levels of proteins; and mRNA's own immunogenicity, which triggers an immune response independent of the desired immune response, that it attempts to produce to the protein it encodes.

DNA and RNA can stimulate the mammalian innate immune system through activation of Toll-like receptors (TLRs). Observation of lack of immunostimulatory effect of DNAs containing methylated CpG motifs and selected nucleosides in naturally occurring methylated or otherwise modified RNAs led to a discovery that was reported in a seminal paper by Kariko et al. They showed that RNA creates signals through human TLR3, TLR7, and TLR8; however, the incorporation of modified nucleosides m5C, m6A, m5U,

FIGURE 1. mRNA Vaccine Design

mRNA, messenger RNA; UTR, untranslated region.

SOURCE: Verbeke R, Lentacker I, De Smedt SC, DeWitt H. Three decades of messenger RNA vaccine development. *NanoToday*. 2019;28(100766). doi:10.1016/j.nantod.2019.100766

or s2U, or of pseudouridine, ablates this activity. Dendritic cells (DCs) exposed to such modified RNA express significantly fewer cytokines and activation markers than those treated with unmodified RNA. This discovery—that modified synthetic nucleosides could both increase protein production from mRNA and suppress the immune system's recognition and degradation of mRNA—helped mRNA vaccine technology evolve further.⁷

Under physiological conditions, RNA molecules are highly unstable and very sensitive to catalytic hydrolysis by ubiquitous ribonucleases.⁸ One of the main challenges for the clinical use of mRNA vaccines has been the difficulty in intracellularly delivering the mRNA. Naked mRNA, delivered by itself, is rapidly degraded after injection. Several mRNA delivery approaches have been tested, using substances including modified RNAs, RNA conjugates, viral vectors, micro-particles, and, most successfully, lipid nanoparticles.⁹⁻¹¹ Lipid nanoparticles are multicomponent lipid systems composed

of an ionizable lipid, a phospholipid, cholesterol, and a polyethylene glycol (PEG)-lipid. The ionizable lipid facilitates the mRNA's formation of a core structure, while helper lipids (phospholipid and cholesterol) envelop the lipid-mRNA complex, and the PEG-lipid protects the nanoparticle shell. Lipid nanoparticles have been the most promising innovation in this field.¹²

For efficacy, adequate in vivo delivery of exogenous mRNA is crucial (**FIGURE 2**). Uptake of mRNA may depend on the physicochemical properties of the mRNA complexes and the cell type. Two main strategies have been utilized for the in vivo delivery of mRNAs. One such approach involves loading mRNA into DCs ex vivo, followed by reinfusion of the transfected cells. This allows precise control of the cellular target and transfection efficiency, but it is expensive and labor intensive. The DC approach elicits a predominantly cell-mediated immune response; it has been explored primarily in cancer treatment.

The second approach is direct parenteral injection of mRNA. This is relatively quick and cost effective, but it may not be as precise and efficient in specific cell delivery. The systemic delivery of vaccine antigens can be facilitated by using RNA-lipoplexes. The lipoplexes protect RNA from extracellular ribonucleases; they mediate the efficient uptake and expression of the encoded antigen.^{13,14} Recently, highly efficient and nontoxic RNA carriers have been developed that allow prolonged antigen expression in vivo.^{15,16} Some vaccine formulations contain novel adjuvants, while others elicit potent responses in the absence of known adjuvants.

Lipid Nanoparticle Approach for mRNA Vaccines

mRNA has a number of benefits over traditional treatments, but its use as a therapeutic molecule has been challenging due to its chemical instability and susceptibility to hydrolysis, catalyzed by ubiquitous RNA nucleases. However, recent advances in nonviral delivery systems and the development of novel effective transfecting nanomaterials have brought some effective resolutions to these challenges.

The encapsulation of mRNA into a carrier is necessary to protect it from extracellular degradation and to stimulate its cellular uptake and endosomal escape.^{17,18} Lipid-based delivery systems of lipoplexes have some drawbacks, including high instability, relatively low transfection efficiency, and poor customizable composition, so the earlier use of these systems^{15,19} has been replaced by lipid nanoparticles. Lipid nanoparticles have demonstrated superior stability and structural plasticity as well as enhanced gene delivery.^{18,20} A lipid nanoparticle is composed of pH-responsive lipids; neutral helper lipids, such as zwitterionic lipid and/or sterol lipid (ie, cholesterol), to stabilize the lipid bilayer of the lipid nanoparticle; and a PEG-lipid to improve the colloidal stability in biological environments.^{18,21} The application of lipid-based nanotechnology delivery

FIGURE 2. **In Vivo Delivery of mRNA Vaccine**

IFN, interferon; MHC, major histocompatibility complex; mRNA, messenger RNA.

SOURCE: Verbeke R, Lentacker I, De Smedt SC, DeWitt H. Three decades of messenger RNA vaccine development. *NanoToday*. 2019;28(100766). doi:10.1016/j.nantod.2019.100766

systems is now enabling the integration of mRNA-based technology with many preexisting anticancer immunotherapeutic approaches, including therapeutic vaccines, monoclonal antibodies, and chimeric antigen receptor T-cell therapy. A deeper understanding of key parameters, such as hydrophobicity and fusogenicity determining the transfection efficiency of the formulation and discoveries of how they can be modulated by varying the lipidic composition or through the introduction of novel lipids, will further enhance the development of better formulations. More research is needed to understand the reasons behind the low mRNA transfection efficiency.

mRNA Vaccines Against Cancer

While mRNA technology is a relatively new and novel approach in cancer vaccine development, vaccines in general have previously been conceptually considered

in cancer immunotherapy, by utilizing viral or bacterial vaccines. In fact, the concept goes as far back as 1891, when Dr. William Coley made the first attempt to stimulate the immune system to improve a patient's condition: He used intratumoral injections of inactivated *Streptococcus pyogenes* and *Serratia marcescens*, a mixture now known as Coley's toxin.²² The bacillus Calmette-Guérin (BCG), a bacterium that functions similarly to Coley's toxin, is currently used to treat superficial bladder cancer.^{23,24}

However, the clinical translation of cancer vaccines into efficacious therapies that could be used widely has been challenging for decades. The 2 very first US FDA vaccine approvals in cancer were for prophylactic use: hepatitis B virus vaccine and human papillomavirus vaccine. The first therapeutic cancer vaccine was not available until 2010, with approval of an

Continued on page 196

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Messenger RNA Vaccines

Continued from page 192

TABLE. **Current Cancer Clinical Trials of mRNA Vaccine^a**

Study title	Tumor type	Intervention	Status
Clinical Study of Personalized mRNA Vaccine Encoding Neoantigen in Patients With Advanced Esophageal Cancer and Non–Small Cell Lung Cancer (NCT03908671)	Esophageal cancer; NSCLC	Biological: personalized mRNA tumor vaccine	Not yet recruiting
Clinical Study of Personalized mRNA Vaccine Encoding Neoantigen in Patients With Advanced Digestive System Neoplasms (NCT03468244)	Advanced esophageal squamous carcinoma; gastric adenocarcinoma; pancreatic adenocarcinoma; colorectal adenocarcinoma	Biological: personalized mRNA tumor vaccine	Recruiting
Messenger RNA (mRNA)-Based, Personalized Cancer Vaccine Against Neoantigens Expressed by the Autologous Cancer (NCT03480152)	Melanoma	Biological: mRNA-4157 Biological: pembrolizumab	Terminated
An Efficacy Study of Adjuvant Treatment With the Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab in Patients With High-Risk Melanoma (KEYNOTE-942; NCT03897881)	Melanoma	Biological: mRNA-4157 Biological: pembrolizumab	Recruiting
Ovarian Cancer Treatment With a Liposome Formulated mRNA Vaccine in Combination With (Neo-)adjuvant Chemotherapy (NCT04163094)	Ovarian cancer	Drug: W ova1 vaccine	Recruiting
Phase 1/2 Study of Combination Immunotherapy and mRNA Vaccine in Subjects With NSCLC (NCT03164772)	Metastatic NSCLC	Drug: durvalumab Drug: tremelimumab Biological: BI 1361849	Recruiting
Safety, Tolerability, and Immunogenicity of mRNA-4157 Alone in Subjects With Resected Solid Tumors and in Combination With Pembrolizumab in Subjects With Unresectable Solid Tumors (NCT03313778)	Solid tumors	Biological: mRNA-4157 Biological: pembrolizumab	Recruiting
Trial of an RNAActive®-Derived Cancer Vaccine in Stage IIIB/IV Non–Small Cell Lung Cancer (NSCLC) (NCT00923312)	NSCLC	Biological: CV9201	Completed
Vaccination With Tumor mRNA in Metastatic Melanoma - Fixed Combination vs Individual Selection of Targeted Antigens (NCT00204516)	Malignant melanoma	Biological: mRNA coding for melanoma-associated antigens Drug: GM-CSF	Completed
PRO-MERIT (Prostate Cancer Messenger RNA Immunotherapy) (NCT04382898)	Prostate cancer	Biological: W pro1 Drug: cemiplimab	Recruiting
Trial of Vaccine Therapy in Recurrent Platinum Sensitive Ovarian Cancer Patients (NCT01334047)	Recurrent epithelial ovarian cancer	Biological: DC-006 vaccine	Terminated
Trial for Vaccine Therapy With Dendritic Cells in Patients With Metastatic Malignant Melanoma (NCT00961844)	Metastatic malignant melanoma	Biological: DCs – transfected with hTERT-, survivin-, and tumor-cell– derived mRNA + ex vivo T-cell expansion and reinfusion Drug: temozolomide	Terminated
Dendritic Cell Vaccination and Docetaxel for Patients With Prostate Cancer (NCT01446731)	Prostatic neoplasms	Biological: mRNA transfected DC Drug: docetaxel	Completed
Transfected Dendritic Cell Based Therapy for Patients With Breast Cancer or Malignant Melanoma (NCT00978913)	Breast cancer; malignant melanoma	Biological: DC vaccine	Completed

immune cell–based vaccine, sipuleucel-T, for prostate cancer refractory to hormone therapy.²⁵

Over the past decades, numerous diverse therapeutic cancer vaccination strategies have been under development. Recent human-use approval of the 2 mRNA vaccines for COVID-19 may mark the end of the beginning of our quest for mRNA vaccine immunotherapy of cancer.^{26,27} The early proof-of-concept studies that provided the evidence for the feasibility of the mRNA vaccine approach were published more than 2 decades ago.^{28,29} Since then, numerous preclinical and clinical research teams have been exploring the viability of this approach. Most cancer vaccines seek to stimulate cell-mediated responses, such as those from cytotoxic T lymphocytes, that are capable of clearing or reducing tumor burden.³⁰ Cancer vaccines can be designed to target tumor-associated antigens that are preferentially expressed in cancerous cells. Growth-associated

factors, or antigens that are unique to malignant cells due to somatic mutations, can be targeted in the design of mRNA cancer vaccines.³¹ While the simplicity of mRNA vaccines greatly reduces the difficulties generally associated with the production of biological vaccines, the route of administration and delivery format greatly influence outcomes. A variety of mRNA cancer vaccines have been studied that utilize the 2 main delivery strategies: direct injection and the DC approach.

Direct Injection mRNA Approach

Direct injection of mRNA can be accomplished through common delivery routes, such as intradermal, subcutaneous, intranasal, and intramuscular, as well as some unconventional routes, such as intranodal, intrasplenic, intratumoral, and intravenous. Systemic administration of mRNAs has been challenging, due to concerns about aggregation with serum proteins and rapid extracellular degradation, which has led to formulations with carri-

er molecules. Numerous delivery formulations have been developed to facilitate mRNA uptake, increase protein translation, and protect mRNA from RNAases, as discussed above.

The intradermal route of delivery has been widely used for mRNA cancer vaccines. The presence of a variety of antigen-presenting cells in the skin makes it an ideal site for immunogen delivery.³² In several mouse tumor models of various cancers, including fibrosarcoma, melanoma, and prostate cancer, vaccines delivered intradermally have been shown to produce antitumor responses.³²⁻³⁴

Intranasal administration, a needle-free, noninvasive delivery model, has also been shown to enable rapid antigen uptake by DCs. In mouse tumor models, intranasal delivery of mRNA complexed with lipid nanoparticles has been shown to induce prophylactic and therapeutic antitumor immunity.³⁵

A rather unconventional but efficient mRNA vaccine delivery approach has

TABLE CONTINUED. **Current Cancer Clinical Trials of mRNA Vaccine^a**

Study title	Tumor type	Intervention	Status
Trial of Vaccine Therapy with mRNA-Transfected Dendritic Cells in Patients With Androgen Resistant Metastatic Prostate Cancer (NCT01278914)	Prostate cancer	Biological: DCs prostate	Completed
Safe Study of Dendritic Cell (DC) Based Therapy Targeting Tumor Stem Cells in Glioblastoma (NCT00846456)	Glioblastoma; brain tumor	Biological: DC vaccine with mRNA from tumor stem cells	—
Trial of Vaccine Therapy With mRNA-Transfected Dendritic Cells in Patients With Advanced Malignant Melanoma (NCT01278940)	Malignant melanoma	Biological: DCs malignant melanoma Procedure: IL-2	Completed
Peptide-Pulsed vs RNA-Transfected Dendritic Cell Vaccines in Melanoma Patients (NCT00243529)	Melanoma, stage III or IV	Biological: autologous DC vaccine	Completed
Carcinoembryonic Antigen-Loaded Dendritic Cells in Advanced Colorectal Cancer Patients (NCT00228189)	Colorectal cancer liver metastases	Biological: CEA-loaded DC vaccine	Completed
Feasibility Study of Acute Myelogenous Leukemia mRNA Plus Lysate Loaded Dendritic Cell Vaccines (NCT00514189)	Leukemia	Biological: autologous DCs	Terminated
Vaccine Therapy in Treating Patients Undergoing Surgery for Recurrent Glioblastoma Multiforme (NCT00890032)	Recurrent central nervous system neoplasm	Biological: BTSC mRNA-loaded DCs	Completed
Efficacy Study of Dendritic Cell Vaccination in Patients With Acute Myeloid Leukemia in Remission (NCT01686334)	Acute myeloid leukemia	Biological: DC vaccine	Recruiting
Dendritic Cell Immunotherapy Against Cancer Stem Cells in Glioblastoma Patients Receiving Standard Therapy (NCT03548571)	Glioblastoma	Biological: DC immunization Drug: adjuvant temozolomide	Recruiting
Autologous Dendritic Cell Vaccination in Mesothelioma (NCT02649829)	Malignant pleural mesothelioma	Biological: DC vaccination plus chemotherapy	Recruiting

DC, dendritic cell; IL, interleukin; mRNA, messenger RNA; NSCLC, non–small cell lung cancer.

^aSource: ClinicalTrials.gov.

been the intranodal administration of unprotected mRNA, directly injected into lymphoid tissue. Intranodally injected mRNAs can stimulate potent prophylactic or therapeutic antitumor T-cell responses.^{36,37} Similar efficacy has been shown by intrasplenic delivery of mRNA melanoma vaccine in mouse tumor models.³⁸ Intranodal injection of naked mRNA encoding tumor-associated antigens in patients with melanoma (NCT01684241) and with hepatocellular carcinoma (EudraCT: 2012-005572-34) is being studied in human clinical trials.

Finally, another unconventional direct delivery method that has been shown to be effective is intratumoral mRNA delivery. Here, intratumoral administration of mRNAs that do not encode tumor-associated antigens seems to stimulate tumor-specific immunity through the intrinsic immunogenic properties of mRNA.³⁹⁻⁴¹

Dendritic Cell mRNA Approach

DCs are the professional antigen-presenting cells of our immune system. They can take up, process, and present antigens to T cells. mRNA is a polyvalent molecule with an attractive safety profile and the ability to induce transient but sufficiently long and high protein expression without the risk of integrating into the host genome. These characteristics make it an attractive vector to deliver tumor antigens to DCs.

The interest in using mRNA as a means of loading tumor antigens onto DCs goes back to the late 1990s, when initial attempts were based on passive pulsing. They relied on the ability of DCs to take up the mRNA, translate it into proteins, then process it into peptides and finally present it to CD8⁺ T cells.^{32,42,43} To increase the efficiency of uptake, investigators have studied several strategies, including electroporation, nucleofection, lipofection, and, more recently, sonoporation.⁴⁴⁻⁴⁷

A variety of immune-regulatory pro-

teins in the form of mRNA-encoded adjuvants or co-stimulatory molecules have been shown to increase the potency of DC cancer vaccines. These molecules include CD83, tumor necrosis factor receptor superfamily member 4 (TNFRSF4; also known as OX40), and 4-1BB ligand. Electroporation of DCs with these mRNAs have resulted in a substantial increase in the immune stimulatory activity of DCs.⁴⁸⁻⁵¹ Further, the use of mRNA-encoded proinflammatory cytokines, such as IL-12, or associated molecules has been shown to enhance and potentiate the efficacy of immune response.⁵²⁻⁵⁵ In a phase 2 trial, the combination of a mRNA DC vaccine approach with an immune checkpoint inhibitor has shown durable tumor response.⁵⁶

Conclusions

Within the past 2 decades, major achievements in the field of mRNA vaccines have created a safe and attractive treatment option for a broad range of diseases, including cancer. Their simplicity, high potency, capacity for rapid development, and potential for low-cost manufacture and safe administration all make mRNA vaccines a very promising alternative to conventional vaccine approaches. Recent improvements in mRNA vaccines to increase protein translation, modulate innate and adaptive immunogenicity, and improve delivery are very encouraging. The combination of mRNA vaccination with adjunctive therapies, such as traditional chemotherapy, radiotherapy, and immune checkpoint inhibitors, may contribute further to the approach's benefit in oncology. Challenges may include scaling up good manufacturing practice production, establishing regulations, further documenting safety, and increasing efficacy. Clinical studies in various cancer types are moving forward, and promising results with favorable clinical outcomes are eagerly awaited (**FIGURE**). Future research should also focus on interpreting the immune pathways activated by various mRNA vaccine platforms and

try to improve current approaches based on these mechanisms. Recent approval of 2 mRNA vaccines for COVID-19 for human use opens the gateway for many future applications of this novel treatment approach. ■

FINANCIAL 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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How to Radiologically Assess and Follow Response After Treatment of Hepatocellular Carcinoma

Alejandro Gabutti, MD; and Tommaso Cascella, MD

THE CASE

A 6-cm liver tumor in segment 8 was found in a woman, aged 36 years, with hepatitis C virus (HCV)-related cirrhosis. The tumor was initially noticed in a screening ultrasound and further characterization was done with a multiphase CT scan. The tumor showed arterial enhancement and venous washout, and hepatocellular carcinoma (HCC) was definitively diagnosed.

For final staging, a chest CT and bone scintigraphy were performed. There was no evidence of extrahepatic disease or vascular invasion. At diagnosis, liver function was well compensated (Child-Pugh A5) and MELD (Model for End-Stage Liver Disease) score was 12. Alfa-fetoprotein plasma level was 7 ng/ml (within normal limits). Also, imaging studies revealed spleen enlargement and collateral venous circulation due to portal hypertension. The patient was classified as stage B according to the Barcelona criteria.

The patient's relevant clinical history included sofosbuvir/velpatasvir (Epclusa) as treatment for HCV, which had been successfully completed 15 months before the HCC diagnosis. A sustained viral response was achieved.

Two weeks after diagnosis, the patient underwent a conventional transarterial chemoembolization (ethiodized oil [Lipiodol] plus doxorubicin, and polyvinyl alcohol [PVA] particles as embolic agent). The first follow-up was done with a multiphase CT 1 month after transarterial

chemoembolization. No arterial enhancement was noticed, but there was a 2-cm area of absent ethiodized oil uptake within the tumor. Because of a high suspicion of tumor persistence, MRI was immediately performed, which showed a 1.8-cm viable residual tumor. A bland embolization with PVA particles was performed because of a doxorubicin shortage. Stable disease was documented. Due to residual tumor size and lack of response to transarterial embolization, a percutaneous ablation was performed. Because of the proximity of the tumor to the diaphragm, chemical ablation with ethanol was employed. Four weeks post treatment, an MRI showed a complete response.

Discussion

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a major global health concern.¹ Its incidence has been rising over the last 20 years and is expected to increase until 2030.² Diagnosis, treatment, and follow-up rely mainly on imaging. Thorough radiological assessment is critical in terms of satisfactory patient management.

HCC treatment must be decided by a multidisciplinary liver tumor board. Medical oncologists play an essential role, especially in patients with intermediate- or advanced-stage disease. Oncologists view the disease as a systemic issue, and along with clinical evaluation, radiological evaluations are probably

What posttreatment follow-up should be done after achieving complete response?

- A. Multiphase abdominal MRI 1 month after treatment
- B. Multiphase abdominal CT 1 month after treatment
- C. Thoracoabdominal CT and bone scan 3 months after treatment
- D. Thoracic CT and multiphase MRI 3 months after treatment

➤ **TURN TO PAGE 200** for the answer and a discussion of this case by experts.

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CORRECT ANSWER: D. Thoracic CT and multiphase MRI 3 months after treatment

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the most important tools to promote the best outcomes.

The therapeutic armamentarium for HCC is broad and heterogeneous and can be divided into treatments with curative and noncurative intent.³ Curative treatments include liver transplantation, resection, and ablation. Noncurative treatments include transarterial chemoembolization (TACE) and variants, transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), and systemic therapies.

HCC treatments are under continuous development and evolution. New therapeutic strategies, including novel antiangiogenic agents, immunomodulators, and combinations with locoregional therapies (LRTs), are currently in the spotlight.⁴ An interesting example is the evolution of TARE. Technical improvements have transformed it to a potentially curative therapy when was it was previously considered a palliative treatment.⁵

How should we assess the response of HCC to treatment? This is a matter of constant debate and discussion.⁶

The radiological evaluation protocols after treatment are heterogeneous and may vary by institution and therapeutic strategy.⁷ The follow-up protocol strength relies on 3 essential points: timing, imaging method, and the chosen radiological response criteria. It is not the aim of this article to deeply review the imaging findings after locoregional or systemic therapies, but rather to review the evidence of when and how to assess response.

When to Assess Response After Treatment

The accepted timing for performing the first imaging study after treatment (LRT or systemic) is 4 to 6 weeks.⁷⁻⁹ An excep-

tion is when the patient has been treated with TARE or SBRT. The first imaging evaluation after a radiation-based LRT, unlike other LRTs, is 3 months.¹⁰ This is because radiation-induced tumor necrosis is often delayed.¹⁰⁻¹² Once 4 to 6 weeks have elapsed, most of the inflammatory changes related to LRTs have resolved. However, inflammation and tumor persistence may be challenging to distinguish with imaging, as both usually appear as areas of arterial hyperenhancement on multiphase CT or MRI.^{13,14}

The first imaging surveillance has 2 main objectives: to identify tumoral viability and early complications.^{8,15} If viable tumor is detected on the first imaging assessment after treatment, it is classified as residual disease.¹⁶ Large areas of residual tumor will be easily seen on the first imaging surveillance. Viable tumor shows the characteristic radiological appearance of HCC, especially arterial enhancement.¹⁷ However, this is not always obvious in small foci of residual tumor, and in such cases diagnosis can be challenging. Not uncommonly, a final diagnosis of tumor viability is made only on further follow-up.

If equivocal findings of residual tumor are detected initially, the imaging evaluation should be repeated no longer than 3 months after treatment (2 months after the first assessment) until a final diagnosis is established.^{12,18} The identification of viable tumor within the first follow-up must lead to a case reevaluation to guide further therapy.^{13,18,19}

Other than detecting tumoral persistence, the first imaging evaluation is also important for early recognition of treatment-related complications, including necrosis infection, biloma formation, bile duct stricture, vascular injuries, or nontarget treatment effects.^{8,19} While the rate of complications after LRTs is low,

typically less than 5%,²⁰ early management of any that are detected is essential to avoid delay in future treatments.

The first radiological assessment can be focused just on local tumor response. Whole-body imaging is not necessary, unless metastatic disease was present at diagnosis. Once there is no evidence of tumor viability, an active surveillance protocol should be begun. Beyond this point, tumoral viability detected within a treated tumor is classified as recurrence.¹⁶

In early-stage HCC, when a curative-intent treatment (ablation or resection) was employed, patients can be monitored every 3 to 4 months during the first 2 years, with surveillance every 6 months thereafter.^{1,2,7} European Association for the Study of the Liver (EASL) guidelines emphasize particularly close follow-up of patients who also had successfully completed hepatitis C virus treatment with direct-acting antivirals.¹

The every-6-months monitoring schedule should continue indefinitely. The majority of HCC cases develop in the context of cirrhosis. Therefore, the surveillance aim is not only the detection of late-onset recurrence, but also to recognize neohepatocarcinogenesis.

For patients with intermediate-stage disease, who are usually treated with embolotherapies, follow-up can be every 3 months.² For patients with advanced-stage disease treated with systemic agents, a radiological evaluation every 2 to 3 months is suggested.⁷ Both schedules aim to monitor for tumor progression to guide future therapeutic decisions.^{2,7} The follow-up protocol should continue indefinitely or until there is a major management change, eg, successfully downstaging with subsequent liver transplantation as the final therapy.

How to Assess Response After Treatment

Two questions may arise in assessing response: First, in which situations should extraabdominal imaging studies be per-

formed? And second, what is the best imaging method for evaluating local response after treatment? While there is lack of consensus or precise recommendations about these issues, certain facts support our recommendations, we believe.

Some clues in answering both questions are provided by the initial disease staging. The HCC work-up typically includes state-of-the-art liver imaging (multiphase CT or MRI), chest CT, and a bone scan.^{1,2} However, the usefulness of bone scan with technetium-99m methyl diphosphonate is controversial. Some authors suggest that in early-stage HCC (within Milan criteria), it is not cost-effective and should not be done.^{21,22}

Even when the disease is radiologically limited to the liver, high tumor burden (index tumor > 5 cm), elevated levels of alpha-fetoprotein (> 400 ng/ml), and vascular invasion are considered major risk factors for extrahepatic disease.²³ Identifying patients with increased risk of metastasis can influence the follow-up protocol. In this particularly high-risk population, it is advisable to consider thoracoabdominal scans in order to detect systemic disease early, as the diagnosis of metastatic disease has a major impact on a patient's management and prognosis.^{23,24}

The treatment goal in early-stage HCC is local tumor eradication, utilizing liver-directed therapies. In this scenario, in patients with low risk of systemic disease, follow-up is focused on the liver, especially after ablation or surgical resection. Also, the option of surgical resection has been explored in patients without portal hypertension and absence of radiological vascular invasion, but with preserved hepatic function, regardless of tumor size.^{25,26} Because the frequency of micrometastases and vascular invasion rises with tumor size, it is advisable to use a thoracoabdominal radiological follow-up in this uncommon subgroup of patients.

In advanced-stage disease, systemic

Figure 1. (a) Baseline CT arterial phase: a 6 cm tumor was located in segment 7/8, it showed the typical features of HCC. (b) Selective cTACE of the tumor. (c) Arterial phase CT 1 month after conventional TACE, the hyperdense material within the tumor corresponds to lipiodol (*). An area of no staining and no enhancement was noticed (arrow). (d) T1+Gd arterial phase MRI, an intense contrast up-take was noticed in the Lipiodol unstained area (arrow). (e) Percutaneous ethanol injection of the viable tumor. (f) T1+Gd arterial phase MRI, no signs of tumor viability were detected.

cTACE, conventional transarterial chemoembolization; T1+Gd, T1-weighted, gadolinium enhanced.

therapy plays the main role. Beyond treatment with tyrosine kinase inhibitors, immunotherapy is currently gaining acceptance and showing promising results.⁴ Also, several therapy combinations are actively under investigation, constantly changing the way HCC is treated. In this scenario, thoracoabdominal imaging follow-up is mandatory.

Intermediate-stage HCC represents a very heterogeneous group of disease scenarios, making decisions difficult to generalize. Patients within intermediate-stage HCC are still candidates for local tumor control with LRTs. However, a sustained complete response is not commonly achieved; therefore, the treatment is most often considered palliative. Patients treated with LRT without curative intent may benefit from a follow-up protocol similar to the one followed by those with advanced-stage disease.

Hepatic Tumor Response Assessment

For systemic and local therapies, the only 2 recommended imaging techniques for response assessment are multiphase CT and MRI.^{1,2} They have comparable diagnostic performance, especially for HCCs larger than 2 cm.²⁷ Below this size cutoff, MRI is considered superior.^{1,27} There is a trend favoring MRI as the posttreatment imaging of choice, especially after LRTs.²⁸

Locoregional Therapies' Response Assessment

Tumor ablation and resection are curative-intent therapies employed in early-stage HCC.^{1,2} The principle of the most popular ablative techniques is tumor destruction, utilizing a thermal or chemical modality.^{29,30} Ablation techniques that are less widely used include irreversible electroporation and laser ablation.

■ **Figure 2.** HCC diagram, encoded in black is the nonviable tumor. RECIST: Response Evaluation Criteria in Solid Tumors, mRECIST: modified RECIST, EASL: European Association for the Study of the Liver, LI RADS: Liver Imaging Reporting and Data System, OPTN: Organ procurement and Transplantation Network

All of the above-mentioned techniques must achieve complete tumor destruction, including a disease-free margin of at least 0.5 cm to 1 cm.³¹ Viable tumor is often characterized by areas of arterial enhancement in the ablation/resection margin with venous washout.¹²

Both CT and MRI can be used to assess the effectiveness of curative-intent therapies. A recurrent or persistent tumor after resection or ablation is often small in size. Because MRI has a better diagnostic performance for small tumor foci detection than CT, it may be the preferred imaging method to evaluate a curative-intent therapy.²⁷ In addition, the use of hepatospecific contrast media improves the diagnostic performance of MRI in this scenario.³²

Embolotherapies include a wide variety of techniques that are conventionally considered palliative. They rely on the selective arterial delivery of an embolizing agent, with or without local chemotherapy. Therefore, tumor destruction is mediated by ischemia and the cytotoxic effect of chemotherapy.³³

The tumor size and the imaging technique employed for diagnosis are

essential factors in considering correct posttreatment follow-up. Transarterial therapies are usually employed in large tumors that are not suitable for ablation/resection. However, in daily practice, small tumors can be treated by embolotherapies when a curative-intent treatment is not technically feasible.³⁴ Conventional TACE (cTACE) is the technique that is most often used and studied. A chemotherapeutic drug is mixed with ethiodized oil resulting in micelles formation. The micelles carry the drug into the tumor and release it selectively over a long time period. This technique ensures a high drug concentration within the tumor, with minimal systemic effect.³⁵

Ethiodized oil contains high amounts of iodine, which makes it intrinsically hyperdense on CT. As such, areas of arterial enhancement could be subtly obscured, limiting the accuracy of an evaluation of response.¹² However, the presence of ethiodized oil only minimally affects an MRI signal, so MRI use is advised to evaluate cTACE effectiveness.¹² The ethiodized oil-free embolotherapies, such as transarterial embolization and drug-eluting beads-TACE (DEB-TACE),

can be evaluated equally with CT or MRI,^{1,2} as there is no tumoral staining with hyperdense agents.

Care must be taken with the intrinsically radiopaque DEBs that are commercially available (eg LUMI). These particular beads contain iodine within their structure.³⁶ When a high intra- or peritumoral concentration is achieved, a ethiodized oil-like effect can be expected on CT images, so here, too, an MRI assessment may be advisable.

Selective internal radiation therapy (SIRT), also known as TARE, consists of selective intraarterial administration of yttrium-90-coated particles. Its tumoricidal effect relies on direct cell destruction mediated by beta particles that have a penetration range of 2.6 mm to 11 mm.¹⁰ The embolic effect of SIRT is minimal, especially when glass spheres are employed, resulting in nonsignificant hypoxia,¹² whereas the hallmarks of acute tumor necrosis due to ischemia are often absent after TARE.

TARE is well tolerated by patients with benign or malignant portal thrombosis.³⁷ Arterial embolization in the setting of portal occlusion may lead to

severe liver ischemia and necrosis. Also, a TARE variant known as radiation segmentectomy can be performed as a curative-intent treatment for early-stage HCC.^{5,38}

Response assessment after SIRT can be challenging. Radiation-induced tumoral and peritumoral changes are highly heterogeneous and can show different enhancement patterns.¹² Tumoral arterial enhancement may not immediately disappear after treatment and may persist for months, even if the tumor was completely treated.³⁹ Therefore, when arterial enhancement persists, progressive tumor shrinkage is the main hallmark of adequate response to TARE.¹²

Perfusional changes in the radiated liver parenchyma are characterized by arterial enhancement.¹² They usually resolve within 6 months but may persist even longer. Therefore, they can be potentially confused with tumoral infiltration. The lack of venous washout and no signal abnormalities on T2 weighted/diffusion images are useful MRI features to distinguish tumoral infiltration from benign post-TARE findings.¹²

MRI and CT can both be used to assess response. For challenging cases, especially when arterial enhancement persists for longer than expected, MRI may provide more accurate information about tumor viability.¹²

SBRT uses multiple focused radiation beams to treat HCC. SBRT and SIRT share several posttreatment radiological features, especially the initial minimal effect on arterial enhancement and size.¹² In fact, 75% of HCC cases treated with SBRT exhibit persistent arterial enhancement for 3 to 6 months.^{40,41} Consequently, assessment of SBRT response can be accomplished using the same recommendations as those for SIRT.

No less important is the patient's compatibility and safety with the selected imaging technique. Patients with an implanted electronic or metallic device should always be checked for compatibility with MRI. Also, metallic artifacts

near the liver may degrade image quality, impairing the diagnostic performance of either MRI or CT. The use of contrast media is mandatory for the posttreatment imaging follow-up. Therefore, renal function must always be evaluated before the employment of any gadolinium- or iodine-based contrast media to avoid complications.

Other imaging modalities include contrast-enhanced ultrasound and PET-CT. Both have been extensively studied and are also suggested as valid resources for response assessment.⁹ However, guidelines currently include only CT and MRI as valid tools in this setting.^{1,2}

Systemic Therapy Response Assessment

For years, the therapeutic armamentarium for advanced-stage HCC was limited to a single drug, sorafenib (Nexavar). Recently, though, new agents, including immunotherapy, have been approved for the treatment of HCC,⁴ and with this therapeutical evolution comes new challenges in response evaluation.

In contrast to LRTs, in which necrosis is induced by a direct insult focused on the tumor, systemic agents cause tumoral death with multiple mechanisms that create microvasculature changes and immune activation.⁴ The functional data obtained with CT, MRI, and nuclear medicine can be applied as biomarkers of tumor viability. Tumoral biomarkers, such as metabolism, perfusion, and cellularity, in combination with morphologic changes, may in the future be the new standard of response evaluation.⁶

Systemic therapy is currently reserved for advanced-stage HCC.⁴² However, its efficacy in combination with LRT in intermediate-stage disease is being explored in multiple clinical trials.⁴³

Beyond the use of tumor burden in response assessment, a patient's performance status and liver function are vitally important to consider. Patients with Child-Pugh stage C are unlikely to derive clinical benefit from systemic

therapy, and best supportive care should be considered when the patient is not a candidate for liver transplantation.¹

Systemic therapy response assessment is not straightforward. It should always be done with multiphase abdominal CT or MRI, plus thoracic imaging. Therefore, CT can be logistically more efficient than MRI. CT, however, can include both the multiphase abdominopelvic exam and a thoracic evaluation. Thoracic MRI is not recommended for oncologic surveillance and abdominal evaluation; it is usually limited to the hepatic area. However, high-quality liver imaging should always be the priority; as such, a CT-MRI combination is feasible and useful.

The multiparametric nature of MRI can accurately depict tumoral necrosis. An MRI "second look" is advisable when CT evaluation is not conclusive. The detection of true necrosis is of main importance, especially when antiangiogenic drugs are used. Changes in the tumoral microvasculature may be represented as the loss of the characteristic arterial enhancement in a viable tumor on CT or MRI.^{6,44} Rather than a true antitumoral effect, this phenomenon can be explained by a reduction of vascular permeability to contrast agents.⁴⁴ Despite this, a decrease in arterial enhancement and tumor necrosis are equally accepted indicators of adequate response after systemic therapy.⁹

Imaging also plays an important role in the surveillance of drug adverse effects, especially when immunotherapy is employed. Bone scintigraphy is not included in the imaging follow-up protocol after systemic therapy.

Imaging Response Criteria

Once timing and imaging technique are established, selecting the imaging response criteria (RC) is the final step in completing the assessment. RC were first created to be used in clinical trials in which tumor response was the primary end point.^{1,45} Today, RC are commonly

employed in daily practice and heavily influence management decisions.⁴⁶

A multidisciplinary team should make the selection of the RC to be employed. Every health professional involved in the management of HCC must clearly understand how to assess and how to classify response.

Further, imaging RC can be divided into 2 main groups: those based on morphologic tumor burden, and those based on the viability of the tumor burden.⁶ The main characteristic of tumor viability is arterial enhancement.

Conventional cytotoxic agents induce rapid tumor shrinkage, but adequate response to HCC-specific therapies is not accurately represented by tumor size changes.^{6,47} Also, posttreatment transient tumoral enlargement is a well-known phenomenon; it should not automatically be considered tumor progression because it could actually be inflammation-mediated.^{9,45,48}

Figure 2 resumes the current and more frequently used response criteria employed for HCC response assessment.

Current viability-based response criteria, such as mRECIST and EASL, were designed specifically for HCC, mainly to assess response after LRTs, although they are also employed for systemic therapy evaluation.⁴⁹ Metastatic disease is assessed with conventional response criteria, with size and not viability the principal characteristic.⁴⁵

American College of Radiology Liver Imaging Reporting and Data System (LI-RADS) treatment response criteria (LR-TR) have been introduced into clinical practice and have gained wide acceptance. LI-RADS classifies post-treatment results (LR-TR) into 3 groups: nonviable, viable, and equivocal. However, importantly, LR-TR cannot be used

to assess systemic therapy response.¹⁸ Unlike mRECIST, the LI-RADS treatment response categories are assigned on a lesion-by-lesion basis and are not assigned to the whole liver or patient.¹⁸

An HCC that has been completely treated with a radiation-based modality can retain arterial enhancement, which can be misinterpreted as viable disease by mRECIST and EASL.¹² If the LI-RADS response algorithm is employed, a persistent arterial enhancement is best classified as LR-TR equivocal or LR-TR not viable as long as the treated tumor is decreasing in size.¹²

Inflammation secondary to immunotherapy can cause initial tumoral enlargement. HCC-designed RC may misclassify this phenomena as progression, leading to unnecessary changes or cessation of therapy. iRECIST was developed to assess response on immunotherapy and precisely defines this phenomena as pseudoprogression. It is characterized by an initial increase in the size of lesions, or the visualization of new lesions followed by a response.⁴⁸

mRECIST is the most studied response system and is frequently compared with RECIST in clinical trials. In several studies, mRECIST has demonstrated an improved prediction of treatment response and overall survival.⁵⁰⁻⁵²

The Organ Procurement and Transplantation Network (OPTN) system is employed to allocate patients on the waiting list for liver transplantation in the HCC setting in the United States.⁵³ OPTN class 5 indicates that a liver tumor meets radiological criteria for HCC (analogous to LI-RADS 5). OPTN has a special category to assess response of previously treated HCCs with locoregional therapy. A class OPTN 5T is given to treated HCCs with any residual viable

tumor or perfusion defect, corresponding to LI-RADS TR viable or equivocal.⁵⁴ As in LI-RADS, the OPTN 5T category cannot be applied to assess response to systemic agents.

Conclusions

Response assessment for HCC relies mainly on imaging, and it should take into account 3 essential aspects: timing, imaging technique, and response criteria to be employed.

The first imaging assessment after LR and systemic therapies is usually done after 4 weeks.

After a complete response is achieved, a follow-up schedule based on 3-month intervals is advisable. Multiphase CT and MRI are the only 2 imaging techniques recommended for HCC response assessment. Contrast-enhanced ultrasound and PET-CT are currently being evaluated for this purpose. MRI diagnostic performance is superior to CT for small tumors (< 2 cm) and those that have been treated with cTACE. HCC that has been treated with radiation-based therapies may show a delayed response, which is characterized by the persistence of arterial enhancement. For accepted radiological response criteria, arterial enhancement is the hallmark of tumor viability. Systemic therapies are continuously evolving; immunotherapies have shown promising results and their response evaluation should include special imaging considerations. ■

FINANCIAL 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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NEW POTENTIAL FRONTLINE STANDARDS FOR RCC ARE SPOTLIGHTED AT GENITOURINARY CANCERS SYMPOSIUM

Written by *ONCOLOGY*[®] staff

Combination therapy coupling immunotherapy with tyrosine kinase inhibitors (TKIs) with activity against VEGF receptors for the treatment of frontline renal cell carcinoma (RCC) took center stage at the 2021 Genitourinary Cancers Symposium, an event cosponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Urologic Oncology.

Namely, the readout of the phase 3 CLEAR trial (NCT02811861) demonstrated that combining lenvatinib (Lenvima) with either pembrolizumab (Keytruda) or everolimus (Afinitor) improved progression-free survival (PFS) and objective response rate (ORR) over sunitinib (Sutent) for the treatment of patients with advanced RCC receiving therapy in the frontline setting.

Additionally, the combination with pembrolizumab was able to improve overall survival (OS) versus the control group in this patient population. These data were simultaneously presented virtually during the Genitourinary Cancers Symposium and published in *The New England Journal of Medicine*.^{1,2}

“I think that lenvatinib [plus] pembrolizumab should be considered a standard treatment program. This awaits

regulatory review and hopefully approval, but certainly from looking at the data, this is a highly effective [treatment regimen],” said Robert J. Motzer, MD in an interview with *ONCOLOGY*[®]. At Memorial Sloan Kettering Cancer Center in New York, he is head of the kidney cancer section, Genitourinary Oncology Service, and holds the Jack and Dorothy Byrne Chair in Clinical Oncology. “Safety is manageable. It’s a very attractive program for first-line therapy for clear cell RCC,” Motzer said.

Another immunotherapy/VEGF-targeting combination, nivolumab (Opdivo) plus cabozantinib (Cabometyx), continued to demonstrate promise according to quality-of-life (QOL) and subgroup analyses from the pivotal phase 3 CheckMate 9ER trial (NCT03141177). This led to the FDA approval of the combination in the frontline setting for RCC in January 2021.³

CLEAR Study

The CLEAR trial included 1069 patients with advanced, treatment-naïve RCC who were randomized 1:1:1 to receive daily oral lenvatinib at 20 mg plus intravenous pembrolizumab at 200 mg every 3 weeks (n = 355); daily oral lenvatinib at 18 mg oral plus everolimus at 5 mg

(n = 357); or daily oral sunitinib at 50 mg for 4 weeks on and 2 weeks off (n = 357). PFS by independent review committee (IRC) per RECIST 1.1 was the primary end point; secondary end points included OS, ORR by IRC per RECIST 1.1, safety, and health-related QOL (HRQOL).

The median PFS with lenvatinib/pembrolizumab was 23.9 months versus 9.2 months with single-agent sunitinib (HR, 0.39; 95% CI, 0.32-0.49; $P < .001$). The lenvatinib/everolimus treatment arm achieved a median PFS of 14.7 months compared with 9.2 months in the sunitinib arm (HR, 0.65; 95% CI, 0.53-0.8; $P < .001$) (**Table**).^{1,2} The PFS benefit extended across all patient subgroups in both active therapy treatment arms.

“The results of the analysis [were] really striking. The primary end points were PFS for both lenvatinib and pembrolizumab [as well as] lenvatinib and everolimus vs sunitinib, and the trial met the primary end point for each of those arms showing a longer PFS compared with sunitinib,” Motzer said.

A median OS was not reached in any of the 3 treatment arms; however, the data indicated that OS was significantly longer in the lenvatinib/pembrolizumab arm compared with the sunitinib arm (HR, 0.66; 95% CI, 0.49-0.88; $P = .005$).

TABLE. Median PFS and OS Across CLEAR Trial Active Therapy Arms^{1,2}

Efficacy measure	Lenvatinib + pembrolizumab	Lenvatinib + everolimus	Sunitinib
PFS (95% CI), months	23.9 (20.8-27.7)	14.7 (11.1-16.7)	9.2 (6.0-11.0)
HR (95% CI), active therapy vs sunitinib	0.39 (0.32-0.49)	0.65 (0.53-0.80)	NA
OS (95% CI), months	NR	NR	NR
HR (95% CI), active therapy vs sunitinib	0.66 (0.49-0.88)	1.15 (0.88-1.50)	NA

NA, not applicable; NR, not reached; PFS, progression-free survival; OS, overall survival.

Motzer noted that there was no observed OS benefit with lenvatinib/everolimus over sunitinib alone (HR, 1.15; 95% CI, 0.88-1.50; $P = .3$).

ORR was higher in both the lenvatinib/pembrolizumab (71%; 95% CI, 66.3%-75.7%) and lenvatinib/everolimus (53.5%; 95% CI, 48.3%-58.7%) treatment arms compared with sunitinib (36.1%; 95% CI, 31.2%-41.1%). Of note, Motzer mentioned the “high complete response rate” of 16.1% in the lenvatinib-plus-pembrolizumab arm.

Patients in the lenvatinib/pembrolizumab arm achieved the longest median duration of response at 25.8 months, compared with 16.6 months and 14.6 months in the lenvatinib/everolimus and sunitinib arms, respectively.

Motzer noted that the safety profiles of both combinations were consistent with the known safety profile of each drug, and toxicities were manageable as needed for dose modifications.

CheckMate 9ER

According to extended follow-up data from CheckMate 9ER, nivolumab plus cabozantinib continued to demonstrate superior efficacy to single-agent sunitinib in the frontline treatment of patients with advanced RCC, and an exploratory subgroup analysis suggested that these survival and response benefits were seen regardless of sarcomatoid histology.⁴

Among patients with sarcomatoid features, the median PFS was 10.3 months in the combination arm vs 4.2 months with sunitinib monotherapy (HR, 0.42;

95% CI, 0.23-0.74). Patients who did not have sarcomatoid histology, on the other hand, had a median PFS of 17.5 months and 9.2 months in the doublet and single-agent arms, respectively (HR, 0.56; 95% CI, 0.45-0.69).

In terms of OS, the median was not reached in patients with or without sarcomatoid features who were treated with nivolumab/cabozantinib, nor was it reached for patients without sarcomatoid histology who were treated with sunitinib. The hazard ratio for OS in the sarcomatoid-positive group was 0.36 (95% CI, 0.17-0.79) and 0.73 (95% CI, 0.54-0.98) in the sarcomatoid-negative group.

Additional data from CheckMate 9ER found that patients with advanced RCC reported improved HRQOL when treated with nivolumab plus cabozantinib compared with treatment with sunitinib.⁵

Moreover, patients treated with the combination experienced a delay in deterioration and a significant decreased risk for confirmed deterioration in HRQOL scores, including disease-related kidney cancer symptoms.

Moving Forward

With these new data regarding immunotherapy combinations in the treatment of frontline RCC, key stakeholders who were in attendance at the meeting seemed optimistic about what these results mean going forward.

“We came all the way from single-agent [TKIs] to immunotherapy single agents; now we’re combining [them and] patients with metastatic RCC are living

way longer, years and years on average,” said Toni Choueiri, MD, director of the Lank Center for Genitourinary (GU) Oncology at Dana-Farber Cancer Institute/Brigham and Women’s Hospital as well as the Jerome and Nancy Kohlberg Chair and professor of medicine at Harvard Medical School in Boston, speaking in an interview about all the new data to come out of the conference.

“Some other studies are moving forward. Another combination trial is being planned—a large phase 3 trial that’s going to be using lenvatinib [plus] pembrolizumab as the standard arm for other combinations,” Motzer concluded. “I see this as setting a new standard, and hopefully [it] will also receive regulatory approval and be available for patients outside of studies.”■

FINANCIAL 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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Strategies for Optimizing Molecular Testing in Non-Small Cell Lung Cancer

Written by *ONCOLOGY*[®] staff

The advent of next-generation sequencing (NGS) has been a key driver in treatment advances and improved outcomes for patients with non-small cell lung cancer (NSCLC). However, implementation of universal molecular testing for patient populations who may benefit the most has been somewhat limited, with long turnaround times and lack of adequate tissue noted as 2 of the main causes.

Multiple clinical practice guidelines for physicians treating patients with this disease recommend that, at minimum, patients be tested for gene mutations in *EGFR*, *ALK*, and *ROS1*, as well as for expression of PD-L1. In addition, expanded panels that check for *BRAF*, *MET*, *RET*, *HER2*, and *KRAS* alterations are also advocated for in the literature given the actionability of these targets.¹⁻³

Given the broad availability of approved therapeutic agents across multiple oncogenic targets, “hot spot” testing—testing that focuses on a specific gene alteration in NSCLC—is being supplanted by broader tumor profiling methods.

“Precision medicine works in NSCLC because of the large number of highly actionable oncogene targets,” said David R. Gandara, MD, director of thoracic oncology at the UC Davis Comprehensive Cancer Center in

Sacramento, California, during a webinar for CancerNetwork[®], the online home of the journal *ONCOLOGY*[®]. “If we consider the 8 actionable oncogenes...more than 50% of patients with nonsquamous NSCLC will have one of those, so the unknown has shrunk considerably.”

Moderator Edgardo S. Santos Castillero, MD, of Florida Precision Oncology in Aventura, and Mark G. Kris, MD, the William and Joy Ruane Chair in Thoracic Oncology at Memorial Sloan Kettering Cancer Center in New York, joined Gandara in discussing the implementation of early molecular testing for patients with NSCLC.

Available Agents for Tumors Harboring Mutations

In addition to immunotherapeutics that are approved to treat patients with high PD-L1 expression, such as single-agent pembrolizumab (Keytruda) for patients with metastatic tumors with expression by tumor proportion score of 1% or more, targeted therapies have trans-

formed the systemic therapy landscape.

Most notably, tyrosine kinase inhibitors (TKIs) against *EGFR* are approved for use in both advanced disease and in adjuvant therapy for resectable tumors.

“Our job as thoracic oncologists is to identify this particular genomic alteration so we can provide to the patient the best therapy possible,” Santos Castillero said. “*EGFR* [as a therapeutic target] has been a great success. We have different TKIs and then also combinations—for example, erlotinib (Tarceva) plus ramucirumab (Cyramza).”

Santos Castillero went on to detail *ALK* TKIs, for which there are currently 5 FDA-approved agents for use across patients in different settings for metastatic disease. Emerging more recently are targeted therapies against *NTRK* fusions, such as larotrectinib (Vitrakvi), and *MET* exon 14 skipping mutations, such as tepotinib (Tepmetko). These alterations are each present in just about 3% of the overall NSCLC population,² but when they are identified, they represent the opportunity for impressive

Transcriptions used in this article have been edited for clarity.
Scan to view the webinar in its entirety.

TABLE. **Select NGS Assays for Testing of Non–Small Cell Lung Cancer Tumors**

Key attributes	Caris MAI	FoundationOne CDx	Oncotype MAP Pan-Cancer Tissue
Turnaround time	8-14 days	14 days	* Results reported in 3-5 business days -QNS reported within 48 hours
Sample requirements	* 10 slides * FFPE samples minimum size of 25 mm ² with ≥20% tumor content * Needle biopsy also acceptable (4-6 cores)	* 10 slides * FFPE samples minimum size of 25 mm ² with ≥20% tumor content	* FNA and FFPE samples as small as 3 mm ² with ≥15% tumor content * Sensitivity ≥ 99% for SNVs and indels, detection down to ≥7.5% MAF with > 99% specificity
Number of genes analyzed	About 22,000; WES	324	* 257 genes, 11 select fusions * More than 25 specific disease panels * CNV, TMB, MSI, and protein expression
IHC markers	About 12	1 (PD-L1)	22 IHC stains, including PD-L1 (22C3, SP142)
Treatment guidance	Caris MAI	CDx-associated findings	* More than 100 therapies * More than 45 combination therapies * More than 650 clinical trials * NCCN Compendium recommendations

CDx, companion diagnostic; CNV, copy number variant; FFPE, formalin-fixed paraffin-embedded; FNA, fine-needle aspiration; IHC, immunohistochemistry; MAF, mutant allele frequency; MAI, molecular artificial intelligence; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; QNS, quality not sufficient; SNV, single nucleotide variants; TMB, tumor mutational burden; WES, whole-exome sequencing

therapeutic responses in patients who may have no other promising options.

Common Testing Platforms

In discussing available NGS testing platforms for patients with metastatic NSCLC, Santos Castillero first reviewed Caris Molecular Intelligence Tumor Profiling, for which the turnaround time is between 8 and 14 days. The tissue sample requirement for this assay is 10 slides with a minimum size of 25 mm² and a 20% or greater tumor content; this platform analyzes approximately 22,000 genes by whole-exome sequencing.

A second assay, FoundationOne CDx, has a turnaround time of 14 days, with tissue sampling requirements that are similar to the Caris test at 10 slides and a minimum size of 25 mm² and 20% or greater tumor content. A total of 324 genes are analyzed and only 1 immunohistochemistry marker, PD-L1,

is included; companion diagnostic tests are available to help guide treatment.

Finally, Santos Castillero discussed the OncoType MAP Pan-Cancer Tissue Test, with a turnaround time of between 3 and 5 business days. “Quality not sufficient” results are reported more quickly, within 48 hours. Samples require tumor content of 15%; the test analyzes 257 genes as well as tumor mutational burden, microsatellite instability, and copy number variant. Twenty-two immunohistochemistry (IHC) markers are also included, by both IHC 223C and SP142, which are companion diagnostic tests for pembrolizumab and atezolizumab (Tecentriq), respectively (Table).

Addressing Challenges With NGS Tumor Testing

Clinicians can face challenges with comprehensive genomic profiling, including obtaining tissue samples that

meet minimum requirements and the tests’ long turnaround times. In addition, once profiling is done and molecular markers are identified, deciding upon the best treatment course can be no easy task.

The event participants shared their experiences regarding minimum tissue sampling requirements:

KRIS: [Meeting] minimum tissue sample requirements is among the biggest challenges [in comprehensive genomic profiling], because the problem is that either the tissue doesn’t exist or, as in my case because I work at a tertiary center, you are getting tissue from another institution, which is very hard. That is the number one problem. So, how do you deal with that? The only solution I can think of is to instill a culture of obtaining adequate tissue at the time of diagnosis, when lung cancer is first suspected. Even if we choose not to send it [immediately]

for NGS testing, obtaining adequate tissue [is important to] make sure it's in the pathology department, in case a decision is made at some point to send it for testing.

GANDARA: I agree that having the minimum sample size requirement was, in the past, a common problem. When we [talk to] community pathologists, twice yearly for lung cancer, we have a webinar discussing all the requirements for molecular testing. Every time a patient is entered on that trial, the pathologist fills out, at his institution, a form about the tumor purity: Are there any issues with the tissue specimen? Any crush artifacts or something else that would make it difficult to interpret? For most of these NGS panels, tumor purity has to be 20% or greater. From a clinician standpoint, the other thing that's evolved very rapidly over the past 5 years, and this goes back to what Dr. Kris saying, is that in many situations we're not accepting fine-needle aspiration. We're having the pulmonologist or the radiologist do a core biopsy. We're taking multiple needle passes to get the adequate amount of issue. Of course, if you have a block on the surgical biopsy or something similar, that's going to be a lot easier for testing. I think this is getting better nationwide.

In discussing turnaround times and the implications for starting therapy, Kris shared best approaches for selecting treatment:

KRIS: When lung cancer is suspected, we are working hard to ensure that whoever does the biopsy does the ordering of the molecular tests. Some reflex testing is also done for some of the targets—specifically ALK, EGFR, and KRAS. NGS testing for us runs about 2 weeks, meaning it takes 2 weeks from when the specimen arrives in the pathology lab to get the results for the full NGS testing. [Results from] blood [arrive back] just a few days sooner than those from tissue.

It's rare that you can't wait until the

result comes back, but there are some special situations where you have to start treatment before [then]. I think what happens is that if you start without the molecular results, it's imperative that you continue whatever treatment you've started until the point where you can ascertain whether that treatment helped and what the tolerance is for therapy. Even if, for example, you found an *EGFR* mutation, if a patient has had a near-complete response and very good tolerance to therapy, I would be loath to change. [My takeaway is that] I would [encourage] everybody on the treatment team, when lung cancer is suspected, to try to get all of the molecular testing that you need.

Moving Forward

To wrap up the event, Gandara shared his thoughts regarding precision approaches in NSCLC. “[At this time,] there is no better tumor type for precision medicine than advanced NSCLC. We had 7 FDA approvals just in May [2020] alone, and 4 of them were genomic-based therapy,” he said.

“Test early, test often, and pay attention to the report for every scrap of information that can help you care for the patient,” concluded Kris. ■

FINANCIAL 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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Gandara, M.D.**

**Edgardo S. Santos
Castillero, M.D.**

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Kris, M.D.**

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FOR YOUR ADULT PATIENTS WITH
PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER.¹

IF SHE RESPONDS TO CHEMOTHERAPY

ZEJULA is the only once-daily, oral, first-line maintenance monotherapy approved for advanced ovarian cancer in complete or partial response to platinum-based chemotherapy, regardless of biomarker status¹⁻³

Indication

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥ 3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥ 3

thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy ($\leq$ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders,

Please see additional Important Safety Information on the adjacent page.

1 DAILY DOSE

Zejula
niraparib
capsules 100 mg

YOU RESPOND WITH ZEJULA¹

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS^{1,4}

OVERALL POPULATION

38% REDUCTION IN THE RISK OF DISEASE
PROGRESSION OR DEATH

MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS
WITH PLACEBO (HR 0.62; 95% CI, 0.50-0.76) $P < 0.0001$

HRd POPULATION

57% REDUCTION IN THE RISK OF DISEASE
PROGRESSION OR DEATH

MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS
WITH PLACEBO (HR 0.43; 95% CI, 0.31-0.59) $P < 0.0001$

Study Design: PRIMA, a randomized double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of once-daily ZEJULA versus placebo (2:1) in 733 women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to first-line platinum-based chemotherapy. The primary endpoint was a hierarchical calculation of PFS: first in patients with HRd tumors and then in all patients. PFS was measured from time of randomization to time of disease progression or death. At the time of PFS analysis, limited overall survival data were available with 11% deaths in the overall population.^{1,4}

Important Safety Information (continued)

especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Embryo-Fetal Toxicity and Lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

The most common adverse reactions (Grades 1-4) in $\geq 10\%$ of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia, (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%),

cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in $\geq 25\%$ of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

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1L, first-line; CI, confidence interval; CR, complete response; HR, hazard ratio; HRd, homologous recombination deficient; PFS, progression-free survival; PR, partial response.

Visit [ZEJULA.COM/HCP](https://www.zejula.com/hcp) to explore the PRIMA data

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NRPJRNA200007 August 2020
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Please see Brief Summary on the following pages.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

ZEJULA (niraparib) capsules, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.ZEJULA.com.

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

ZEJULA is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

1.3 Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, or
- genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy [see *Clinical Studies (14.3)* of full prescribing information].

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZEJULA monotherapy in clinical trials. In 1785 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZEJULA in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with ZEJULA.

In PRIMA, the overall incidence of Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

In NOVA, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients.

In QUADRA, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 1% of patients.

Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy ($\leq$ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics [see *Dosage and Administration (2.3)* of full prescribing information].

5.3 Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 3-4 hypertension occurred in 6% of ZEJULA-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3-4 hypertension occurred in 9% of ZEJULA-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRA, Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary [see *Dosage and Administration (2.3)* and *Nonclinical Toxicology (13.2)* of full prescribing information].

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)* of full prescribing information]. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see *Warnings and Precautions (5.2)* and *Nonclinical Toxicology (13.1)* of full prescribing information]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

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

- Myelodysplastic Syndrome/Acute Myeloid Leukemia [see *Warnings and Precautions (5.1)*]
- Bone Marrow Suppression [see *Warnings and Precautions (5.2)*]
- Cardiovascular Effects [see *Warnings and Precautions (5.3)*]

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 most common adverse reactions of all grades in >10% of 1314 patients who received ZEJULA in the pooled PRIMA, NOVA and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZEJULA in PRIMA

Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (one patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

Table 1 and Table 2 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in all patients treated with ZEJULA in the PRIMA study.

Table 1: Adverse Drug Reactions Reported in $\geq 10\%$ of All Patients Receiving ZEJULA in PRIMA^a

	Grades 1-4 ^b		Grades 3-4 ^b	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Blood and Lymphatic System Disorders				
Thrombocytopenia	66	5	39	0.4
Anemia	64	18	31	2
Neutropenia ^c	42	8	21	1
Leukopenia ^d	28	9	5	0.4
Gastrointestinal Disorders				
Nausea	57	28	1	1
Constipation	40	20	1	0.4
Vomiting	22	12	1	1
General Disorders and Administration Site Conditions				
Fatigue	51	41	3	1
Investigations				
AST/ALT elevation	14	7	3	0.8
Metabolism and Nutrition Disorders				
Decreased appetite	19	8	1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	39	38	1	0
Nervous System Disorders				
Headache	26	15	0.4	0
Dizziness	19	13	0	0.4
Psychiatric Disorders				
Insomnia	25	15	1	0.4
Renal and Urinary Disorders				
Acute kidney injury ^e	12	5	0.2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	22	13	0.4	1
Cough	18	15	0	0.4
Vascular Disorders				
Hypertension	18	7	6	1

^aAll adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

^bCTCAE=Common Terminology Criteria for Adverse Events version 4.02

^cincludes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

^dincludes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

^eincludes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, blood creatine increased.

Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA				
	Grades 1-4		Grades 3-4	
	ZEJULA N=484 %	Placebo N=244 %	ZEJULA N=484 %	Placebo N=244 %
Decreased hemoglobin	87	66	29	1
Decreased platelets	74	13	37	0
Decreased leukocytes	71	36	9	0
Increased glucose	66	57	3	3
Decreased neutrophils	66	25	23	1
Decreased lymphocytes	51	29	7	3
Increased alkaline phosphatase	46	21	1	0
Increased creatinine	40	23	0	0
Decreased magnesium	36	34	1	0
Increased aspartate aminotransferase	35	17	1	0.4
Increased alanine aminotransferase	29	17	2	1

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA

Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of the treatment was 11.0 months (range: 1 day to 16 months).

Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in > 2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3.0% each), and nausea (2.4%).

Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA.

Table 3: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA ^a				
	Grades 1-4 ^b		Grades 3-4 ^b	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Blood and Lymphatic System Disorders				
Thrombocytopenia	54	5	21	1
Anemia	50	28	23	1
Neutropenia ^c	36	8	15	1
Leukopenia ^d	28	11	5	0
Gastrointestinal Disorders				
Nausea	53	21	1	0
Constipation	31	15	1	1
Vomiting	17	9	0	1
General Disorders and Administration Site Conditions				
Fatigue	48	36	3	0
Metabolism and Nutrition Disorders				
Decreased appetite	19	5	1	0
Nervous System Disorders				
Headache	22	17	1	0
Dizziness	14	13	0	0
Psychiatric Disorders				
Insomnia	21	14	0	0

Table 3: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA ^a Cont'd				
	Grades 1-4 ^b		Grades 3-4 ^b	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Renal and Urinary Disorders				
Acute kidney injury ^e	12	5	1	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	18	10	0	1
Vascular Disorders				
Hypertension	17	9	5	2

^aAll adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

^bCTCAE=Common Terminology Criteria for Adverse Events version 4.02

^cincludes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

^dincludes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

^eincludes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, blood creatine increased.

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA				
	Grades 1-4		Grades 3-4	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Decreased hemoglobin	81	70	21	0
Decreased leukocytes	70	36	6	0
Decreased platelets	63	15	18	0
Increased glucose	63	56	2	1
Decreased neutrophils	60	27	15	0
Decreased lymphocytes	52	30	5	4
Increased alkaline phosphatase	43	17	1	0
Decreased magnesium	44	30	0	0
Increased creatinine	41	22	0	0
Increased aspartate aminotransferase	31	19	1	0
Increased alanine aminotransferase	28	15	2	2

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZEJULA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA				
	Grades 1-4 ^a		Grades 3-4 ^a	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Blood and Lymphatic System Disorders				
Thrombocytopenia	61	5	29	0.6
Anemia	50	7	25	0
Neutropenia ^b	30	6	20	2
Leukopenia	17	8	5	0

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA Cont'd				
	Grades 1-4 ^a		Grades 3-4 ^a	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Cardiac Disorders				
Palpitations	10	2	0	0
Gastrointestinal Disorders				
Nausea	74	35	3	1
Constipation	40	20	0.8	2
Vomiting	34	16	2	0.6
Mucositis/stomatitis	20	6	0.5	0
Dyspepsia	18	12	0	0
Dry mouth	10	4	0.3	0
General Disorders and Administration Site Conditions				
Fatigue/Asthenia	57	41	8	0.6
Metabolism and Nutrition Disorders				
Decreased appetite	25	15	0.3	0.6
Infections and Infestations				
Urinary tract infection	13	8	0.8	1
Investigations				
AST/ALT elevation	10	5	4	2
Musculoskeletal and Connective Tissue Disorders				
Back pain	18	12	0.8	0
Nervous System Disorders				
Headache	26	11	0.3	0
Dizziness	18	8	0	0
Dysgeusia	10	4	0	0
Psychiatric Disorders				
Insomnia	27	8	0.3	0
Anxiety	11	7	0.3	0.6
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis	23	14	0	0
Dyspnea	20	8	1	1
Cough	16	5	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	21	9	0.5	0
Vascular Disorders				
Hypertension	20	5	9	2

^aCTCAE=Common Terminology Criteria for Adverse Events version 4.02

^bincludes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in NOVA				
	Grades 1-4		Grades 3-4	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Decrease in hemoglobin	85	56	25	0.5
Decrease in platelet count	72	21	35	0.5
Decrease in WBC count	66	37	7	0.7
Decrease in absolute neutrophil count	53	25	21	2
Increase in AST	36	23	1	0
Increase in ALT	28	15	1	2

N=number of patients; WBC=white blood cells; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood

alkaline phosphatase increased, weight decreased, depression, epistaxis.

Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

The safety of ZEJULA monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1-4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.

Table 7: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA		
	Grades 1-4 ^a N=463 %	Grades 3-4 ^a N=463 %
Blood and Lymphatic System Disorders		
Anemia ^a	51	27
Thrombocytopenia ^c	52	28
Neutropenia ^d	20	13
Gastrointestinal Disorders		
Nausea	67	10
Vomiting	44	8
Constipation	36	5
Abdominal pain	34	7
Diarrhea	17	0.2
General Disorders and Administration Site Conditions		
Fatigue	56	7
Infections and Infestations		
Urinary tract infection	15	2
Investigations		
Blood alkaline phosphatase increased	11	2
AST/ALT elevation	11	1
Metabolism and Nutrition Disorders		
Decreased appetite	27	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	29	3
Nervous System Disorders		
Headache	19	0.4
Dizziness	11	0
Psychiatric Disorders		
Insomnia	21	1
Renal and Urinary Disorders		
Acute kidney injury	17	1
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	22	3
Cough	13	0
Vascular Disorders		
Hypertension	14	5

^aCTCAE=Common Terminology Criteria for Adverse Events version 4.02

^bAnemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normochromic normocytic anemia.

^cThrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.

^dNeutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection and neutropenic sepsis.

Table 8: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA		
	Grades 1-4 N=463 %	Grades 3-4 N=463 %
Decreased hemoglobin	83	26
Increased glucose	66	5
Decreased platelets	60	28
Decreased lymphocytes	57	18
Decreased leukocytes	53	9
Decreased magnesium	46	1
Increased alkaline phosphatase	40	4
Increased gamma glutamyl transferase	40	8
Increased creatinine	36	0.4
Decreased sodium	34	6
Decreased neutrophils	34	15
Increased aspartate aminotransferase	29	2
Decreased albumin	27	2

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZEJULA. 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: hypersensitivity (including anaphylaxis)

Nervous System Disorders: posterior reversible encephalopathy syndrome (PRES)

Psychiatric Disorders: confusional state/disorientation, hallucination, cognitive impairment

Respiratory, Thoracic, and Mediastinal Disorders: non-infectious pneumonitis

Skin and Subcutaneous Tissue Disorders: photosensitivity

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women [see *Clinical Pharmacology* (2.1) of full prescribing information]. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see *Warnings and Precautions* (5.2) and *Nonclinical Toxicology* (13.1) of full prescribing information]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

A pregnancy test is recommended for females of reproductive potential prior to initiating ZEJULA treatment.

Contraception

Females

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

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months following the last dose.

Infertility

Males

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

8.5 Geriatric Use

In PRIMA, 39% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mild (CLcr: 60 to 89 mL/min) to moderate (CLcr: 30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria. The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown.

10 OVERDOSAGE

There is no specific treatment in the event of ZEJULA overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

17 PATIENT COUNSELING INFORMATION

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

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZEJULA [see *Warnings and Precautions* (5.1)].

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection [see *Warnings and Precautions* (5.2)].

Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first two months, then monthly for the first year of treatment, and then periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated [see *Warnings and Precautions* (5.3)].

Dosing Instructions

Inform patients on how to take ZEJULA [see *Dosage and Administration* (2.2) of full prescribing information]. ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA, not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [see *Warnings and Precautions and Use in Specific Populations* (8.1)].

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after receiving the last dose [see *Use in Specific Populations* (8.3)].

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose [see *Use in Specific Populations* (8.2)].

124212BRS 04/2020

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Research Triangle Park, NC 27709
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NRPJRNA200007 August 2020
Produced in USA.

Relapsed/Refractory HER2+ Metastatic Breast Cancer

MEET OUR EXPERT PANEL

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To watch the full event, go
to [CancerNetwork.com/
AroundthePractice](https://CancerNetwork.com/AroundthePractice)

Improvements in extracranial disease control and survival of patients with HER2-positive (+) metastatic breast cancer have led to an increased proportion of patients living long enough to develop central nervous system (CNS) metastases. The recent development of HER2-targeted therapies with CNS activity may improve survival of patients with CNS metastases and prevent development of new CNS metastases. Experts discussed this in a virtual CancerNetwork® Around the Practice presentation, “Relapsed/Refractory HER2+ Metastatic Breast Cancer,” held January 21, 2021, and moderated by **Adam M. Brufsky, MD, PhD**. The presentation also included an interactive online platform for members of the audience to submit responses to polling questions that were subsequently discussed by the panelists.

Treatment of HER2+ Metastatic Breast Cancer

The standard-of-care therapy in the frontline setting for patients with HER2+ metastatic breast cancer is taxane chemotherapy with the HER2-targeted monoclonal antibodies trastuzumab and pertuzumab. This regimen is based on results from the CLEOPATRA trial (NCT00567190), which showed that treatment with trastuzumab, pertuzumab, and docetaxel led to median progression-free survival (PFS) of 18.7 months and a median overall survival (OS) of 57 months in women with HER2+ metastatic breast cancer.^{1,2} The HER2-targeted antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1) is commonly used in the second-line setting. In the EMILIA trial (NCT00829166), it was associated with an OS rate of 30.9 months and median PFS of 9.6 months in patients with locally advanced or metastatic HER2+ metastatic breast cancer previously treated with trastuzumab and a taxane.³ No standard of care has been

established for third or later lines of therapy; with current options, the response rate and median PFS are modest (9%-31% and 3-6 months, respectively).⁴

In clinical practice, docetaxel is often substituted for paclitaxel to provide a treatment option with an alternative dosing schedule, said **Neil M. Iyengar, MD**. “In our anecdotal experience here, [it is] a little easier to manage adverse events [AEs] with docetaxel,” he said. “As we start to talk about metastatic disease where median PFS continues to be prolonged, a treatment approach that is more manageable in the long term is important.” Docetaxel treatment may be discontinued when the patient achieves treatment response and reinitiated if there is disease progression, or when docetaxel is appropriate in combination with a HER2-targeted antibody. Iyengar noted that this intermittent dosing approach for docetaxel is also a promising area of research for reducing chemotherapy-related AEs and prolonging the period of maintenance antibody-based therapy with a nonchemotherapy partner agent.

V. K. Gadi, MD, PhD, added that with the improvement in long-term outcomes of adjuvant treatment of HER2+ metastatic breast cancer, a greater proportion of metastatic disease presentations are in patients who have not received prior treatment and, thus, are potentially curable (as opposed to presentations in patients who had received prior treatment for early-stage disease and had a metastatic recurrence). “A lot of those patients [with treatment-naïve disease] can get very good, stable, long-term disease control, and, at some point, we might just call that a cure,” said Gadi.

However, **Sara A. Hurvitz, MD**, cautioned that the identification of patients who can safely discontinue therapy is challenging and requires shared decision-making with the patient. “For some patients, in a shared

way, we've decided to stop therapy and watch closely and see what happens," she said. "It really does, given the lack of evidence, need to be a shared decision."

Management of CNS Metastases in HER2+ Metastatic Breast Cancer

Despite the effective treatment of early-stage disease and extracranial metastases, rates of CNS metastases remain high with HER2+ metastatic breast cancer, occurring in approximately 40% to 50% of patients.⁵ During the event, 50% of audience members identified that the rate of progression is an important factor when deciding whether to continue current systemic therapy or switch to local therapy for a patient who develops CNS progression after starting frontline therapy. Other answer choices that received responses included disease extent and location (25%) and presence of symptoms (25%).

For patients with CNS metastases, stereotactic radiosurgery (SRS) has the potential to provide durable therapeutic responses and is a preferred therapeutic option. SRS delivers photon radiation with high precision compared with whole-brain radiation. Whole-brain radiation is associated with cognitive function AEs and impairments in quality-of-life outcomes. Despite the benefits of SRS, it is also associated with a high rate of neurologic complications, which can vary.⁶ Despite the benefits of SRS, it is also associated with a high rate of neurologic complications, which can vary based on the involved brain regions.⁶ Surgical resection may also be considered for patients with limited sites of disease that are surgically accessible and within a reasonable functional status.⁶

Local therapy is generally indicated for patients whose disease has adequate systemic control, thus highlighting a need for systemic-based therapies for patients who also have extracranial metastases.⁶

Gadi said that a multidisciplinary

approach, crafted with input from a neuroradiation oncologist and possibly a neurooncologist, is important for optimal management of patients with CNS metastases. Patient symptoms should guide the management approach, he added. "If a patient has symptoms, then you need to address the symptoms," he said. "If the patient doesn't have symptoms or it's an incidental finding or something that could be managed with SRS, that becomes a viable option as well."

Gadi added that tucatinib is also a promising option in this setting for some patients, based on recent data from the phase 3 HER2CLIMB trial (NCT02614794). The results showed that, compared with placebo, tucatinib added to trastuzumab and capecitabine led to a 68% reduction in risk for brain progression and death, as well as a 42% reduction in risk of death in patients with HER2+ metastatic breast cancer that had metastasized to the brain and had been treated previously with trastuzumab, pertuzumab, and T-DM1.⁷ The median duration of PFS in the CNS was 9.9 months in the tucatinib arm and 4.2 months in the placebo arm; estimated OS at 1 year was 70.1% and 46.7% in the

tucatinib and placebo arms, respectively.⁷

"I think [decisions must] still [be made on] a case-by-case basis, but it gives us a pretty powerful tool to proactively manage the CNS metastasis with or without SRS," said Gadi.

However, whether tucatinib should be used before or instead of SRS is currently unclear and likely depends on the number of metastases in the brain, according to Iyengar. "If it's a question about something like SRS to a single lesion, my preference and the preference of our neuroradiation oncologist is generally to proceed with SRS to the single lesion," Iyengar said. "If we're talking about more diffuse, maybe multiple parenchymal metastases, and the question is whole brain versus something like tucatinib, I think that's more of a discussion. We tend to err on the side of local therapy, followed by perhaps a switch of [the] systemic therapy [regimen] until we see more data for that cohort of untreated brain metastases population."

With PFS and OS consistently lower in patients with brain metastases, figuring out optimal sequences of locoregional and systemic therapy continues to be important, according to Hurvitz. She pointed out

CASE 1: What treatment would you recommend for this patient?^a

50%
voted

Tucatinib, trastuzumab,
and capecitabine

VS

50%
voted

Stereotactic radiosurgery
to CNS metastases

CNS, central nervous system. HER2+, HER2-positive.

^aCase 1: A woman, age 48 years, with HER2+ metastatic breast cancer, 3 lesions in the liver, and no CNS metastases at initial presentation. She received 6 cycles of docetaxel, trastuzumab, and pertuzumab, followed by trastuzumab and pertuzumab for an additional 12 months. She developed 2 new liver lesions and about 30 small lesions scattered throughout the brain.

that patients in the HER2CLIMB study who had a CNS progression on trial were allowed to receive SRS or radiation therapy and to continue in the trial if they did not have extracranial progression. “We can do that in clinical practice where patients are started on tucatinib-based therapy, and if they have an isolated CNS progression, you have data to support treating it locoregionally and continuing systemic therapy,” she said.

Although tucatinib is the only approved agent for metastatic HER2+ metastatic breast cancer and the only one that has demonstrated substantial response in the brain, some data suggest that certain HER2-targeted therapies may delay time to initial development of brain metastases. Results of the NEfERT-T trial (NCT00915018) of patients with treatment-naïve, HER2+ metastatic breast cancer showed that neratinib and trastuzumab had a similar objective response rate and duration of response when added

to paclitaxel, but the neratinib regimen was associated with significantly lower estimated Kaplan-Meier 2-year incidence of CNS recurrences (16.3% vs 31.2%; $P = .004$).⁸

Gadi also noted the possibility of T-DM1 delaying the onset of CNS metastases, although the ADC’s large molecular size was traditionally thought to preclude CNS access. “If you have a drug that is very, very good at maintaining systemic disease at a low level...then you would interpret that as an effect in the brain,” said Gadi. “But now I think there’s some emerging evidence that these molecules are actually crossing the blood-brain barrier. They’re detectable in the CNS, and maybe they are actually [reaching the brain] in enough quantity to impart an effect directly on brain metastases.”

Case 1: The panelists discussed their approach to management of the case of a woman, age 48 years, with HER2+ metastatic breast cancer, 3 lesions in the liver, and no CNS metastases at initial presentation. She received 6 cycles of docetaxel, trastuzumab, and pertuzumab, followed by trastuzumab and pertuzumab for an additional 12 months, to which the breast lesion had a partial response and the liver lesions had a full response. Then, she developed 2 new liver lesions and approximately 30 small lesions scattered throughout the brain.

Case 1 Discussion

Half of the audience revealed that 50% of respondents recommended tucatinib, trastuzumab, and capecitabine for this patient and the other 50% recommended SRS to the brain metastases.

Hurvitz pointed out that SRS and switching systemic therapy should be considered because of the systemic progression in the liver in addition to new-

onset brain metastases. “I like tucatinib because it does penetrate the blood-brain barrier, but I probably would talk to my radiation oncology and neurosurgery colleagues,” she said. “I’m thinking we’d probably end up doing both the SRS and tucatinib-based therapy.”

Iyengar added that the relatively good tolerability of the tucatinib-based regimen makes it a reasonable option and that although diarrhea is a common AE, it usually improves or resolves with initiation of antidiarrheal agents. He also noted that many of the AEs with the regimen are likely related to capecitabine, and most practices are experienced with managing these and modifying the dose as necessary.

Gadi concluded that it is important to continue to assess the data on patient-reported outcomes from the studies of tucatinib with capecitabine, as the regimen’s high pill burden may negatively affect patient quality of life. “From our perspective as physicians, yeah, this is a slam dunk, it’s easy to give. But that’s not the perspective that matters sometimes,” he pointed out.

Treatment After Progression on More Than 2 Prior Lines of Anti-HER2 Targeted Therapy

In a poll of the audience, 92% of respondents stated that selection of a treatment approach for a patient with HER2+ metastatic breast cancer who has progressed on 2 or more prior lines of therapy should consider all the listed factors (ie, nature and depth of progression, duration of response to previous therapy, mechanism of action and exposure to certain molecules in the early-stage setting, tolerance to previous therapy, site[s] of progression), whereas the remaining 8% selected nature and depth of progression plus duration of response to previous therapy as the primary factors to consider.

Hurvitz said that she does not use neratinib frequently in her practice because the toxicity profile is difficult for patients to manage. “We don’t have evidence that neratinib works well after

Poll Results: Treatment Decision-Making in the Third-Line Treatment Setting

What factors are important when considering a treatment approach for a patient with HER2+ MBC that has progressed on at least 2 prior lines of therapy?

HER2+, HER2-positive; MBC, metastatic breast cancer.

*All factors included nature and depth of progression; duration of response to previous therapy, mechanism of action, exposure to certain molecules in the early-stage setting, tolerance to previous therapy, and site(s) of progression.

CASE 2: What treatment would you recommend for this patient?^a

T-DM1, trastuzumab emtansine.

^aCase 2: A woman, age 61 years, who had a pathologic complete response to neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab and received adjuvant trastuzumab and pertuzumab, to complete 1 year of therapy. She received T-DM1 for disease progression 8 months later, then developed metastases in her liver and left lung after 24 months of stable disease on T-DM1.

tucatinib, which is where I would place it,” she said. “We need evidence of whether or not neratinib works in brain metastases and in systemic metastases, post tucatinib. If it does, that’s probably where I’ll use it.”

Hurvitz said that, in contrast, she is a “big fan” of trastuzumab deruxtecan (DS-8201), an ADC consisting of a humanized HER2-targeted monoclonal antibody with the same amino acid sequence as trastuzumab, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor as the cytotoxic drug (ie, payload).⁴ Trastuzumab deruxtecan also

has a higher drug-to-antibody ratio than T-DM1 (approximately 8:1 vs 3-4:1) while maintaining a favorable pharmacokinetic profile.⁴ Results of the phase 2 DESTINY-Breast01 trial (NCT03248492) showed a response rate of 60.9%, median PFS duration of 16.4 months, and estimated 12-month OS rate of 86.2% in patients with heavily pretreated metastatic HER2+ metastatic breast cancer who had a median of 6 prior lines of therapy for metastatic disease.⁴

Hurvitz cautioned that treatment-related interstitial lung disease (ILD), which was reported in 13.6% of patients in the

DESTINY-Breast01 trial, can mimic lung disease induced by COVID-19; Iyengar added that the drug-related ILD can progress rapidly, and the risk of ILD needs to be weighed against the potential benefit in treatment response.⁴ Iyengar added that he orders baseline pulmonary function testing to assess the patient’s function prior to starting the drug. Assessing for history of prior lung disease and risk for Coronavirus 2019–related lung disease is important prior to starting trastuzumab deruxtecan, he noted.

Case 2: The panelists discussed treatment options for the case of a woman, age 61 years, who had a pathologic complete response to neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab and received adjuvant trastuzumab and pertuzumab, and completed 1 year of therapy. She received T-DM1 for disease progression 8 months later, then developed metastases in her liver and left lung after 24 months of stable disease on T-DM1.

Case 2 Discussion

An audience poll revealed that an equal number of clinicians would recommend tucatinib, trastuzumab, and capecitabine or trastuzumab deruxtecan (38%); 15% would recommend neratinib plus capecitabine; and 8% would recommend a clinical trial.

Hurvitz said that she favors tucatinib in this scenario even though the patient does not have brain metastases, given its reasonably good tolerability and the randomized data that support its efficacy. “We don’t yet have randomized data supporting the use of trastuzumab deruxtecan, so I like the tucatinib idea, hoping that maybe it will postpone or mitigate the risk of progression in the brain,” she said.

Similarly, Gadi said that he favors tucatinib in this case, given its robust evidence, but he noted, “I don’t fault anybody for picking the deruxtecan here because it is such an active agent in somebody with rapid progression.”

The ongoing phase 3 DESTINY-Breast03 trial (NCT03529110), which is comparing trastuzumab deruxtecan with T-DM1 in patients with metastatic HER2+ metastatic breast cancer previously treated with trastuzumab and taxane chemotherapy, will provide randomized data regarding the efficacy and safety of trastuzumab deruxtecan and has an estimated completion date of April 2023.⁹ However, Gadi said that he is unlikely to preferentially use it over tucatinib, given the potential toxicities associated with trastuzumab deruxtecan, although having both drugs to sequence will be beneficial. “The one other concern I have with deruxtecan is

whether patients will be fit to try another line of therapy after it,” he said. “If we know the drug is going to work after other stuff has worked, I might try the other stuff first and then have this available to me in that third-line setting.” However, all the panelists agreed that although they would prefer tucatinib, either tucatinib or trastuzumab deruxtecan is appropriate in this setting, provided the patient is healthy enough from a pulmonary standpoint. ■

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Lenvatinib Combined With Pembrolizumab or Everolimus Lengthens Survival in Advanced Renal Cell Carcinoma

Expert Interview With Robert J. Motzer, MD; and Toni Choueiri, MD

Motzer and Choueiri review recent clinical data from the phase 3 CLEAR study and discuss the clinical implications this combination may have for patients with advanced renal cell carcinoma.

To see the full videos with Dr Motzer and Dr Choueiri, scan the code.

KEY TAKEAWAYS:

- Combination therapy that includes an immune checkpoint inhibitor and a tyrosine kinase inhibitor is a promising first-line treatment for advanced clear cell renal cell carcinoma.
- Lenvatinib/pembrolizumab enabled longer progression-free survival and overall survival and better objective response in patients with renal cell carcinoma than sunitinib did.
- Severe adverse events were common but typically effectively managed with dose reductions.
- Starting therapy at a high dose and then lowering it as toxicities develop is an effective strategy for maintaining efficacy.

This year, about 76,000 cases of renal cell carcinoma (RCC) will be diagnosed in the United States, of which roughly 80% will be clear cell renal cell carcinoma (ccRCC). ccRCC has a 5-year survival rate of 50% to 69%. When tumors are large or have metastasized, the 5-year survival rate drops to 10%.¹

Patients with advanced RCC with clear cell histology typically are given VEGF receptor tyrosine kinase inhibitors (TKIs), such as sunitinib, as a first-line treatment. Often, however, medication resistance results in disease relapse. An alternative is the use of immune checkpoint inhibitors (ICIs), which can be bundled with TKIs. Combination therapies that include ICIs have been shown to provide better outcomes than sunitinib in patients with metastatic RCC.²

The multitargeted TKI lenvatinib and the PD-1 inhibitor pembrolizumab have individually demonstrated promise as agents against RCC. Results from the

phase 3 KEYNOTE-581/CLEAR trial, unveiled at the 2021 virtual American Society of Clinical Oncology Genitourinary Cancers Symposium, and published in *New England Journal of Medicine*, showed that lenvatinib and pembrolizumab together offer longer progression-free survival (PFS) and overall survival (OS) than does sunitinib.^{2,3} Investigators are hopeful that this combination therapy will soon be approved by the FDA as frontline treatment for advanced or metastatic RCC.

Study Design

The phase 3 KEYNOTE-581/CLEAR trial, led by investigators at Memorial Sloan Kettering (MSK) Cancer Center in New York, New York, and Dana-Farber Cancer Institute in Boston, Massachusetts, recruited patients globally from October 2016 to July 2019. A total of 1069 patients with previously untreated advanced RCC were randomized based on geographic

location and MSK prognostic risk group. Median ages across treatment groups were 61 to 64 years, and 72% to 77% of participants were men.²

Subjects were randomized in a 1:1:1 ratio to receive one of these regimens: 20 mg of lenvatinib taken orally once daily, plus 200 mg of intravenous pembrolizumab on day 1 of every 3-week cycle; 18 mg of lenvatinib taken orally once daily, plus 5 mg of everolimus, an mTOR kinase inhibitor, taken orally once daily for every 3-week cycle; or 50 mg of sunitinib taken orally once daily for 4 weeks, followed by 2 weeks without treatment.²

The trial's primary end point was PFS as determined by an independent review committee using RECIST guidelines, version 1.1. Secondary end points included OS and objective response, and additional end points included safety and response duration.²

Trial Outcomes

The lenvatinib/pembrolizumab combination resulted in significantly longer PFS than did sunitinib (median, 23.9 vs 9.2 months; HR for disease progression or death, 0.39; 95% CI, 0.32-0.49; $P < .001$). Lenvatinib plus everolimus also yielded significantly longer PFS than sunitinib (median, 14.7 vs 9.2 months; HR, 0.65; 95% CI, 0.53-0.80; $P < .001$). The OS rates were 79.2% for the lenvatinib/pembrolizumab arm, 66.1% for the lenvatinib/everolimus arm, and 70.4% for the sunitinib arm. The OS difference was significant between lenvatinib/pembrolizumab and sunitinib (HR for death, 0.66; 95% CI, 0.49-0.88; $P = .005$) but not between lenvatinib/everolimus and sunitinib (Table).²

Objective response rates as assessed by an independent review committee were 71.0%, 53.5%, and 36.1% for patients taking lenvatinib/pembrolizumab, lenvatinib/everolimus, and sunitinib, respectively; the complete response (CR) rates were 16.1%, 9.8%, and 4.2%, respectively.²

"The outcome of the trial showed that there was a really powerful effect on PFS with lenvatinib/pembrolizumab (with

TABLE. **CLEAR Trial: Efficacy and Safety Results at 24 Months**²

	Lenvatinib + pembrolizumab	Lenvatinib + everolimus	Sunitinib
Median PFS (months)	23.9	14.7	9.2
OS at 24 months	79.2%	66.1%	70.4%
Objective response rate	71.0%	53.5%	36.1%
AEs $\geq$ grade 3	82.4%	83.1%	71.8%

AE, adverse event; OS, overall survival; PFS, progression-free survival.

a median PFS of more than 23 months) compared with sunitinib," said investigator Robert J. Motzer, MD, head of the kidney cancer section of MSK's Genitourinary Oncology Service. "There was a high response rate of now more than 70%. It's the first time we've crossed that margin, and—also notable—[achieved] a 16% complete response rate by independent review." Fewer than 5% of patients experienced overt disease progression in the trial, Motzer added.

In the trial's lenvatinib/pembrolizumab arm, median length of treatment was 17.0 months compared with 11.0 months in the lenvatinib/everolimus arm and 7.8 months in the sunitinib arm. At data cutoff in August 2020, 40% of those taking lenvatinib/pembrolizumab were still receiving treatment compared with 31.4% and 18.8% of those taking lenvatinib/everolimus and sunitinib, respectively. The primary reason for discontinuation in any group was disease progression.²

Adverse Events

Nearly every study participant in the lenvatinib/pembrolizumab (99.7%), lenvatinib/everolimus (99.7%), and sunitinib groups (98.5%) experienced at least 1 adverse event (AE) during the trial. A total of 82.4% of participants in the lenvatinib/pembrolizumab arm experienced at least one grade 3 or higher event vs 83.1% in the lenvatinib/everolimus arm and 71.8% in the sunitinib arm.²

Diarrhea was the most common AE, reported by 61.4% in the lenvatinib/

pembrolizumab arm, 66.5% in the lenvatinib/everolimus arm, and 49.4% in the sunitinib arm. Other AEs of grade 3 or higher reported by 10% or more participants in any group included hypertension, fatigue, increased lipase level, nausea, and elevated triglycerides.²

In the lenvatinib/pembrolizumab group, AEs led to discontinuation of 1 or both drugs in 37.2% of patients: 25.6% stopped lenvatinib, 28.7% stopped pembrolizumab, and 13.4% stopped both. A total of 68.8% of participants needed to lower the lenvatinib dose, and in 78.4% of participants in the same arm, use of either or both drugs was interrupted due to AEs.²

For patients in the lenvatinib/pembrolizumab group who discontinued treatment because of AEs, median time to discontinuation was 8.97 months. Median time to discontinuation in the lenvatinib/everolimus group was 5.49 months. Of those taking lenvatinib/everolimus, 27.0% experienced AEs that led to a discontinuation of 1 or both drugs: 22.0% stopped lenvatinib, 24.8% stopped everolimus, and 18.9% stopped both. A total of 73.2% in this group required dose reductions of 1 or both drugs, and 83.4% experienced an interruption in their regimen. In the sunitinib group, 50.3% of patients required a dose reduction and 53.8% had their treatment interrupted. A total of 14.4% of the sunitinib group experienced AEs sufficient to discontinue treatment; the discontinuers received the drug for a median of 4.57 months.²

Dosing Strategy

According to Motzer and colleagues, pausing and restarting lenvatinib treatment or lowering the dose is a common technique for providing patients longer-term benefits while guarding against the drug's AEs, which can be managed appropriately if recognized early in a patient's course of treatment.

Motzer has considerable experience treating patients with the lenvatinib/pembrolizumab combination, and he feels patients tend to tolerate it well. "The key is to start out with the full recommended dose of lenvatinib, and then, as toxicities or AEs are seen, to individualize treatment by dose reduction of the lenvatinib," he said. More than half of his patients end up on reduced doses of lenvatinib, typically at a maintenance dose of 10 mg, which he noted is a comfortable long-term dose. "But I do think the high dose early on may be important for the extreme efficacy that's seen with the regimen," Motzer said.

Investigator and trial co-lead Toni Choueiri, MD, director of the Lank Center for Genitourinary Oncology and the Kidney Cancer Center at Dana-Farber, agreed with the strategy of beginning treatment at a high dose and then reducing it. "That's not a bad [option], as long as you know how to manage toxicities," he said. "Some patients are going to stay on

lenvatinib at 20 mg daily; others may need to decrease to 18 mg or 14 mg or even lower as long as their disease is controlled."

Choueiri also pointed out that toxicities are relative in cancer medications: "The good thing is that the grade 3 or 4 specific treatment-related adverse events [with lenvatinib/pembrolizumab] tend to be low." Although data on patients' self-reported quality of life can provide a more complete picture of the success of a drug or drug combination than toxicity data, Choueiri noted that the oncology community has yet to get that data on lenvatinib/pembrolizumab.

How Combinations Compare

Although both lenvatinib regimens showed longer PFS than sunitinib, only lenvatinib/pembrolizumab showed greater OS. Investigators said this finding confirms that a combination therapy encompassing an ICI and a TKI is a key first-line treatment in advanced RCC.

Motzer highlighted the importance of the CLEAR trial as compared with past trials that tested combinations such as ipilimumab/nivolumab, axitinib/pembrolizumab, and nivolumab/cabozantinib, all of which showed benefit for patients with advanced kidney cancer. The CLEAR trial, in contrast to these, was a 3-arm study in which 2 arms were compared directly

with the control arm of sunitinib—long a dominant monotherapy—and not with each other.

"It's really the first of these trials to have a contemporary control arm that does not include an immunotherapy or PD-1 agent," Motzer said. "So its significance, to me, is that it really shows proof of principle about the importance of immunotherapy therapy in first-line RCC treatment to achieve that OS benefit, and benefits in progression-free survival and response rate were seen as well."

Investigators have been seeking an alternative to sunitinib because of deficits in its ability to significantly lengthen PFS and OS and because of decreases in patients' quality of life, according to Choueiri. ■

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Editor's Note: Interview quotes slightly modified for readability.

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Treatment Considerations for PARP Inhibitors in First-Line Maintenance Therapy in Patients With Advanced Ovarian Cancer

Expert Interview With Rebecca Previs, MD

Previs provided insights and best practices on the use of PARP inhibitors for first-line maintenance therapy in patients with advanced ovarian cancer.

To see the full video with Dr Previs, scan the code.

KEY TAKEAWAYS:

- Despite available treatments, 85% of patients with advanced ovarian cancer will experience recurrence at some point after chemotherapy.
- For patients with advanced ovarian cancer, emerging evidence shows that poly (ADP-ribose) polymerase (PARP) inhibitors are effective for first-line maintenance after chemotherapy.
- The choice of first-line maintenance therapy in patients with advanced ovarian cancer should be individualized based on molecular status and initial therapy.

Ovarian cancer is the fifth most common cause of cancer deaths in women and the leading cause of death among cancers of the female reproductive system in the United States. More than 21,400 women in the United States are expected to be diagnosed with the disease in 2021, and 13,770 will die from it.¹ Up to 90% of ovarian cancer cases are epithelial in origin, and 7 of every 10 epithelial ovarian cancers are high-grade serous tumors.²

First-line treatment for ovarian cancer typically involves surgical staging, followed by debulking surgery and, in most patients, platinum- and taxane-based chemotherapy with or without bevacizumab, a monoclonal antibody.³ Some patients require neoadjuvant chemotherapy to shrink the tumor before surgery. Usually, 3 cycles of chemotherapy are

given before surgery, with at least 3 cycles after surgery.⁴ Adjuvant therapy with hormonal agents may also be an option for patients with tumors of specific histologic subtypes.³ Despite these treatments, 85% of patients with advanced ovarian cancer will experience recurrence at some point after chemotherapy.⁵

First-line therapy is often followed by maintenance therapy. According to Rebecca Previs, MD, a gynecologic oncologist at Duke Cancer Center in Durham, North Carolina, all patients should be offered first-line maintenance therapy. “The concept of maintenance,” Previs explains, “is to enable patients to have a higher rate of cure and to prevent the cancer from coming back, because we know once a cancer comes back, it’s even more difficult to treat.”

Whether or not a patient elects to start maintenance therapy depends on her preferences, her goals of care, and her understanding of the data. Previs counsels patients about Food and Drug Administration (FDA) approvals of all frontline maintenance options, including potential adverse effects (AEs). “Those patients who require multiple blood transfusions and multiple dose reductions are the patients who may opt not to continue maintenance therapy. It is a very personal [choice in] each patient’s cancer journey,” she said.

Choosing a Maintenance Therapy

A number of options are available for patients who elect to undergo maintenance therapy. The choice of maintenance therapy must be individualized based on the patient’s clinical features and preferences, with consideration of the National Comprehensive Cancer Network (NCCN) guideline recommendations and FDA-approved indications. For patients with stage IV disease or recurrent ascites, Previs typically recommends bevacizumab as maintenance therapy. “I have a very honest conversation with patients at the time of diagnosis and treatment to really discuss that the addition of bevacizumab, while it has shown an improvement in progression-free survival, [it has not] translated in follow-up with overall survival,” she explained. “It’s really important to break these clinical trials down to a patient level and explain, ‘What does progression-free survival mean?’ ‘How does this translate into overall survival?’ ‘What are the costs associated with additional maintenance therapy?’ By cost, I mean financial as well as the time burden to patients.”

For patients with advanced ovarian cancer, emerging evidence shows that PARP inhibitors are effective for first-line maintenance after chemotherapy.³ Two PARP inhibitors, olaparib and niraparib, were approved by the FDA in 2020 for use in this setting. Olaparib was

“The concept of maintenance is to enable patients to have a higher rate of cure and to prevent the cancer from coming back, because we know once a cancer comes back, it’s even more difficult to treat.”

approved for maintenance treatment of *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary perineal cancer in complete or partial response to first-line platinum-based chemotherapy.⁶ Niraparib was approved for maintenance treatment in patients with advanced epithelial ovarian, fallopian tube, or primary perineal cancer who have had surgery and are in complete or partial response to first-line platinum-based chemotherapy, regardless of biomarker status.⁷ NCCN recommends PARP inhibitors in the first-line maintenance setting as well, but further specifies that olaparib alone or in combination with bevacizumab be used for maintenance in patients who received a bevacizumab-containing regimen as initial therapy.³

The question of whether to offer a PARP inhibitor as a maintenance therapy, and which one to offer, depends on a number of factors, Previs said. “What is the patient’s tumor stage, what is the grade of that tumor, and what is the specific histologic subtype?” Previs asks after primary treatment. “When [the patient] had her primary debulking, what was the volume of residual disease? What other medical problems does she have?” She also considers a patient’s age, nutritional status, transportation options, and, importantly, what the patient herself desires from treatment before making her recommendation.

“In my patient practice, I recommend that all patients with epithelial ovarian cancer undergo genetic counseling and testing,” Previs said. “At a minimum, this should be for *BRCA1* and *BRCA2* germline and somatic mutations. I also order testing on tumors to evaluate for

homologous recombination deficiency. Together, these 2 tests inform my counseling of patients with ovarian cancer, because they really help me predict the benefit from a PARP inhibitor in the maintenance setting.”

“Those tumors that have inherent mismatch repair or DNA damage repair mechanisms—and that can be with homologous recombination [or] nonhomologous end joining—we know are also susceptible to PARP inhibitors,” she continued. “So that is why I’m offering PARP inhibitor maintenance to those patients with homologous recombination deficiency.”

Latest Data on PARP Inhibitors

Olaparib, the first PARP inhibitor approved by the FDA, is recommended by the NCCN guidelines as a maintenance drug therapy for ovarian cancer patients who have germline or somatic *BRCA* mutations.³ American Society of Clinical Oncology (ASCO) also recommends olaparib for maintenance in women who have, or likely have, germline or somatic *BRCA* mutations.²

The FDA’s approval of olaparib for frontline maintenance therapy was based on the results of the phase 3 SOLO-1 clinical trial, which compared olaparib with placebo in 391 patients with newly advanced ovarian cancer. Study results indicated that after the median follow-up of 41 months, patients with suspected or confirmed *BRCA1/2* mutation who were taking olaparib had a 70% lower risk of disease progression or death than those taking placebo (Kaplan–Meier estimate of the rate of freedom from disease progression and from death at

3 years, 60% vs 27%; HR for disease progression or death, 0.30; 95% CI, 0.23-0.41; $P < .001$).⁸

The results of the PAOLA-1 trial similarly confirmed the benefits of olaparib when combined with bevacizumab in patients with newly diagnosed, advanced, high-grade ovarian cancer. A total of 806 patients were randomized 2:1 to receive either olaparib + bevacizumab ($n = 537$) or placebo + bevacizumab ($n = 269$). Results indicated that after a median follow-up of 22.9 months, patients in the olaparib group experienced a median progression-free survival (PFS) of 22.1 months (vs 16.6 months in the placebo group [HR for disease progression or death, 0.59; 95% CI, 0.49-0.72; $P < .001$]). The largest benefits were shown in patients with *BRCA* mutations and those with positive homologous recombination deficiency (HRD) status.⁹

NCCN guidelines include niraparib as maintenance therapy for patients with *BRCA1/2* mutations. For patients who have *BRCA1/2* wild-type, or whose *BRCA* status is unknown, NCCN guidelines include niraparib as a maintenance therapy in patients achieving partial or complete remission after platinum-based chemotherapy without bevacizumab. If the patient does not have a *BRCA* mutation or if her *BRCA* status is unknown, HRD status can help physicians determine the likely benefit to be derived from niraparib.³

Niraparib is not recommended as maintenance therapy for patients with *BRCA* wild-type or unknown *BRCA* status who have received chemotherapy with bevacizumab. In these patients, the PARP inhibitor olaparib is recommended in combination with bevacizumab. Niraparib or olaparib may be considered for patients with germline or somatic *BRCA* mutations who received chemotherapy with bevacizumab and achieved a partial or complete response, although data on maintenance therapy with single-agent PARP inhibitors are limited.³

ASCO guidelines include a strong rec-

“I recommend that all patients with epithelial ovarian cancer undergo genetic counseling and testing. At a minimum, this should be for *BRCA1* and *BRCA2* germline and somatic mutations. I also order testing on tumors to evaluate for homologous recombination deficiency. Together, these 2 tests inform my counseling of patients with ovarian cancer, because they really help me predict the benefit from a PARP inhibitor in the maintenance setting.”

ommendation that niraparib or olaparib be offered as maintenance therapy to patients with newly diagnosed stage III-IV epithelial ovarian cancer who have completely or partially responded to platinum-based first-line chemotherapy and have never received a PARP inhibitor.²

The approval of niraparib as a first-line maintenance therapy comes in the wake of results of clinical trials such as PRIMA, in which 733 patients with newly diagnosed advanced ovarian cancer were randomized to receive either niraparib or placebo after response to platinum-based chemotherapy. Median PFS with niraparib was 13.8 months vs 8.2 months with placebo (HR, 0.62; 95% CI, 0.50-0.76; $P < .001$).⁵

In patients with HRD tumors, median PFS was 21.9 months with niraparib compared with 10.4 months with placebo (HR for disease progression or death, 0.43; 95% CI, 0.31-0.59; $P < .001$). The study's authors concluded that niraparib provided a benefit to patients with advanced ovarian cancer regardless of HRD status.⁵

“I do offer patients with HRD in their tumor niraparib maintenance,” said Previs. “In my mind, when reviewing the trials, the statistically significant benefit of progression-free survival was substantial. So, for these patients, I am strongly recommending niraparib maintenance.”

In the ENGOT-OV16/NOVA trial, 533 patients with platinum-sensitive, recur-

rent ovarian cancer were categorized by presence or absence of a germline *BRCA* mutation and randomized to receive niraparib (300 mg) or placebo once a day. In both the *BRCA*-mutated and wild-type groups, patients randomized to niraparib experienced significantly longer PFS than those randomized to placebo ($P < .001$). Median PFS was 21.0 months in the *BRCA*-mutated group compared with 5.5 months in the placebo group (HR, 0.27; 95% CI, 0.17-0.41; $P < .001$). In women who received niraparib in the overall non-*gBRCA* cohort, median PFS was 9.3 months vs 3.9 months (HR, 0.45; 95% CI, 0.34-0.61; 95% CI; $P < .001$). Those in the non-*BRCA* niraparib cohort who had HRD tumors had a median PFS of 12.9 months vs 3.8 months (HR, 0.38; 95% CI, 0.24-0.59; $P < .001$).¹⁰

“What's different about niraparib is that this approval comes irrespective of *BRCA* mutational status or homologous recombination deficiency,” Previs said. “What we saw is that, regardless of those different statuses, there was an improvement in progression-free survival in all of the different groups. The biggest progression-free survival benefit, however, was in the *BRCA*-mutated patients, followed by the patients with homologous recombination deficiency, and then patients with homologous recombination-proficient (HRP) tumors.” For patients with HRD tumors, Previs recommends niraparib for first-line maintenance therapy.

Adverse Events and Dosing

In the ENGOT-OV16/NOVA trial, thrombocytopenia and neutropenia were reported at 3 months in 33% and 18%, respectively, of patients who received niraparib. Dose reduction due to treatment-emergent adverse events (TEAEs) occurred in 68.9% of patients overall, and the discontinuation rate due to TEAEs was 14.7%, including 3.3% due to thrombocytopenia. Further analysis revealed that lower baseline platelet counts (<180,000/ μ L) were associated with thrombocytopenia grade 1 or higher in 71.1% of participants and with thrombocytopenia grade 3 or higher in 42.2% of participants.¹¹

Baseline body weight was also correlated with AEs leading to dose reduction, with these events occurring more frequently in patients weighing less than approximately 58 kg (51%) compared with patients weighing at least 77 kg (33%).¹¹

Because low baseline body weight and low platelet counts were predictive of AEs in patients who received 300 mg of niraparib daily, the starting dose was reduced to 200 mg in patients who weighed less than 77 kg or who had platelet counts of less than 150,000/ μ L in ongoing clinical trials.¹¹

Starting doses were also individualized in the NORA study, which randomized 265 patients with platinum-sensitive recurrent ovarian cancer to receive either niraparib or placebo. Patients weighing less than 77 kg and with a platelet count of less than 150,000/ μ L received 200 mg of niraparib daily, and patients weighing at least 77 kg and with a platelet count of at least 150,000/ μ L received 300 mg of niraparib daily.¹²

Previs explained that she introduces niraparib at a dose of 200 mg daily for patients weighing less than 77 kg and whose starting platelet count is less than 150,000/ μ L. For patients beginning at a dose of 300 mg of niraparib daily, Previs ensures they understand that fatigue, anemia, and thrombocytopenia are commonly experienced.

“What is really exciting about niraparib is that it comes in capsules that are easily administered,” she said. “They’re in 100-mg increments. So based on follow-up data, we know that if we do have to reduce a patient’s dose to 200 mg based on their hematologic blood counts, then I can tell my patient that it is as effective.”

An Emerging PARP Inhibitor

Another PARP inhibitor, veliparib, is currently being tested in ovarian cancer. The VELIA trial studied veliparib added to first-line induction chemotherapy and continued as maintenance monotherapy in 1140 patients with previously untreated stage III or IV high-grade serous ovarian carcinoma. Overall, patients who received veliparib achieved a median PFS duration of 23.5 months in the induction and maintenance groups compared with 17.3 months for placebo (HR for disease progression or death, 0.68; 95% CI, 0.56-0.83; $P < .001$).¹³

For patients with a *BRCA* mutation, median PFS was 34.7 months in patients taking veliparib throughout the study, compared with 22.0 months in the control group (HR, 0.44; 95% CI, 0.28-0.68; $P < .001$). For patients with positive HRD status, median PFS was 31.9 months compared with 20.5 months in the control group (HR, 0.57; 95% CI, 0.43-0.76; $P < .001$).¹³

Looking Forward

The past few years of ovarian cancer research have yielded new maintenance therapies but, according to Previs, more research is needed for women who do not have a *BRCA* germline or somatic mutation and who do not have HRD tumors.

“We know that the addition of niraparib offers a small improvement in progression-free survival in the frontline setting, but these patients aren’t deriving the same degree of benefit as patients who have an actual mutation or have HRD in their tumor,” she said. “So, I would love for future clinical trials to really focus on this patient population and think about

ways that we can make these tumors more susceptible to the great maintenance therapies that we have available for a lot of our patients.” ■

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Editor's Note: Interview quotes slightly modified for readability.

CONTINUING MEDICAL EDUCATION (CME)

Targeting Folate Receptor- α in Ovarian Cancer

FACULTY

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LEARNING OBJECTIVES

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

- Describe the physiologic function of folate receptor- α (FR α) in ovarian cancer
- Explain the rationale for targeting FR α as a mechanism for treating ovarian cancer
- Assess key data from ongoing clinical trials evaluating emerging FR α targeting agents for the treatment of ovarian cancer

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EXPIRATION DATE: April 1, 2022

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As the seventh most common cancer globally, ovarian cancer is diagnosed in approximately 240,000 women each year.¹ The 5-year survival rate from the time of diagnosis is 45%. Currently, standard first-line treatment options for patients with advanced ovarian cancer recommended in National Comprehensive Cancer Network (NCCN) guidelines include chemotherapy-containing regimens such as paclitaxel/carboplatin and paclitaxel/carboplatin + bevacizumab.² However, the majority of women who receive first-line platinum doublet chemotherapy develop recurrent disease.^{3,4} Treatment recommendations for patients with recurrent ovarian cancer are dependent on whether the disease is platinum-sensitive or platinum-resistant.² Women who relapse less than 6 months following completion of chemotherapy are considered by current NCCN guidelines to have platinum-resistant disease, for which treatment options are limited to clinical trial enrollment and best supportive care. Preferred systemic therapy options for patients with recurrent platinum-sensitive disease are limited to combination platinum-based chemotherapy in addition to clinical trial enrollment. Additional treatment options for these patients include monotherapy with targeted agents such as bevacizumab or a Poly (ADP-ribose) polymerase (PARP) inhibitor. This unmet need has resulted in increased efforts for identifying therapeutic targets for ovarian cancer. Folate receptor- α (FR α) is a promising therapeutic target that continues to be investigated. The rationale for FR α -directed agents is due to its limited expression in nonmalignant cells and its expression in over 80% of ovarian cancer.⁵

Kathleen Moore, MD, MS, reviews the most recent advances regarding FR α -targeting therapy as for ovarian cancer.

Q: What is the physiologic function of FR α ?

MOORE: FR α is an interesting protein. It is a transmembrane glycoprotein with the role of unidirectional transport of folate into cells.⁶ Specifically, FR α transports folate

by something called receptor-mediated endocytosis, which becomes important regarding the therapeutic opportunities for targeting FR α . Other aspects that make FR α an attractive target for ovarian cancer is that it is constitutively expressed in over 80% of tumors to varying degrees.⁵ Prognostically, there is some evidence that its expression may be associated with poor outcomes, although this has yet to be fully demonstrated.⁷ FR α also has a restricted distribution pattern in normal tissues. In healthy kidney and lung tissues, FR α is confined the apical surface of the epithelium.⁵ And that's important because the apical surface of the epithelium is not in direct contact with the circulation, thereby reducing the risk of off-target toxicity.

Q: How prevalent is FR α expression across different cancer types?

MOORE: FR α expression is of interest across a number of cancer types. FR α is expressed in nasopharyngeal epidermoid carcinomas, cervical cancer, some uterine cancers (metastatic and usually a uterine papillary serous), renal cancers, and metastatic pancreatic cancers.⁸ Due to the high prevalence of FR α expression in epithelial nonmucinous ovarian cancer, research efforts have focused on this area.

Q: What makes FR α an appealing target for the treatment of ovarian cancer?

MOORE: FR α is an appealing target for the treatment of nonmucinous epithelial ovarian cancer for a few key reasons. First, the expression of FR α is very common in nonmucinous epithelial ovarian cancers, with about 80% having any expression and 40% having high expression.⁵ Secondly, FR α takes in whatever it binds by endocytosis; that's important because it allows the receptor to bring a large molecule, such as an anticancer therapy, inside the cancer cell. Thirdly, FR α has a differentiated distribution in cancers versus normal tissue.⁵ FR α is found on normal cells, but the expression is apical and not facing the

circulation. Thus, the risk of delivering a toxic payload in normal cells is much lower. So this differential distribution of FR α between normal and cancer cells, allows the delivery of toxic payloads to cancer cells with a high level of confidence. To date, studies indicate that FR α expression is retained and recurring in metastatic tumors. Expression also does not alter in response to chemotherapy, although it might alter in response to FR α -directed therapies, and we have to study that over time.

Q: What have been the successes and failures of FR α -targeting therapies for the treatment of ovarian cancer?

MOORE: The first effort to target FR α involved anti-FR α monoclonal antibodies. This is the naked antibody called farletuzumab, which binds the FR α receptor and relies on antibody-dependent cell mediated cytotoxicity.⁹ It had a good safety profile and combined well with carboplatin and paclitaxel; response rates were encouraging.¹⁰ Farletuzumab was studied in a platinum-sensitive population.¹⁰ However, despite initial promise, the attempt was unsuccessful. There is a lot of discussion about why it did not work. One of several reasons may be that patients were not selected effectively. There was patient selection based on receptor status relying on the fact that 80% of ovarian cancers express some FR α . But is some enough? And how much expression is needed? There are a lot of questions with farletuzumab. It should have worked but unfortunately did not.

The next attempt at targeting FR α was along the lines of trying to deliver an active drug to FR α -positive cells in the form of a small-molecule drug conjugate. There have been a few folate-directed small-molecule drug conjugates developed with a number of different payloads evaluated. Probably the most successful of this class is vintafolide (EC145), which was directed at FR α and conjugated to a vinca alkaloid.¹¹ There was a precedent trial of vintafolide with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin

alone in platinum-resistant cancer. The combination produced better results than pegylated liposomal doxorubicin alone.¹² Unfortunately, the confirmatory PROCEED study had to be terminated at the interim analysis because the combination didn't meet the prespecified criteria for progression free survival.¹³ Here they were trying to not only select for FR α but also for the heterogeneity that is seen across the different metastatic sites. Nonetheless, the phase 3 trial was not successful. There are probably many reasons for this. The drug clearly was active in the earlier phases of study. One thought is that vinca alkaloid is a p-glycoprotein substrate. Perhaps an efflux led to vintafolide resistance, and that may have contributed to a poor outcome in the phase 3 trial. But again, this is disappointing because that therapy "should have" worked.

The third attempt is with antibody-drug conjugates. They are very complex molecules that we have been attempting to use for several decades. Finally, with very well-designed linkers, we have hit upon and are moving some of these into FDA approvals in other disease sites. It is now being evaluated for ovarian cancer. Mirvetuximab soravtansine is a humanized anti-FR α antibody with a payload of a maytansinoid called DM4, a microtubule toxin.¹⁴ This was not studied in a phase 2 trial, but there was a large phase 1 study conducted in patients with either high- or moderate-FR α expressing tumors. The response rate was in the 30% to 40% range, with durable responses. The FORWARD I study was a randomized phase 3 trial in medium- and high-FR α expressing tumors.¹⁵ The patients had platinum-resistant disease with 1 to 3 prior rounds of treatment and were randomized to mirvetuximab or to physician's choice chemotherapy, which could be any of three monotherapy options. They were stratified by the choice of chemotherapy and FR α -expression, medium or high. Safety data did show a differentiated toxicity profile in favor of mirvetuximab over chemotherapy. Unfortunately, it missed its primary end

point of progression-free survival on both the intention to treat group and the FR α high group. There was some clinical benefit in both groups, but neither met statistical significance. There was a deep dive into what happened. Some of it was the statistical design, where we use these criteria for the order in which we evaluated the end point. However, the fatal flaw is related to the biomarker testing used.

We went back in a purely exploratory manner to determine why the study was not positive and had the slides for the patients who participated in FORWARD I rescored using the original scoring¹⁵ and we found that 30% of the women who were included in FORWARD I actually weren't eligible because they weren't FR α medium or high. We also found that half of the women who were previously classified as FR α high, which was one of our primary end points, were actually medium—so we diluted out one of our primary end points. I do have to emphasize that this is exploratory, but when we reran the statistics, we found the exact improvement in progression-free survival that we would have expected from the original trial.

These exploratory findings are what justified the redo of FORWARD I, called MIRASOL.¹⁶ There are subtle differences. Instead of 2:1 randomization, it was 1:1, and this allows for the investigator to assess progression free survival instead of using a central assessment. But only in FR α -high this time with what's called PS2 scoring. So there were some important tweaks to the design, and it is currently up and running.

I would be remiss if I didn't mention the other antibody drug conjugate, STRO-002, which is also in clinical trials, although it is still in phase 1 at this time.¹⁷ STRO-002 is also an antibody-drug conjugate that targets FR α and has gone through dose escalation thus far.

Q: Which strategies are currently being explored for the development of FR α targeting agents for the treatment of ovarian cancer?

MOORE: Combination therapies with fo-

late-receptor targeting therapies include combinations with antiangiogenic agents such as bevacizumab. As we reflect on options for women with platinum-resistant disease, the standard of care remains monotherapy. Chemotherapy in combination with bevacizumab per the AURELIA study was appropriate, but not an option for the increasing number of women who have had bevacizumab already before they become platinum resistant.¹⁸ In addition, the AURELIA study was done almost entirely in a bevacizumab-naïve population, which isn't to say bevacizumab can't work in an experienced population.

Exciting data were presented last year at ASCO and will be updated this year. This includes a study evaluating mirvetuximab combined with bevacizumab in women with recurrent disease.¹⁹ This study allowed women who were platinum resistant but also those who were technically considered platinum sensitive but for whom the provider felt like carboplatin wasn't suitable, which was not a small number of patients. Women had high or medium expression of FR α per the PS2 scoring, the correct scoring. The majority of them were platinum resistant, with 53% having been so for less than 6 months. About one third had platinum-free intervals of 6 to 12 months. Overall response rate was 47% across the entire cohort, 64% in patients with FR α high, 59% in the platinum-resistant subset and 69% in the platinum-sensitive subset. In the waterfall plot, 92% of 60 total participants had some reduction in their tumor burden during participation or during receipt of combination therapy. A year ago when these data were presented, the duration of response in progression-free survival was too immature to report, but updated data will be presented this year at ASCO. No unexpected toxicities or toxicities were observed. Of the patients, 22% discontinued bevacizumab and/or mirvetuximab due to treatment-related adverse events, which is typical for bevacizumab-containing regimens.

Questions regarding combinations are whether mirvetuximab can replace

paclitaxel in platinum-sensitive disease. We've demonstrated that it is safe to use carboplatin and mirvetuximab and then mirvetuximab as maintenance as well as bevacizumab and mirvetuximab and then mirvetuximab as maintenance in single-arm studies. The next step will be to evaluate these combinations in randomized trials.

Q: What are the major adverse events that have been associated with FR α -targeting agents?

MOORE: Although FORWARD I did not result in FDA approval, the study did provide safety data for mirvetuximab compared with single-agent chemotherapy. And what it really showed us is that we have a very differentiated toxicity profile that across the board favors mirvetuximab over single-agent chemotherapy.¹⁴ There were almost no hematologic toxicities compared with chemotherapy, which of course affects bone marrow. There was no alopecia, and lower rates of neuropathy, especially compared to paclitaxel. Mirvetuximab was associated with relatively frequent but low-grade GI toxicity, mainly diarrhea, which could be managed quite easily with prompt attention and over-the-counter agents. Somewhat surprisingly for FORWARD I, we did notice infusion-related nausea that really hadn't been reported in the phase 1 study. And so antiemetic prophylaxis has been built in to the MIRASOL study, and so we hope to ameliorate the nausea by adjusting the dosing. I think the biggest differentiated toxicity is the ocular toxicity with antibody drug conjugates, including mirvetuximab. Keratopathy associated with antibody drug conjugates can lead to blurry vision, and this is pretty common. We saw it in about 50% of women who received mirvetuximab on FORWARD I, largely grade 1, but some grade 2. There was no grade 3 or 4 because of the mitigation strategies that were built into FORWARD I (lubricating eye drops followed by steroid eye drops). Only one patient on FORWARD I discontinued due to ocular toxicities. So importantly, while it

was somewhat frequent, it did not result in discontinuation of study treatment.

Q: How do you anticipate FR α targeting agents will be integrated into the treatment landscape in managing patients with ovarian cancer?

MOORE: The first option for incorporating mirvetuximab, which is the only agent in a registration trial right now, will be based on how it was studied in those trials. If approved, mirvetuximab will be incorporated into the treatment paradigm for women with platinum-resistant ovarian cancer who have previously been treated with bevacizumab. This approach will likely be broadened and confirmed when results emerge from other studies. Once mirvetuximab is approved and given the upcoming data in combination with bevacizumab, my hope would be that especially given the number of patients who have received combination bevacizumab, that the NCCN guidelines will adopt this as a recommended combination therapy. I think mirvetuximab will first be approved for monotherapy, and then as more efficacy data come out about combinations, it may be moved up in lines of therapy for platinum-resistant disease. Eventually studies may determine whether mirvetuximab can replace paclitaxel in a biomarker directed-population and used with carboplatin in platinum-sensitive disease, and potentially even in the frontline setting. ■

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