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PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

JANUARY 2023 | Vol 37 • No 1

BREAST CANCER: ORIGINAL RESEARCH

Shorter Time to Treatment Is Associated With **Improved Survival in Rural Patients With Breast Cancer** Despite Other Adverse Socioeconomic Factors

INTERVIEW

Kevin Kalinsky, MD, MS, Discusses the Past, Present, and Future of Breast Cancer Research

KEVIN KALINSKY, MD, MS

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20th Annual Winter Lung Cancer CONFERENCE®

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LEARNING OBJECTIVES

- Describe molecular testing strategies to refine treatment selection in patients with oncogene-driven cell lung cancer
- Outline current and emerging approaches for patient selection and decisions concerning the use of immunotherapy and targeted agents
- Discuss clinical trial data on therapeutic approaches for early-stage and locally advanced lung cancer

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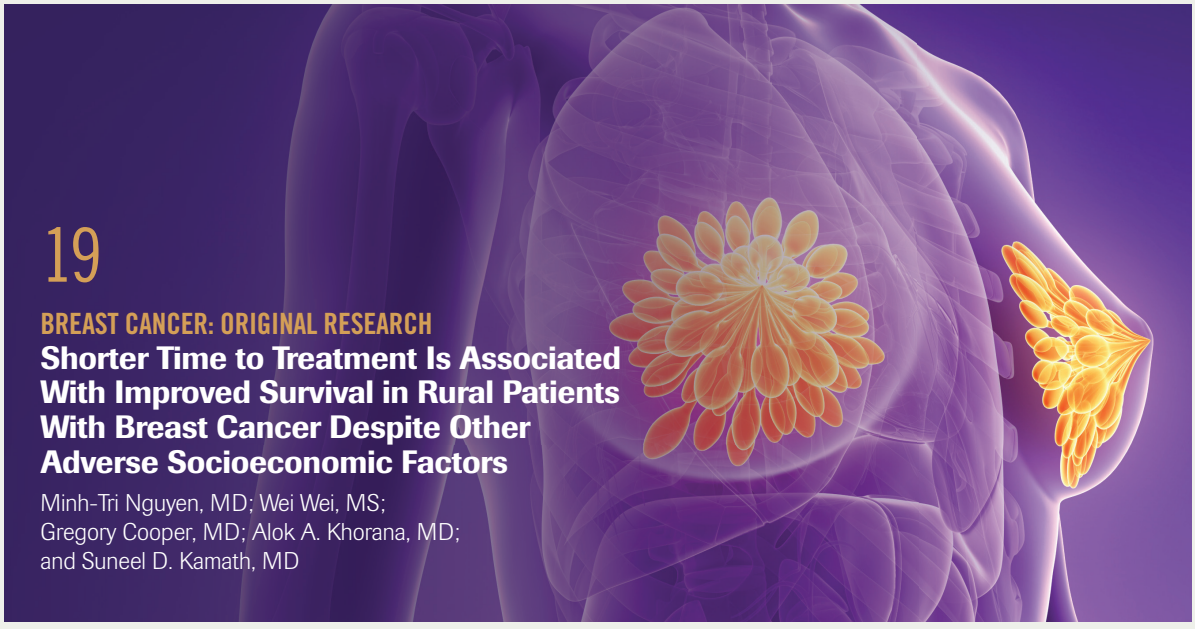

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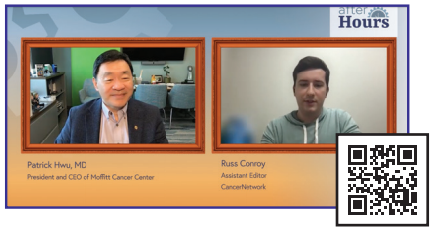

AFTER HOURS®

THE REMISSIONS

Patrick Hwu, MD, president and chief executive officer of Moffitt Cancer Center, along with fellow physicians is part of a band called the ReMissions. In this special episode, Hwu details being a guitarist and pianist, the teamwork that goes into performing, and the diverse selection of genres he enjoys playing.

TO WATCH VISIT: **https://bit.ly/3X6WJzM**

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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, $275 and Canada, $303; students and nurses, $96; international, $366. 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. For address changes, please notify the Circulation Department by visiting www.surveymonkey.com/s/subscriptions, or by mail to *ONCOLOGY®*, PO Box 457, Cranbury NJ 08512-0457. Send old address, new address and attach a copy of mail label, if possible.

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JANUARY 2023 ▪ VOL. 37 ▪ NO. 1

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Increasing Breast Cancer Diagnosis in Rural Areas and the Evolving Access to Health Care

We assume health care in rural areas is worse than it is at the bastions of education. However, the report by Ngyuen et al from the Cleveland Clinic titled "Shorter Time to Treatment Is Associated With Improved Survival in Rural Patients With Breast Cancer Despite Other Adverse Socioeconomic Factors" shows us this is not necessarily the case. The authors reviewed more than 1 million patients with stage I to III breast cancer in the National Cancer Database (NCDB) from 2004 to 2012. This is a select population out of about 4 million patients with such diagnoses in this period. According to the study's findings, rural patients had a shorter time from diagnosis to first therapeutic intervention and a somewhat higher overall survival (OS) rate. Many of us find this surprising, but there are certainly interesting questions raised by the data.

However, additional thought should be given to this population. For example, sample bias is a key issue since patient records selected for listing in NCDB are only from Commission on Cancer–accredited institutions. In this report, this results in only 1.5% of patients coming from "rural" areas by the definition in the paper. This contrasts with 18% of the general US population in such sectors, so these few patients receive optimal care in rural health care delivery. The difference in time to intervention is a week shorter for rural patients than for nonrural patients, which results in a statistical difference in OS, although clinically nonsignificant, which the authors note.

More surprising is that these results occur despite some other adverse factors in the rural patient population including older age, lower education level, more intercurrent illness, and much lower income levels. On the other hand, the rural patient group is predominantly White. The strongest key factor affecting OS is surgery as initial therapy (representing curative cases), and this is higher in the rural group also. Other key factors associated with worse outcomes include having stage III disease, nearly as great as having surgery first, being 65 years or older, having government insurance, and race (either Black or White).

The key issue here is access to medical care. Where there is good access to comprehensive care, it does not matter if you are treated in a community center or an academic one. We need to lower these barriers to care everywhere. It will be interesting to see such an analysis with improved access through Medicaid expansion. Maybe some of the problem of poorer outcomes in academic centers comes from the higher private insurance rate, which, for practitioners, puts additional barriers in place through the precertification process every day of our lives. As practitioners, we know how much time we spend on getting approvals for all kinds of testing and treatment, such as PET scans and chemotherapy preapprovals and even obtaining the pain medications patients so desperately need, all of which results in key treatment delays. We must stand for equal and unfettered access to care, be it in a rural or urban setting. ■

LENVIMA® + everolimus

The only TKI-mTOR inhibitor combination approved for adults with aRCC following prior anti-angiogenic therapy[1,2]

14.6 months median PFS in 2L[1]*

14.6 months 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

NCCN **RECOMMENDED** OPTION

Lenvatinib (LENVIMA) + everolimus has a National Comprehensive Cancer Network® (NCCN®) category 2A **Preferred Recommendation** as a subsequent therapy option for patients with relapse or stage IV clear cell RCC†‡

*Major efficacy outcome.

†Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

‡Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2023 © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed September 22, 2022. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

INDICATION

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

SELECTED SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), 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 (hepatocellular carcinoma), 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.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

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 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 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.

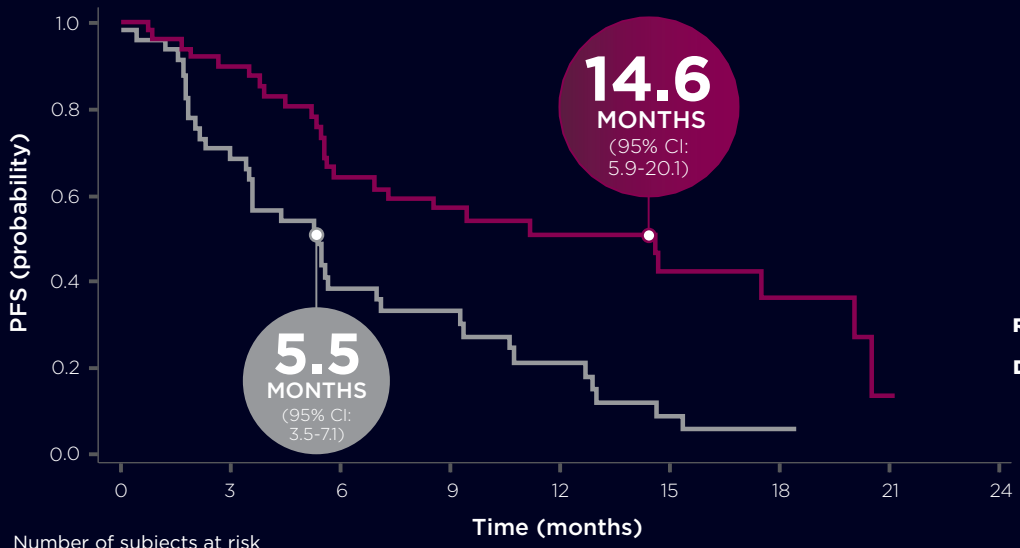
Renal Failure or Impairment. Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with 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 ≥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 alone[1]



63%

REDUCTION IN THE RISK OF PROGRESSION OR DEATH WITH LENVIMA + EVEROLIMUS VS EVEROLIMUS ALONE

Number of subjects at risk

LENVIMA + everolimus	**51**	**41**	**27**	**23**	**16**	**10**	**5**	**1**	**0**
Everolimus	50	29	15	11	7	3	1	0	

- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm[1]
  - 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 arm[1]
- 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 rate[1,3]

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

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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 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.

Please see all Selected Safety Information throughout and accompanying Brief Summary of full Prescribing Information.

Visit **www.LENVIMA.com/hcp** to learn more

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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 (≥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 (≥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 (≥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, RCC, or EC (endometrial carcinoma) and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC 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, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

Please see Brief Summary on the following pages.

References: 1. LENVIMA [package insert]. Nutley, NJ: Eisai Inc. **2.** AFINITOR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020. **3.** Data on file. Eisai Inc.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

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

INDICATIONS AND USAGE

LENVIMA is a kinase inhibitor that is indicated:

Differentiated Thyroid Cancer (DTC)

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

Renal Cell Carcinoma (RCC)

- In combination with pembrolizumab, for the first line treatment of adult patients with advanced renal cell carcinoma (RCC).
- In combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

Hepatocellular Carcinoma (HCC)

- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

Endometrial Carcinoma (EC)

- In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

DOSAGE AND ADMINISTRATION

Patient Selection

For the pMMR/not MSI-H advanced endometrial carcinoma indication, select patients for treatment with LENVIMA in combination with pembrolizumab based on MSI or MMR status in tumor specimens.

Information on FDA-approved tests for patient selection is available at: http://www.fda.gov/CompanionDiagnostics.

An FDA-approved test for the selection of patients who are not MSI-H is not currently available.

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

Single Agent Therapy:

- DTC: The recommended dosage is 24 mg orally once daily.
- HCC: The recommended dosage is based on actual body weight: 12 mg orally once daily for patients greater than or equal to 60 kg or 8 mg orally once daily for patients less than 60 kg.

Combination Therapy:

- EC: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
- RCC: The recommended dosage is:
  - 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
  - 18 mg orally once daily with everolimus 5 mg orally once daily.

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[a]	Dosage Modifications for LENVIMA
Hypertension	Grade 3	• 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	• Permanently discontinue.
Cardiac Dysfunction	Grade 3	• 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	• Permanently discontinue.
Arterial Thromboembolic Event	Any Grade	• Permanently discontinue.
Hepatotoxicity	Grade 3 or 4	• 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	• 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	• 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	• Permanently discontinue.
Fistula Formation	Grade 3 or 4	• Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	• 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 Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
	Grade 4 adverse reaction	• Permanently discontinue.

[a] 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
Endometrial Carcinoma	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
• Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
• Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue

Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Pembrolizumab

When administering LENVIMA in combination with pembrolizumab, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA as shown in Table 1. Refer to pembrolizumab prescribing information for additional dose modification information.

Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Everolimus

When administering LENVIMA in combination with everolimus, withhold or 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, RCC, or endometrial carcinoma 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
- Endometrial carcinoma: 10 mg orally once daily

Dosage Modifications for Severe Hepatic Impairment The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma 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
- Endometrial carcinoma: 10 mg 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.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

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 (ONJ) 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), LENVIMA with pembrolizumab in 406 patients with endometrial carcinoma (Study 309), LENVIMA with everolimus in 62 patients with RCC (Study 205), and LENVIMA with pembrolizumab in 352 patients with RCC (CLEAR). 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 1557 patients enrolled in randomized, active-controlled trials (REFLECT; Study 205; CLEAR; Study 309), or a randomized, placebo-controlled trial (SELECT). The median duration of exposure to LENVIMA across these five 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

(*continued*)

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 (%)

[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.

First-Line Treatment of Renal Cell Carcinoma in Combination with Pembrolizumab (CLEAR)

The safety of LENVIMA in combination with pembrolizumab was investigated in CLEAR *[see Clinical Studies (14.2)]*. Patients received LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks (n=352), or LENVIMA 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of LENVIMA and pembrolizumab was 17 months (range: 0.1 to 39).

Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA in combination with pembrolizumab, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 37% of patients; 26% LENVIMA only, 29% pembrolizumab only, and 13% both drugs. The most common adverse reactions (≥2%) leading to permanent discontinuation of LENVIMA, pembrolizumab, or both were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with pembrolizumab. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-plantar erythrodysesthesia (11%), nausea (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), and vomiting (6%), increased ALT (5%), and increased amylase (5%).

Tables 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in ≥20% of patients treated with LENVIMA and pembrolizumab in CLEAR.

Table 5: Adverse Reactions in ≥20% of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)

Adverse Reactions	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=352		Sunitinib 50 mg N=340	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	63	9	56	8
Gastrointestinal				
Diarrhea[b]	62	10	50	6
Stomatitis[c]	43	2	43	2
Nausea	36	3	33	1
Abdominal pain[d]	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
Musculoskeletal and connective tissue				
Musculoskeletal pain[e]	58	4	41	3
Endocrine				
Hypothyroidism[f]	57	1	32	0
Vascular				
Hypertension[g]	56	29	43	20
Hemorrhagic events[h]	27	5	26	4
Metabolism				
Decreased appetite[i]	41	4	31	1
Skin and subcutaneous tissue				
Rash[j]	37	5	17	1
Palmar-plantar erythrodysaesthesia syndrome[k]	29	4	38	4
Respiratory, thoracic, and mediastinal				
Dysphonia	30	0	4	0
Renal and urinary				
Proteinuria[l]	30	8	13	3
Acute kidney injury[m]	21	5	16	2
Investigations				
Weight decreased	30	8	9	0
Hepatobiliary				
Hepatotoxicity[n]	25	9	21	5
Nervous system				
Headache	23	1	16	1

[a] Includes asthenia, fatigue, lethargy and malaise
[b] Includes diarrhea and gastroenteritis
[c] Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis
[d] Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, and upper abdominal pain
[e] Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and pain in jaw
[f] Includes hypothyroidism, increased blood thyroid stimulating hormone and secondary hypothyroidism
[g] Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure
[h] Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include: Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, and upper gastrointestinal hemorrhage
[i] Includes decreased appetite and early satiety
[j] Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular
[k] Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome and plantar erythema
[l] Includes hemoglobinuria, nephrotic syndrome, and proteinuria
[m] Includes acute kidney injury, azotaemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininaemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic
[n] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, and gamma-glutamyltransferase increased

Clinically relevant adverse reactions (<20%) that occurred in patients receiving LENVIMA/pembrolizumab were myocardial infarction (3%) and angina pectoris (1%).

Table 6: Laboratory Abnormalities in ≥20% (All Grades) of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)

Laboratory Abnormality[a]	LENVIMA 20 mg in combination with Pembrolizumab 200 mg		Sunitinib 50 mg	
	All Grades %[b]	Grades 3-4 %[b]	All Grades %[b]	Grade 3-4 %[b]
Chemistry				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased aspartate aminotransferase (AST)	58	7	57	3
Hyperglycemia	55	7	48	3
Increased alanine aminotransferase (ALT)	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Decreased albumin	34	0.3	22	0
Increased alkaline phosphatase	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16

[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/pembrolizumab (n=343 to 349) and sunitinib (n=329 to 335).

(*continued*)

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed in 3 patients on rechallenge in patients receiving LENVIMA and 10 patients receiving both LENVIMA and pembrolizumab.

Previously Treated Renal Cell Carcinoma in Combination with Everolimus (Study 205)

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 7 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 7.

Table 7: 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[e]	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[g]	35	0	40	0
Vascular				
Hypertension/Increased blood pressure	42	13	10	2
Hemorrhagic events[h]	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 hematocele

In Table 8, Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA with everolimus arm are presented.

Table 8: 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 9 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 9.

Table 9: 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

(*continued*)

Table 9: 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 (%)

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

Table 10: 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)

Endometrial Carcinoma

The safety of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial carcinoma that are pMMR or not MSI-H received LENVIMA 20 mg orally once daily with pembrolizumab 200 mg intravenously every 3 weeks (n=342); or received doxorubicin or paclitaxel (n= 325).

For patients with pMMR or not MSI-H status, the median duration of study treatment was 7.2 months (range 1 day to 26.8 months) and the median duration of exposure to LENVIMA was 6.7 months (range: 1 day to 26.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and pembrolizumab, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving LENVIMA and pembrolizumab. Serious adverse reactions with frequency ≥3% were hypertension (4.4%), and urinary tract infection (3.2%).

Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of these patients. The most common (≥1 %) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.8%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%).

Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common (≥5%) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthenia (5%), and weight decreased (5%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (≥2%) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (6%), decreased appetite (5%), vomiting (5%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2%).

Tables 11 and 12 summarize adverse reactions and laboratory abnormalities, respectively, in patients receiving LENVIMA in Study 309.

Table 11: Adverse Reactions in ≥20% of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Adverse Reaction	All Grades[a] (%)	Grades 3-4 (%)	All Grades[a] (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism[b]	67	0.9	0.9	0
Vascular				
Hypertension[c]	67	39	6	2.5
Hemorrhagic events[d]	25	2.6	15	0.9

(*continued*)

Table 11: Adverse Reactions in ≥20% of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Adverse Reaction	All Grades[a] (%)	Grades 3-4 (%)	All Grades[a] (%)	Grades 3-4 (%)
General				
Fatigue[e]	58	11	54	6
Gastrointestinal				
Diarrhea[f]	55	8	20	2.8
Nausea	49	2.9	47	1.5
Vomiting	37	2.3	21	2.2
Stomatitis[g]	35	2.6	26	1.2
Abdominal pain[h]	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders[i]	53	5	27	0.6
Metabolism				
Decreased appetite[j]	44	7	21	0
Investigations				
Decreased weight	34	10	6	0.3
Renal and Urinary				
Proteinuria[k]	29	6	3.4	0.3
Infections				
Urinary tract infection[l]	31	5	13	1.2
Nervous System				
Headache	26	0.6	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	22	0	0.6	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia[m]	23	2.9	0.9	0
Rash[n]	20	2.3	4.9	0

[a] Graded per NCI CTCAE v4.03
[b] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, primary hypothyroidism, and secondary hypothyroidism
[c] Includes hypertension, blood pressure increased, hypertensive crisis, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, and blood pressure fluctuation
[d] Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, injection site hemorrhage, melena, purpura, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, coital bleeding, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, and vessel puncture site bruise
[e] Includes fatigue, asthenia, malaise, and lethargy
[f] Includes diarrhea and gastroenteritis
[g] Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, and tongue ulceration
[h] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, and epigastric discomfort
[i] Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw
[j] Includes decreased appetite and early satiety
[k] Includes proteinuria, protein urine present, hemoglobinuria
[l] Includes urinary tract infection, cystitis, and pyelonephritis
[m] Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, and skin reaction
[n] Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, and application site rash

Table 12: Laboratory Abnormalities Worsened from Baseline[a] Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Laboratory Test[b]	All Grades[c] (%)	Grades 3-4 (%)	All Grades[c] (%)	Grades 3-4 (%)
Chemistry				
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased aspartate aminotransferase	58	9	23	1.6
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	53	6	32	3.8
Increased alanine aminotransferase	55	9	21	1.2
Hypercholesteremia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased alkaline phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.7
Increased lipase	36	14	13	3.9
Increased creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased amylase	25	7	8	1
Hyperkalemia	23	2.4	12	1.2
Increased creatine kinase	19	3.7	7	0
Increased bilirubin	18	3.6	6	1.6
Hematology				
Lymphopenia	50	16	65	20
Thrombocytopenia	50	8	30	4.7

(*continued*)

Table 12: Laboratory Abnormalities Worsened from Baseline[a] Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Laboratory Test[b]	**All Grades[c] (%)**	**Grades 3-4 (%)**	**All Grades[c] (%)**	**Grades 3-4 (%)**
Anemia	49	8	84	14
Leukopenia	43	3.5	83	43
Neutropenia	31	6	76	58

[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/pembrolizumab (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients)
[c] Graded per NCI CTCAE v4.03

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 (retroesophageal 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 352 patients with renal cell carcinoma (RCC) who received LENVIMA with pembrolizumab in CLEAR, 45% were ≥65 years of age and 13% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Of the 62 patients with 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 (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with DTC, RCC, and endometrial carcinoma and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, and endometrial carcinoma 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, RCC, and endometrial carcinoma and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC, RCC, and endometrial carcinoma and severe hepatic impairment (Child-Pugh C). Reduce the dose for patients with DTC, RCC, and endometrial carcinoma 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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MEET OUR EXPERT

Kevin Kalinsky, MD, MS, is an associate professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine. He also is the Louisa and Rand Glenn Family Chair in Breast Cancer Research, director of the Glenn Family Breast Center, and director of breast medical oncology at Winship Cancer Institute of Emory University in Atlanta, Georgia.

Kevin Kalinsky, MD, MS, Discusses the Past, Present, and Future of Breast Cancer Research

"Nonetheless, we saw tremendous benefits for these patients, patients who didn't benefit from other treatments, and it was exciting to be involved with this early research."

Developments in the field of breast cancer abounded in 2022, not the least of which were the dramatic results of the phase 3 DESTINY-Breast04 trial (NCT03734029). However, challenges remain copious, and research efforts promise to refine the options available to clinicians across different patient groups. A diverse amount of therapies and agents, coupled with a deeper knowledge of breast cancer subtypes, may allow greater personalization of treatment for patients.

In a recent interview with *ONCOLOGY*®, **Kevin Kalinsky, MD, MS,** spoke about developments in breast cancer, some of the most crucial changes to standards of care, and research on the horizon for 2023. He touched on some of the antibody-drug conjugates (ADCs) and CDK4/6 inhibitors currently under review and the potential implications for clinical practice.

Q: What are some of the notable therapies you've worked with in clinical research?

KALINSKY: One of my most meaningful experiences [in clinical research] was being an early investigator into sacituzumab govitecan-hziy [Trodelvy]. We participated in the phase 1/2 trial [NCT01631552] that led to its initial approval in patients with metastatic triple-negative breast cancer [TNBC].[1] It was a meaningful experience because we could watch patients who hadn't benefited much from other treatments benefit from [sacituzumab govitecan] in real time. The drug was reasonably well tolerated [but did have some] adverse effects we often see with sacituzumab: diarrhea, fatigue, and sometimes [reduced] blood cell counts.[2] Nonetheless, we saw tremendous benefits for these patients, patients who didn't benefit from other treatments, and it was exciting to be involved with this early research. Sacituzumab govitecan later received a full [FDA] approval based upon the randomized phase 3 ASCENT trial [NCT02574455], which showed the same level of response and overall survival [OS] benefit vs standard of care chemotherapy.[3]

This approval was for patients with metastatic TNBC. We were also involved in the basket trial examining [sacituzumab govitecan in] patients with hormone receptor [HR]–positive, HER2-negative disease, and we've now seen from the phase 3 TROPiCS-02 study [NCT03901339] that there's an OS advantage with this drug vs physician's-choice chemotherapy.[4]

Q: Can you tell me about the phase 3 RxPONDER trial [NCT01272037]?

KALINSKY: One of the greatest unmet needs has been [the difficulty of determining] which patients need chemotherapy. We want patients to be able to opt out of treatments they don't need [to avoid] unnecessary toxicity. We know lymph node involvement is an independent predictor of risk. When I was a resident studying for the boards, a patient with lymph node–positive breast cancer [always] received chemotherapy. That was the standard.

RxPONDER was conducted based on another prospective retrospective analysis of clinical data, the phase 3 SWOG-8814 trial [NCT00929591]. This was a pivotal study led by Kathy S. Albain, MD, that demonstrated the potential benefit of anthracycline-based chemotherapy. It also demonstrated that there may be a role for oncotype in the determination of risk.[5]

In RxPONDER, we randomly assigned patients with a recurrence score between 0 and 25 to receive or not receive chemotherapy. All patients received endocrine therapy. Ultimately, for postmenopausal patients with 1 to 3 involved nodes and HER2-negative disease, there was no benefit to chemotherapy. That group included two-thirds of the [total] population, so this is a very meaningful outcome.[6]

[As a result], we can now avoid those unnecessary toxicities and costs for thousands of patients who fit these criteria. And when I say costs, I also mean the quality-of-life costs that can be associated with chemotherapy.

For the remaining one-third of patients who are premenopausal, we're still seeing a benefit from chemotherapy, but this is where the greatest [lingering] questions lie. What is [the nature of] that benefit? Does it occur because there are patients stuck having their periods, or is there a relevant difference in the biology of pre- and postmenopausal patients? This remains unanswered. There's a study planned by NRG Oncology that will help address this question.

At the 2022 San Antonio Breast Cancer Symposium [SABCS], [we presented data showing] that HER2 expression was not related to outcome.[7] HER2-low disease is of significant interest in the field now, especially for metastatic disease, given the approval of fam-trastuzumab deruxtecan-nxki [Enhertu].

There were also outcome differences between non-Hispanic White and non-Hispanic Black patients that will likely cause some discussion. Non-Hispanic Black patients seemed to experience worse outcomes despite having equivalent levels of adherence to endocrine therapy in the first year. This [disparity] is hypothesis generating: Why are we seeing this? Is it correlated to differences in access to care? We also [have to proceed with] the understanding that non-Hispanic Black patients remain [broadly] underrepresented in clinical trials. But this disparity remains a critical question.

Q: What are some other unmet needs in breast cancer?

KALINSKY: Patients with HR-positive, HER2-negative breast cancer can have late recurrences, meaning recurrences after 5 years. The question is: How can we identify who those patients are? One avenue of research focuses on circulating biomarkers, such as circulating tumor DNA [ctDNA], to determine who might be at risk for recurrence. We have an ongoing substudy of RxPONDER [in which we're] collecting blood markers such as ctDNA from patients who haven't yet had a recurrence and are less than 8 years out from randomization to see if we can find indicators for late recurrence.

Moreover, [another question is]: Are these markers simply prognostic or are they predictive? Would they enable you to change an agent and maybe [use] a new hormonal therapy, such as an oral selective estrogen receptor degrader? Would [this kind of treatment] change the biology of the cancer? These are all [lingering questions].

Q: Is there a problematic scarcity of genomic testing in this breast cancer space?

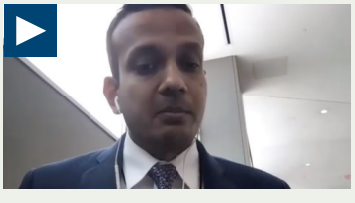
KALINSKY: The genomic assays for [HR-positive/HER2-negative] breast cancer have been commercially available since the mid-2000s. Some clinicians made use of these tools in patients with node-positive breast cancer before we even had the data, [when] we didn't know what to do. There are generalizability issues; even in RxPONDER, there wasn't a large population of patients with tumors greater than 5 cm. Most of the patients had 1 involved node, and less than 10% had 3. So there's always nuance. Differences in practice patterns [surrounding genomic testing] are primarily based on how to interpret results, as opposed to conducting vs not conducting the test.

Q: What are some up-and-coming biomarkers on the horizon?

KALINSKY: The [major] lingering questions concern the role of circulating biomarkers because tumor biomarkers are static. What has the greatest utility in the early-stage treatment setting? [Should we rely on] bespoke markers for minimal residual disease? For those, you examine the tumor tissue and then look for specific alterations in the blood based on what you see in the tissue. Can [we instead rely on] tissue-agnostic markers?

Again, though, the [crucial] question is: How do you respond to the results? Can you [use them] to change outcomes? That's the next frontier. ■

For references and full interview visit cancernetwork.com/1.23



Study Findings Will Generate Better Treatment Discussions With Providers and Patients

Recent study findings related to risk factors for developing contralateral breast cancer may better influence treatment decisions between patients and physicians, according to Siddhartha Yadav, MD, MBBS.

Cancernetwork.com/SABCS_1.23

Shorter Time to Treatment Is Associated With Improved Survival in Rural Patients With Breast Cancer Despite Other Adverse Socioeconomic Factors

Minh-Tri Nguyen, MD[1]; Wei Wei, MS[2]; Gregory Cooper, MD[3]; Alok A. Khorana, MD[4]; and Suneel D. Kamath, MD[5]

ABSTRACT

BACKGROUND. Cancer care in rural areas poses unique challenges, including access and proximity to care. This study examined differences in time to treatment initiation (TTI), a potential surrogate for access, and predictors of overall survival (OS) between rural and nonrural patients with breast cancer.

METHODS. Women with stage I to III breast cancer diagnosed between 2004 and 2012 in facilities accredited by the National Cancer Database of Commission on Cancer (CoC) were included. Differences between rural and nonrural patients in demographics, disease and treatment characteristics, socioeconomic factors, and TTI were assessed by χ^2 test. The effects on OS of age, insurance status, cancer center type, community median income, percentage of the community who had not graduated from high school, and TTI were assessed using Cox models.

RESULTS. The study population was composed of 1,205,031 patients, 18,417 (2%) of whom were rural. Compared with nonrural patients, rural patients were more likely to be older, to be White, to receive care at nonacademic centers, to have government insurance or annual income less than $38,000, and to be less educated ($P < .0001$). Rural patients also had shorter median TTI (3 vs 4 weeks; $P < .0001$), which was associated with improved OS ($P < .0001$), and were more likely to have TTI less than 4 weeks and less than 8 weeks ($P < .0001$ for both). Shorter TTI (both <4 weeks vs 8 weeks and 4-8 weeks vs >8 weeks) was also associated with improved OS ($P < .0001$ for both). After adjusting for disease stage and demographic-, socioeconomic-, and treatment-related factors, rural status was associated with improved OS compared with nonrural status (HR, 0.92; 95% CI, 0.89-0.96; $P < .0001$).

CONCLUSIONS. Despite several adverse demographic and socioeconomic factors, rural patients with breast cancer with access to CoC-accredited facilities had significantly shorter TTI and better OS compared with nonrural patients. The clinical significance of this is undetermined; however, these data suggest that improving TTI can mitigate disparities in rural cancer care.

PERSPECTIVE

Richard L. Martin III, MD, MPH; and Stephen Schleicher, MD, MBA share a perspective on rural cancer care on page 25

Introduction

Patients with cancer who live in rural communities face unique barriers to receiving high-quality cancer care. The geographic misdistribution of health systems that provide screening, preventive services, oncology specialty care, and clinical trials reduces access to care for rural patients.[1,2] Additionally, rural communities have lower median annual income and education levels compared with urban communities, which can lead to lower health literacy. Rural patients are more likely to be uninsured or underinsured through Medicaid or Medicare compared with their urban counterparts.[3] These adverse factors lead to lower screening rates, more cancer diagnoses at advanced stages, and lower adherence to standard-of-care therapies for patients in rural

communities.[4-7] As a result, rural patients have higher cancer incidence and mortality compared with patients in urban areas.[8] Although cancer mortality rates have declined overall in the United States, the rate of decline has been slower in rural communities, further exacerbating existing disparities in outcomes.[9,10]

Improving time to treatment initiation (TTI), a potential surrogate for access, may be an effective strategy to improve outcomes for rural patients with cancer.[11] For example, a prior study of both the Surveillance, Epidemiology, and End Results (SEER) database of female breast cancer and the National Cancer Database (NCDB) showed that significant delays between diagnosis and time of surgery led to worse overall survival (OS) for patients with stage I and II breast cancer.[12] A more recent study showed that median TTI for women with stage I to III breast cancer increased from 18 days in 2004 to 28 days in 2013, and treatment at an academic center was associated with an increase in median TTI of 4.1 days. For women with stage I or II breast cancer, every week of increased TTI was associated with a relative 1.8% and 1.2% increased risk of death, respectively.[13] How TTI might specifically affect rural patients with cancer remains unknown.

In this study, we examined the NCDB to better understand demographic, socioeconomic, disease, and treatment differences between rural and nonrural women with breast cancer and their association with outcomes. We also investigated how TTI might affect survival in both the rural and nonrural populations.

TABLE 1. **Demographics and TTI Between Rural and Nonrural Participants**

	Rural n = 18,417 (1.5%)	Nonrural n = 1,205,031 (98.5%)	*P*[b]
Age >65 years	8201 (44.5%)	479,983 (40.4%)	< .0001
Race			
White	16,839 (91.4%)	1,004,476 (84.7%)	< .0001
Black	1140 (6.2%)	128,989 (10.9%)	
Other[a]	303 (1.7%)	40,737 (3.4%)	
Unknown	135 (0.7%)	12,412 (1.1%)	
Charlson-Deyo score			
0	15,270 (82.9%)	1,010,741 (85.2%)	< .0001
1	2569 (14.0%)	144,574 (12.2%)	
2 or higher	578 (3.1%)	31,299 (2.6%)	
Cancer stage			
I	9120 (49.5%)	604,621 (51.0%)	< .0001
II	6023 (32.7%)	383,000 (32.3%)	
III	2322 (12.6%)	132,548 (11.2%)	
Unknown	952 (5.2%)	66,445 (5.6%)	
First treatment			
Chemotherapy	1465 (8.0%)	109,843 (9.3%)	< .0001
Radiation	45 (0.2%)	4224 (0.4%)	
Surgery	16,903 (91.8%)	1,072,128 (90.4%)	
Other	4 (0.02%)	419 (0.04%)	
TTI			
≤4 weeks	12,332 (67.0%)	680,686 (57.4%)	< .0001
4–8 weeks	4918 (26.7%)	385,870 (32.5%)	
>8 weeks	1167 (6.3%)	120,058 (10.1%)	
Median TTI (IQR)	**3 weeks (2-5 weeks)**	**4 weeks (2-6 weeks)**	**< .0001**

Methods

The study cohort was obtained from the NCDB, a joint program of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. The NCDB is a hospital-based, prospectively collected outcomes database that includes approximately 70% of all new invasive cancer diagnoses and more than 1500 CoC-accredited facilities in the United States. Data collection is standardized based on the Facility Oncology Registry Data Standards, and data were generated using the Participant Use Data File program. For this study, women diagnosed with stage I to III breast cancer between 2004 and 2012 were included; these were the most recent data available at the time of data abstraction. Because the data set is deidentified and publicly available, this study was granted exempt status by the institutional review board of the Cleveland Clinic Taussig Cancer Center.

Data abstracted included age, sex, race, community median income, insurance status, community education level, county urbanization, year of diagnosis, American Joint Committee on Cancer stage, tumor grade, cancer center type, first treatment modality, and TTI. TTI was calculated using the dates of initial cancer diagnosis and earliest cancer-directed therapy (surgery, radiation, or systemic therapy). Level of comorbidity was measured using the Charlson-Deyo score.[14]

Patients were then categorized into rural and nonrural groups. Data on rural status were provided in the NCDB data set, which uses a classification schema based on county population size, degree of urbanization, and proximity to a metropolitan area. A rural com-

TABLE 1 CONT. **Demographics and TTI Between Rural and Nonrural Participants**

	Rural n = 18,417 (1.5%)	Nonrural n = 1,205,031 (98.5%)	*P*[b]
Cancer center type			
Academic	2812 (15.3%)	327,773 (27.6%)	< .0001
Community	14,984 (81.4%)	800,551 (67.5%)	
Unknown	621 (3.4%)	58,290 (4.9%)	
Insurance			
Private	7895 (42.9%)	626,372 (52.8%)	< .0001
Government	9802 (53.2%)	513,201 (43.3%)	
No insurance	370 (2.0%)	23,981 (2.0%)	
Unknown	350 (1.9%)	23,060 (1.9%)	
Community median income			
<$38,000 vs ≥$63,000	7664 (41.6%)	176,530 (14.9%)	< .0001
$38,000-$48,000 vs ≥$63,000	6558 (35.6%)	255,324 (21.5%)	
$48,000-$62,999 vs ≥$63,000	3495 (19.0%)	316,727 (26.7%)	
≥$63,000	603 (3.3%)	422,489 (35.6%)	
Unknown	97 (0.5%)	15,544 (1.3%)	
Proportion without high school degree			
≥21%	5647 (30.7%)	165,227 (13.9%)	< .0001
13.0%-20.9%	5678 (30.8%)	279,805 (23.6%)	
7.0%-12.9%	5121 (27.8%)	391,705 (33.0%)	
<7.0%	1897 (10.3%)	334,830 (28.2%)	
Unknown	74 (0.4%)	15,047 (1.3%)	

[a]All races other than White or Black.
[b]*P* values are for overall comparisons within each variable (eg, race, Charlson-Deyo score).
TTI, time to treatment initiation.

TABLE 2. **Summary of TTI by Rural Status and Race, in Weeks**

	N	25th percentile	Median	75th percentile	*P*
Rural status					
Nonrural	1,186,614	2	4	6	< .0001
Rural	18,417	2	3	5	
Race					
White	1,021,315	2	4	6	< .0001
Black	130,129	2	5	7	
Other[a]	41,040	2	4	6	
Unknown	12,547	2	4	6	

TTI, time to treatment initiation.
[a]All races other than White or Black.

munity was defined either by having an urban population smaller than 2500 or by being completely rural. Urban counties included both urban and metropolitan counties as defined by the NCDB.

Statistical analyses evaluated associations between patient socioeconomic and disease attributes and TTI with OS. Baseline characteristics were summarized using percentages for categorical variables and medians with IQRs for continuous variables. TTI was divided into 3 categories: less than 4 weeks, 4 to 8 weeks, and greater than 8 weeks. OS was calculated from diagnosis to death or last follow-up, and an OS event was defined as death by any cause. OS was estimated using the Kaplan-Meier method. Survival time was censored for patients who were alive at the end of the study period.

Baseline characteristics between rural and nonrural groups were analyzed using the χ^2 test for categorical variables and the Wilcoxon Rank Sum Test for continuous variables. The Cox proportional hazards model was used for univariate and multivariate regression analyses of OS, which included all baseline characteristics, rural vs nonrural status, and TTI as variables. The final multivariate Cox model was stratified by year of diagnosis. A 2-sided *P* value of less than .05 was used to indicate statistical significance. A summary of TTI (in weeks) by rural status and race was completed by using Wilcoxon Rank Sum Test. All data analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC).

Results

The study population was composed of 1,205,031 patients, 18,417 (1.5%) of whom were rural. The median follow-up of all included patients was 55.6 months (range, 0.1-133.3 months). Most patients did not have a prior history of cancer (85%); this included 84% of nonrural patients and 85% of rural patients. Most of our participants (55% rural; 60% nonrural) were 65 years or younger. Our study population was diagnosed predominantly with stage I (50% rural; 51% nonrural) and stage II (33% rural; 32% nonrural) breast cancer, and surgery was overwhelmingly the first treatment they received (92% rural; 90% nonrural). Higher proportions of rural vs nonrural patients were older than 65 years at diagnosis (45% vs 40%, respectively) and were White (91% vs 85%; *P* < .0001 for both). Compared with nonrural patients, rural patients were more likely

to receive care at nonacademic centers (85% vs 72%, respectively), to have government insurance (53% vs 43%) and a median income less than $38,000 (42% vs 15%), and to live in less-educated communities (61% vs 38%; *P* < .0001 for all). These data are summarized in **Table 1**. Overall, Black patients had significantly longer TTI than White patients (**Table 2**).

While the data showed statistically significant differences in Charlson-Deyo score and breast cancer stage between rural and nonrural patients, these differences were small and not clinically meaningful. As depicted in Table 1, rural vs nonrural patients had shorter median TTI (3 vs 4 weeks, respectively; *P* < .0001). Additionally, more rural patients had TTI of less than 4 weeks (67% vs 57%) and less than 8 weeks (94% vs 90%; *P* <.0001 for both). **Table 3** shows that a shorter TTI (both < 4 weeks vs 8 weeks and 4-8 weeks vs >8 weeks) was associated with improved OS (HR 0.84; 95% CI, 0.82-0.86; *P* < .0001; and HR 0.82; 95% CI, 0.81-0.83; *P* < .0001, respectively). As depicted in the **Figure**, shorter TTI improved outcomes for both rural and nonrural patients; this was more pronounced for rural patients earlier in follow-up (by 24-36 months) than for nonrural patients (by 48-60 months).

After adjusting for disease stage and demographic-, socioeconomic-, and treatment-related factors, rural status was associated with significantly better OS compared with nonrural status (HR, 0.92; 95% CI, 0.89-0.96; *P* < .0001). Other multivariable regression analyses are shown in Table 3 and a forest plot showing Cox model HRs is shown in the Figure.

TABLE 3. **Multivariate Regression for Overall Survival in Breast Cancer**

Factor	Comparison	HR	95% LCL	95% UCL	*P*
Rural status	Rural vs others	0.924	0.889	0.96	< .0001
Age	<65 vs ≥65 years	0.437	0.431	0.444	< .0001
Race	White vs other[a]	1.413	1.36	1.468	< .0001
	Black vs other	1.698	1.63	1.768	
Insurance	No insurance vs government	0.933	0.897	0.97	.0005
	Private vs government	0.618	0.609	0.627	< .0001
Cancer center type	Nonacademic vs academic	1.131	1.118	1.145	< .0001
Community median income	<$38,000 vs ≥$63,000	1.217	1.193	1.241	< .0001
	$38,000-$48,000 vs ≥$63,000	1.15	1.131	1.169	
	$48,000-$63,000 vs ≥$63,000	1.082	1.066	1.099	
Community % without high school degree	≥21% vs <7%	1.05	1.028	1.073	< .0001
	13%-20.9% vs <7%	1.077	1.058	1.096	
	7%-12.9% vs <7%	1.083	1.067	1.1	
Stage	I vs III	0.292	0.288	0.296	< .0001
	II vs III	0.496	0.489	0.502	
Charlson-Deyo score	0 vs >0	0.6	0.593	0.607	< .0001
History of cancer	No vs yes	0.628	0.62	0.635	< .0001
TTI	≤4 vs >8 weeks	0.842	0.828	0.857	< .0001
	4-8 vs >8 weeks	0.819	0.805	0.834	

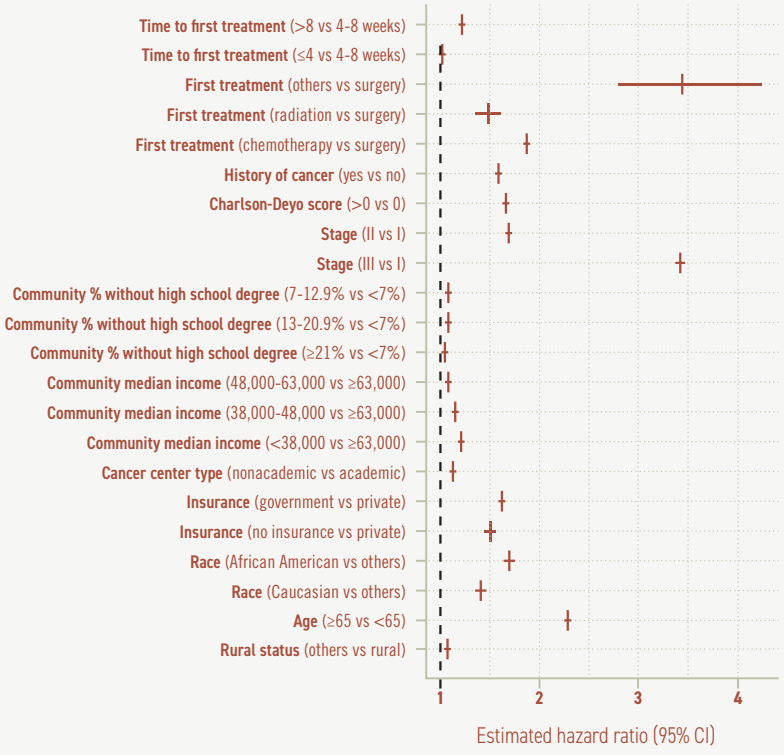
LCL, lower confidence interval; TTI, time to treatment initiation; UCL, upper confidence interval
[a]All races other than **White or Black**.

Discussion

Cancer mortality rates are generally higher in rural than nonrural populations in the United states.[4,9] Many barriers exist for patients with cancer who live in rural communities.[15] Consistent with our findings, previous studies have shown that rural patients are more likely to have lower income and to be less educated.[15] These socioeconomic disparities can lead to low health literacy[16,17] and being underinsured,[18] and they can ultimately limit help-seeking behaviors. Geographically, patients living in rural settings often lack easy access to CoC-accredited facilities, including oncology specialty care and clinical trials.[3] Unsurprisingly, rurality has been correlated with not obtaining guideline-directed care[19] and is associated with more advanced cancer stage at diagnosis.[20] For this reason, TTI has been used as a surrogate to measure access to care, with shorter intervals correlated with better outcomes.[11] Increasingly, more studies have reported shorter time to diagnosis and TTI for rural patients with breast cancer than for those in urban areas.[21-25] Our study also found that rural patients with breast cancer were statistically more likely to have better TTI than their urban counterparts. Additionally, we showed that delayed TTI correlated with worse outcomes, with the biggest difference in OS seen with a TTI of greater than 8 weeks.

Our results contrast with previous findings suggesting that rurality leads to delays in TTI for patients with breast cancer, resulting in poorer outcomes.[12,13,26] The complexity of care for rural patients may offer possible reasons for these trends. Qualitative studies have looked at patient attitudes concerning the concept of choice of treatment provider and facilities. These studies have suggested that because of limited resources, provider/facility choice seem somewhat irrelevant for rural patients. Although there may be fewer options for treatment

FIGURE. **Forest Plot of Estimated Hazard Ratios by Variables**



facilities in rural settings, those facilities may have more quickly available openings for new patients compared with some large metropolitan health systems.

Rural patients also noted limited capacity to obtain second opinions when it came to their treatment.[27] The utilization of a second opinion has been reported to be higher in patients living in urban or metropolitan areas, those with higher socioeconomic status, and those who are privately insured.[28-30] However, while there are potential benefits to obtaining a second opinion, the second opinion process can lead to delays in cancer treatment initiation.[28] It is possible that rural patients in our study had shorter TTI in part because they were less likely to seek second opinions. However, this study did not directly measure utilization of second opinions. Given that patients with cancer increasingly seek second opinions and that the benefits of this process remain unclear,[28] it would be important to characterize this process further among rural and nonrural patients to determine differences in TTI and outcomes.

Prior studies in breast cancer have demonstrated that Black and Hispanic women experience more treatment delays than White women, including delays of surgery and radiation as well as delayed or incomplete chemotherapy.[31-37] Both our rural population and nonrural population predominantly included White women (91.4% and 84.7%, respectively), which is consistent with previously published data.[35] In a study of 8860 adolescent and young-adult patients with breast cancer from the California Cancer Registry, 15.4% of Black women experienced delayed TTI compared with 8.1% of White women.[36] It has been well documented that Black women with breast cancer are disproportionately affected by treatment delays,[24,33,35,40] including of surgery[38] and chemotherapy.[32,42] One study that stratified TTI within a rural population found that Black women experienced longer TTI compared with their White counterparts.[40] Our study showed that Black patients overall had significantly longer TTI. While our study showed that rural patients were more likely to have shorter TTI, an overwhelming majority of our rural population was White. These data suggest that while differences in outcomes exist for rural and nonrural patients, racial inequities may be an important factor in explaining why nonrural patients in our study had less favorable outcomes and TTI.

Limitations

We showed that the biggest decrease in OS was associated with TTI greater than 8 weeks for all patients, suggesting that delayed TTI is associated with worse OS. The difference in OS between TTI of less than 4 weeks and TTI of 4 to 8 weeks was statistically significant due to large sample size, but it is likely not clinically significant. Similarly, our study also found a statistically significant 1-week difference in median TTI among rural vs nonrural patients. Given that most patients in our study population presented with early stage I/II breast cancer and that most are estrogen receptor positive, it is unclear how clinically relevant this 1-week difference is to OS. Further research will need to evaluate whether factors such as aggressive subtypes or specific treatment modalities contribute to longer TTI. As there are no defined or validated TTI cutoffs, the cutoffs of 4 weeks and 8 weeks used in this study are arbitrary, although no more so than any others. Our study looked at TTI generally; future work may investigate the impact of times to initiation

of specific treatments such as radiation, surgery, and neoadjuvant therapy.

As discussed, other variables—such as likelihood to seek second opinions, socioeconomic factors, and race—may also need to be explored further to fully understand the overall impact of these associations. We acknowledge that the NCDB relies on CoC-accredited hospitals, and these data may not be generalizable to all patients. Because of this, only 1.5% of our study population was composed of rural patients, compared with 18% in the general US population. Still, our findings help to define trends in a currently limited body of knowledge and to further the work in this field.

Additionally, future work may investigate data aggregated beyond 2012, particularly evaluating how the COVID-19 pandemic may have offset some factors causing disparities. One potential benefit is that during the pandemic, virtual visits became more widely available, particularly for patients who lived far from their providers. Still, rural patients are less likely to have adequate connectivity, and thus the ability of telehealth to equalize the level of access for rural and nonrural patients remains to be seen. If issues of connectivity to state-of-the art cancer care, timely second opinions, and access to subspecialists can be mitigated by telehealth, it is reasonable to be optimistic about its role in eliminating some rural health disparities.[41] Until then, strategies that aim to shorten TTI using results from this study and other studies may provide a timely impact on eliminating rural health disparities.

Conclusions

Our study adds to a growing body of literature aimed at informing strategies that can be easily reapplied to other institutions. This study demonstrates that despite many adverse clinical and socioeconomic factors, rural women with early-stage breast cancer experience shorter TTI and better outcomes compared with urban women—this is particularly true for those with a TTI of less than 8 weeks. Our findings highlight the complexity of rural health disparities, particularly issues pertaining to access. Additionally, our study results suggest not only that TTI correlates with survival outcomes, but also that understanding these trends may help to facilitate much-needed strategies to reduce health disparities for rural patients with breast cancer. In an era when novel cancer therapies that provide survival advantages of several months (or more) are rapidly changing national guidelines, it is worth considering the connection between shortened TTI and improved OS. ■

DISCLOSURE: **AAK** has served as a consultant for Anthos, Bayer, Bristol Myers Squibb, Janssen Pharmaceuticals, Pfizer, and Sanofi; **SDK** has served as a consultant or paid advisory board member for Exelixis and Tempus.

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PERSPECTIVE BY

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Progressing From Disparity to Equity: Untangling the Complexities of Timely Care and the Rural Cancer Experience

In the wake of increasing attention to health equity and value-based care, Nguyen et al offer a fitting study examining the timeliness of care among rural patients with breast cancer. The authors combine the results of 2 hypotheses—(1) "Is rurality associated with time to treatment initiation (TTI)?" and (2) "Is TTI associated with overall survival (OS)?"—to conclude that "rural women with early-stage breast cancer experience shorter TTI and better outcomes vs urban women, particularly in those with TTI of less than 8 weeks."

In their discussion, the authors realize a major validity issue with this 2-step approach, noting that (1) race significantly correlated with rurality and TTI, and (2) racial disparities in both TTI and OS have been observed cohorts within rural breast cancer. Nguyen et al also raise concerns about the generalizability of their findings. Attempting to study rural access challenges—"TTI, a potential surrogate for access"—they use National Cancer Database (NCDB) data, which select for the exceptionally rare rural population (1.5% compared with 18% nationally) with access to Committee on Cancer (CoC)-accredited facilities. Because CoC accreditation depends on meeting timely care standards, use of this data set also likely influences TTI estimates. Finally, the authors conclude that even if their observations achieved statistical significance, they may not be clinically relevant.

Therefore, the results of this study are best described as hypothesis generating, and further research is needed to untangle the relationships among rurality, TTI, and breast cancer survival. This perspective offers some considerations that may strengthen future studies.

If left undetected and untreated for perpetuity, all cancers will grow and spread until they become life limiting. The question is not whether TTI is associated with OS, but rather, for a given cancer, the questions are how much could TTI be reduced through more efficient and accessible care, and whether this reduction could lead to improvements in quality of life, disease-free status, or OS. Far from being arbitrary, understanding and selecting appropriate time intervals for time analyses is critical. For example, imagine comparing TTI of less than 4 weeks, 4 to 8 weeks, and greater than 8 weeks for acute promyelocytic leukemia (APL) or Rai stage 0 chronic lymphocytic leukemia (CLL). For APL, everyone in the 4- to 8-weeks and greater than 8 weeks groups would be dead, while all 3 groups of patients with CLL would be alive.

For nonmetastatic breast cancer, approximate time intervals for completing surgery and adjuvant therapies are known. Such knowledge-guided triaging decisions during the COVID-19 pandemic to minimize harms from care delays. CoC breast cancer performance standards include timeliness of radiation (<1 year), endocrine therapy (<1 year), and chemotherapy (<4 months). These time intervals vary by treatment modality, reflecting the varying importance of timely care by breast cancer stage and subtype. TTI must also be considered in the context of quality of care (ie, safe, effective, patient-centered, efficient, and equitable). To the extent that these other quality aims have existing measures (ie, fine needle or core biopsy, lumpectomy for non-nodal in situ/low tumor stage disease, sentinel lymph node and axillary lymph node dissection operative standards), they should be included in analyses.

With respect to rurality, selecting the appropriate population for the research question and intended audience is critical. This can be particularly challenging in the United States, where, unlike most developed countries, our rural populations and health systems are profoundly heterogenous. From rural tribal reservations to Appalachian "tobacco belt" communities, or even neighboring rural communities bordering states with vastly different Medicaid policies, the cultural norms, exposures, opportunities, and health systems vary dramatically across communities. Adjusting out these factors may be necessary to understand the isolated contribution of a variable, but in practice, they are inseparable from the rural cancer experience.

If we are ever to progress from identifying disparities to studying equity-oriented solutions, we must develop and analyze more local rural community and health systems data. This will involve incorporating rural communities as equal stakeholders who can provide insights on perceived barriers and facilitators to care. The ideas and solutions generated from these communities can then be evaluated, adapted, and scaled to increasingly dissimilar communities. ■

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Survival of Patients With Inoperable Non–Small Cell Lung Cancer With Baseline Severe Pulmonary Dysfunction: Impacts of Thoracic Radiotherapy and Predictive Analysis for Acute Radiation Pneumonitis

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ABSTRACT

BACKGROUND AND PURPOSE. Currently, there is no standard treatment for patients with lung cancer with deteriorated pulmonary function. In this study, we aimed to assess the efficacy of thoracic radiotherapy for unresectable non–small cell lung cancer (NSCLC) with baseline severe pulmonary dysfunction and severe acute radiation pneumonitis (SARP).

METHODS. Patients were categorized into a radiotherapy group and a nonradiotherapy group, followed by analysis of clinical variables. A Cox regression was used to evaluate the impact of various factors on overall survival (OS). Each SARP factor's predictive value was assessed using logistic regression, receiver operating characteristic curve, and Kaplan-Meier analyses.

RESULTS. The median OS in the radiotherapy group was 21.6 months vs 8.9 months in the nonradiotherapy group. Cox analysis revealed that chemotherapy (HR, 0.221; 95% CI, 0.149-0.329; $P < .001$) and radiotherapy (HR, 0.589; 95% CI, 0.399-0.869; $P = .008$) are independent prognostic factors for the current cohort. The data suggested that the ipsilateral lung V10 (iIV10, the percentage of the lung volume that received more than 10 Gy) was an independent predictor of SARP.

CONCLUSIONS. Our findings suggested that thoracic radiotherapy might be associated with clinical benefits to inoperable NSCLC in patients with severe pulmonary dysfunction and that iIV10 may be involved in the prediction of risk for SARP in these patients.

KEYWORDS. Severe pulmonary dysfunction; non–small cell lung cancer; thoracic radiotherapy; predictive factors; severe acute radiation pneumonitis

Introduction

Smokers with chronic obstructive pulmonary disease (COPD) have a 2 to 5 times higher lung cancer risk than non-COPD smokers.[1-4] According to international guidelines, a ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) of less than 0.70 after inhaling bronchodilators is a diagnostic criterion for COPD.[5] Patients with COPD or pulmonary interstitial diseases and lung cancer also have pretreatment pulmonary dysfunction. Currently, no standard treatment is available for those patients with baseline severe pulmonary dysfunction who might not tolerate surgery or definitive concurrent chemoradiotherapy (CCRT). Those patients who have impaired pulmonary function were often subjected to stereotactic radiotherapy treatment in early-stage cases, whereas advanced-stage cases could only receive medical treatment without thoracic radiotherapy.[6-10]

As part of either definitive or palliative therapy, radiotherapy may help treat all stages of NSCLC and small cell lung

cancer.[11,12] The role of conventional-fractionated thoracic radiotherapy in patients with NSCLC and serious pulmonary dysfunction was unclear due to the consideration of severe acute radiation pneumonitis (SARP). According to the results of our previously reported study, the mean lung dose (MLD) and carbon monoxide diffusing capacity of the lungs (DLCO%) possess the potential to predict the SARP risk in patients with NSCLC and baseline moderate pulmonary dysfunction.[13] To date, no research has evaluated the effectiveness and radiotoxicity of thoracic radiotherapy in patients with NSCLC and severe pulmonary dysfunction at the outset. In the study reported below, we gathered information on clinical causes, treatment, survival status, dosimetric parameters, and SARP frequency in these patients to assess the clinical benefits of thoracic radiotherapy and to identify possible risk factors for SARP.

Patients and Methods

Patients

A total of 33,582 patients who had been diagnosed with NSCLC pathologically in West China Hospital and Sichuan Provincial People's Hospital between January 2014 and December 2018 were retrospectively reviewed. Among these, the records of 795 demonstrated evidence of pretreatment severe pulmonary dysfunction. Severe pulmonary dysfunction was defined according to the American Thoracic Society and the European Respiratory Society; the actual or estimated ratio of FEV1 ranged from 35% to 49%.[14,15] The current study has not included patients with extremely severe pulmonary dysfunction (FEV1 <35%) because they were often unable to receive most tumor-related therapy due to poor pulmonary function. The predetermined inclusion criteria were NSCLC with a definite pathological diagnosis, pretreatment severe pulmonary dysfunction, and an ECOG performance status of 0 to 2. Patients who had undergone surgery, targeted therapy, or stereotactic radiation were excluded from the study. Ultimately, 170 patients were eligible for the study and were divided into 2 groups: a radiotherapy group (53 patients) and a nonradiotherapy group (117 patients).

Introduction to Clinical and Dose-Volume Histogram Factors

Clinical factors including age, ECOG performance status, gender, pathological diagnosis, laterality, sites of the tumor, smoking status, tumor-node-metastasis stage, pulmonary function, radiotherapy procedures, chemotherapy treatments, and survival were recorded. Restaging of all patients was conducted according to the staging scheme of the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer to improve data comparability.[16] To obtain the lung volume, the gross tumor volume (GTV) was subtracted from the total lung volume (TLV).[17,18] The proportion of lung/heart volume that received greater than variable x Gy was known as Vx. From the dose-volume histogram (DVH), we extracted and collected the following parameters: total/ipsilateral /contralateral lung $V_{5/10/20/30}$, heart $V_{10/20/30/40/50}$, mean dose (MD), planning target volume (PTV) radiation dose, and TLV. The convolution/superposition algorithm was used to measure all of these parameters from the planned dose distribution. The conversion of DVH parameters was done for patients who had not completed their radiotherapy treatment schedule.

Radiotherapy

Of the 53 patients who received thoracic radiotherapy, 3 received radiotherapy alone, 21 received concomitant chemoradiotherapy, and 29 received sequential chemoradiotherapy. Intensity modulated radiation therapy (IMRT) with a cumulative dose of 36 Gy-66 Gy, at 1.8 Gy-3 Gy per fraction, was administered 5 days a week. Targets were defined based on reports 62 and 83 of the International Commission on Radiation Units and Measurements.[19-21] GTV was identified as a tumor that could be seen macroscopically on CT images, including lymph nodes with a diameter of greater than 1 cm. To account for setup instability and respiratory motion, the GTV plus a 5- and 10-mm margin around the affected lymph nodes and lung tissue, respectively, comprised the PTV. For normal tissues, the following dose-volume constraints were established:

- to the whole lung, V20 ≤30%-35% and MLD ≤15 Gy;
- to the heart, V50 ≤25% and MD ≤20 Gy;
- to the spinal cord, ≤50 Gy; and
- to the esophagus, MD ≤34 Gy.

Chemotherapy

Chemotherapy was given to 114 patients, with 50 receiving concurrent or sequential radiotherapy. Chemotherapy was given every 21 days with a median of 7 cycles (range, 2-12). First-line chemotherapy included docetaxel, paclitaxel, pemetrexed, and etoposide combined with carboplatin or cisplatin. Combination treatment with bevacizumab had a significant effect on patients with nonsquamous cell lung cancer. Pemetrexed and docetaxel were given as second-line therapy for patients with nonsquamous and squamous cell lung cancer. None of the studied population had received immune checkpoint inhibitors. The National Comprehensive Cancer Network (NCCN) protocols were used to determine all doses and changes to the chemotherapy regimen.[11]

End Point Definitions

Determination of overall survival

TABLE 1. **Baseline Characteristics of All Patients (N = 170)**

Characteristics	Total (%) (N = 170)	RT (%) (n = 53)	Non-RT (%) (n = 117)	*P*
Age (years)				
<60	67 (39.4)	22 (41.5)	45 (38.5)	.706
≥60	103 (60.6)	31 (58.5)	72 (61.5)	
Gender				
Male	140 (82.4)	46 (86.8)	94 (80.3)	.307
Female	30 (17.6)	7 (13.2)	23 (19.7)	
ECOG performance status				
0	54 (31.8)	21 (39.6)	33 (28.2)	.139
1-2	116 (68.2)	32 (60.4)	84 (71.8)	
Pathological diagnosis				
SCC	92 (54.1)	36 (67.9)	56 (47.9)	.015
Non-SCC	78 (45.9)	17 (32.1)	61 (52.1)	
Tumor site				
Upper lobe	95 (55.9)	34 (64.2)	61 (52.1)	.144
Middle/lower lobe	75 (44.1)	19 (35.8)	56 (47.9)	
Laterality				
Left	75 (44.1)	26 (49.1)	49 (41.9)	.383
Right	95 (55.9)	27 (50.9)	68 (58.1)	
Smoking status				
Yes	130 (76.5)	39 (73.6)	91 (77.8)	.551
No	40 (23.5)	14 (26.4)	26 (22.2)	
Tumor stage				
T1-2	55 (32.4)	17 (32.1)	38 (32.5)	.958
T3-4	115 (67.6)	36 (67.9)	79 (67.5)	
N stage				
N0-1	29 (17.1)	8 (15.1)	21 (17.9)	.647
N2-3	141 (82.9)	45 (84.9)	96 (82.1)	
Tumor stage				
III	73 (42.9)	35 (66.0)	38 (32.5)	<.001
IV	97 (57.1)	18 (34.0)	79 (67.5)	

N, node; RT, radiotherapy; SCC, squamous cell carcinoma.

(OS) was assessed by using the date of pathologic diagnosis of lung cancer to the date of all-cause death or the last date of follow-up for all patients in the survival study. In the case of radiation pneumonitis (RP), the primary end point was the occurrence of SARP at grade 3 or above with 3 months of radiotherapy. According to the Common Terminology Criteria for Adverse Events (version 5.0), grade 3 RP was classified as an asymptomatic disease affecting daily events and requiring oxygen inhalation or hospital support.[22] Based on clinical signs, changes in CT pictures and proof of oxygen inhalation, and corticosteroid administration in medical records, a minimum of 2 experienced radiation oncologists jointly supported the diagnosis of SARP.

Statistical Analysis

Chi-squared tests were employed to evaluate the relative balance of baseline characteristics between the radiotherapy and nonradiotherapy groups. The Kaplan-Meier test and log-rank test were conducted to calculate OS and to determine the significance of the differences between the 2 groups. The effect of various factors on OS was studied using univariable and multivariable Cox proportional hazards models. First, with the univariate Cox regression, we assessed the predictive value of individual factors for OS. Second, in multivariate analysis, factors with $P < .05$ by univariate analyses were included.

In 53 patients who received radiotherapy, a univariate logistic regression model was utilized to assess the ability of every single factor to predict SARP. In the multivariate logistic regression model, only univariate variables with $P < .05$ were included. The optimal cutoff value of the predictor was determined using receiver operating characteristic (ROC) curve analysis. The Kaplan-Meier test was performed to obtain the hazard ratio for SARP and incidence curves. All tests were 2-sided and a *P* value of less than .05 was considered statistically significant. IBM SPSS statistics software version 27.0 was used to analyze the data.

Results

Patient Characteristics

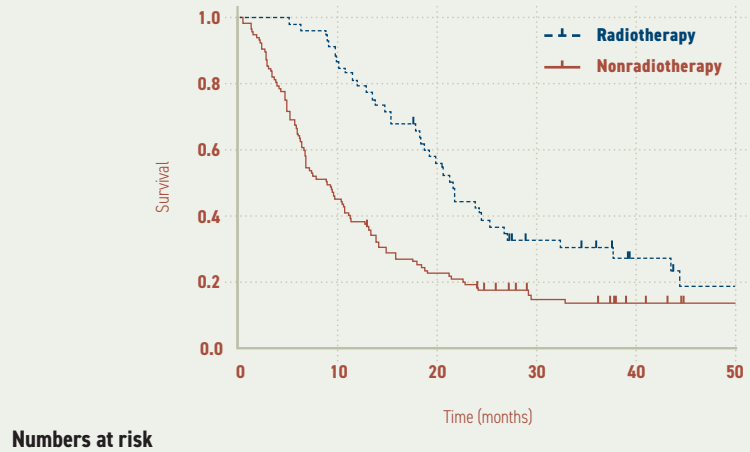
Table 1 summarizes baseline features of the sample population. The majority of patients were men who had previously smoked. Of 170 patients, 114 (67.1%) received chemotherapy and 53 (31.2%) received radiotherapy. There was a significant variation in tumor stage between the radiotherapy and nonradiotherapy groups ($P < .001$).

The mean radiation dose in the radiotherapy group was 54.5 Gy (range, 36-66 Gy).

Survival Outcomes

In this study, 138 deaths were recorded with a median follow-up time of 38.0 months (95% CI, 36.1-39.9). The median OS was found to be 12.9 months (95% CI, 10.6-15.2). Of the 170 analyzed patients, 32 were still alive at the final analysis, 14 (26.4%) in the radiotherapy group and 18 (15.4%) in the nonradiotherapy group, respectively. In the radiotherapy group, the median OS was 21.6 months (95% CI, 19.5-23.7) while in the nonradiotherapy group, it was 8.9 months (95% CI, 6.5-11.4; HR, 0.481; 95% CI, 0.344-0.673; $P < .001$; **Figure 1**).

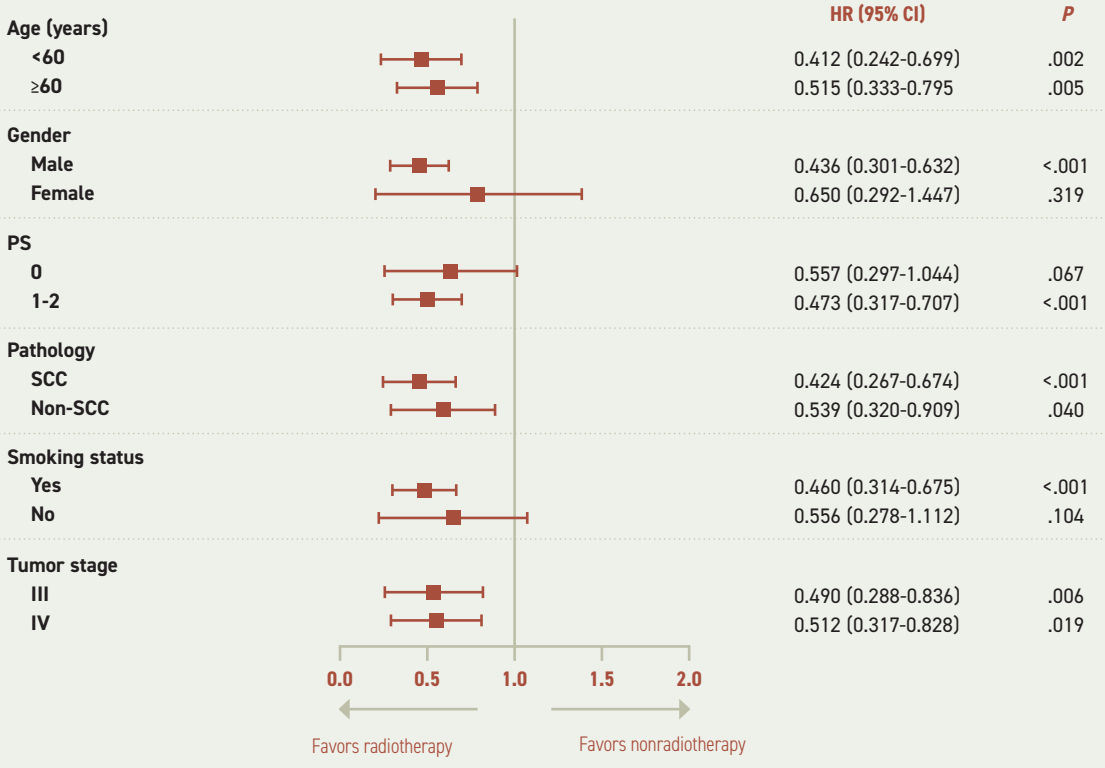
FIGURE 1. **Overall Survival of Patients in the Present Study, by Treatment**



Numbers at risk

Radiotherapy	53	46	29	14	7	4
Nonradiotherapy	117	53	26	12	5	1

FIGURE 2. **Overall Survival in Subgroups Between Radiotherapy and Nonradiotherapy Groups**



PS, performance status; SCC, squamous cell carcinoma.

We evaluated the OS in radiotherapy and nonradiotherapy groups who were stratified by age, gender, performance status, pathology, smoking status, and tumor stage (**Figure 2**). Our study found that radiotherapy could improve OS in all subgroups except females (HR, 0.650; 95% CI, 0.292-1.447; $P = .319$), patients with performance status of 0 (HR, 0.557; 95% CI, 0.297-1.044; $P = .067$), and nonsmokers (HR, 0.556; 95% CI, 0.278-1.112; $P = .104$).

Univariate and Multivariate Analyses for OS

In univariate analysis, tumor stage, chemotherapy, and radiation were found to be statistically associated with OS (**Table 2**). Chemotherapy (HR, 0.221; 95% CI, 0.149-0.329; $P < .001$) and radiotherapy (HR, 0.589; 95% CI, 0.399-0.869; $P = .008$) were found to be independent prognostic factors for OS in the current cohort by multivariate analysis.

Incidence of Toxicity

Among 53 patients who had received radiotherapy, radiation esophagitis was diagnosed in 4 patients (7.5%), 2 (3.8%) developed grade 2 or grade 3 radiation esophagitis, and 16 (30.2%) were diagnosed with SARP (grade 3, 15 patients [28.3%]; grade 4, 1 patient [1.9%]). The median time between the end of radiotherapy and the onset of SARP was 42 days (range, 16-85).

Univariate and Multivariate Analyses for Predicting SARP

In univariate analysis, total lung V_{10}, total lung V_{20}, total lung V_{30}, total lung mean dose, ipsilateral lung (il) V_5, ilV_{10}, ilV_{20}, ilV_{30}, ipsilateral lung mean dose, heart V_{10}, heart mean dose, TLV, age, and tumor stage were statistically associated with SARP, as seen in **Table 3**. These factors were all involved in the multivariate analysis. Only ilV_{10} (odds ratio 1.093; 95% CI, 1.030-1.161; $P = .004$) was found to be an independent predictor of SARP by multivariate analysis.

TABLE 2. **Cox Regression Analysis for Overall Survival**

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)				
≥60 vs <60	0.956 (0.680-1.345)	.796	—	—
Gender				
Female vs male	1.259 (0.821-1.932)	.291	—	—
ECOG PS				
1-2 vs 0	1.440 (0.993-2.089)	.055	—	—
Pathology				
Non-SCC vs SCC	1.252 (0.895-1.751)	.190	—	—
Smoking status				
Yes vs no	1.065 (0.717-1.582)	.754	—	—
T stage				
T3/T4 vs T1/T2	1.014 (0.713-1.444)	.937	—	—
N stage				
N2/N3 vs N0/N1	1.068 (0.687-1.661)	.769	—	—
Tumor stage				
IV vs III	1.548 (1.100-2.177)	.012	—	—
Chemotherapy				
Yes vs no	0.201 (0.138–0.297)	<.001	0.221 (0.149-0.329)	<.001
Radiotherapy				
Yes vs no	0.473 (0.326–0.688)	<.001	0.589 (0.399-0.869)	.008

N, node; PS, performance; RT, radiotherapy; SCC, squamous cell carcinoma.

ROC Curve and Cox Regression Analyses for SARP

According to the ROC curve, the area under the curve of ilV10 was 0.785 (95% CI, 0.661-0.909; $P = .001$), with an optimal threshold above 50.7% (**Figure 3a**). The patients were then grouped according to the mean ilV_{10}. Compared with the ilV_{10}-low group ($ilV_{10} \leq$ mean), the ilV_{10}-high group ($ilV_{10} >$ mean) possessed higher SARP risk (HR, 5.33; 95% CI, 1.99-14.29; $P = .003$; **Figure 3b**).

Discussion

Several studies[6-10] have examined the treatment of NSCLC in patients with impaired pulmonary function, while others[23-27] have focused on the risk factors for SARP. This is the first study to assess the clinical value of conventional-fractionated thoracic radiotherapy for advanced-stage NSCLC in patients with severe pulmonary dysfunction and risk factors for SARP. Our findings showed that thoracic radiotherapy may be associated with survival benefits in this particular population and that ilV_{10} had predictive value for the incidence of SARP in this cohort.

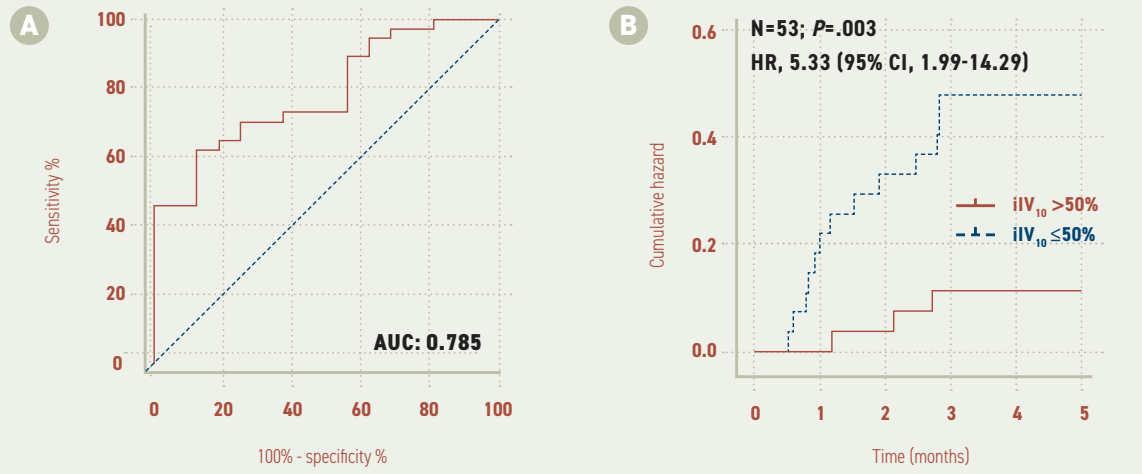
Induction chemotherapy before radiotherapy has been reported to increase response rate in locally advanced, unresectable NSCLC as compared with radiotherapy alone.[28] The randomized phase

TABLE 3. **Logistic Regression Analysis of the DVH Parameters and Clinical Factors in Predicting SARP (n = 53)**

	With SARP (n = 16)	Without SARP (n = 37)	Univariate analysis		Multivariable analysis	
	Median (IQR)	Median (IQR)	OR (95% CI)	*P*	OR (95% CI)	*P*
DVH parameters						
Total lung						
V_5 (%)	51.06 (37.66-60.23)	44.27 (31.72-52.45)	1.042 (0.994-1.093)	.084	—	—
V_{10} (%)	38.87 (29.30-44.75)	31.95 (24.32-37.44)	1.069 (1.002-1.142)	.045	—	—
V_{20} (%)	24.57 (20.59-26.76)	21.00 (14.43-26.49)	1.105 (1.002-1.218)	.046	—	—
V_{30} (%)	15.68 (13.59-18.65)	12.48 (7.96-17.98)	1.143 (1.002-1.304)	.047	—	—
MD (cGy)	1295 (1136-1452)	1010 (799-1334)	1.002 (1.000-1.005)	.025	—	—
Contralateral lung						
V_5 (%)	29.20 (16.87-49.34)	25.66 (11.10-43.13)	1.012 (0.980-1.045)	.463	—	—
V_{10} (%)	18.21 (9.45-30.74)	15.46 (7.64-27.72)	0.998 (0.990-1.006)	.666	—	—
V_{20} (%)	6.71 (3.95-13.24)	5.59 (2.22-11.99)	1.001 (0.923-1.086)	.976	—	—
V_{30} (%)	2.49 (1.53-6.31)	0.99 (0.14-5.77)	1.006 (0.880-1.150)	.928	—	—
MD (cGy)	609 (365-900)	547 (274-804)	1.001 (0.999-1.002)	.457	—	—
Ipsilateral lung						
V_5 (%)	70.69 (65.73-79.72)	60.39 (45.89-70.86)	1.071 (1.018-1.128)	.009	—	—
V_{10} (%)	59.09 (53.89-69.26)	47.22 (34.36-60.07)	1.093 (1.030-1.161)	.004	1.093 (1.030-1.161)	.004
V_{20} (%)	44.19 (40.16-57.11)	32.84 (24.73-47.37)	1.109 (1.036-1.187)	.003	—	—
V_{30} (%)	34.16 (29.03-39.43)	21.56 (13.12-35.12)	1.105 (1.028-1.187)	.007	—	—
MD (cGy)	2268 (1942-2617)	1631 (1196-2159)	1.002 (1.001-1.004)	.003	—	—
Heart						
V_{10} (%)	45.52 (28.08-68.85)	23.84 (16.08-43.07)	1.023 (1.001-1.046)	.040	—	—
V_{20} (%)	32.01 (17.57-46.25)	15.79 (7.12-31.80)	1.030 (0.999-1.062)	.058	—	—
V_{30} (%)	20.15 (9.50-33.33)	9.60 (3.21-20.56)	1.037 (0.997-1.079)	.070	—	—
V_{40} (%)	9.85 (3.84-17.37)	4.26 (0.32-11.36)	1.054 (0.994-1.118)	.077	—	—
V_{50} (%)	2.92 (1.19-7.96)	1.02 (0.00-3.80)	1.081 (0.977-1.196)	.131	—	—
MD (cGy)	1550 (977-2248)	863 (521-1501)	1.001 (1.000-1.002)	.029	—	—
Radiation dose (Gy)	60.0 (50.1-60.0)	50.4 (50.0-60.0)	1.001 (1.000-1.001)	.263	—	—
BED (Gy)	72.0 (60.0-72.0)	60.0 (60.0-72.0)	1.000 (1.000-1.001)	.288	—	—
PTV (cm^3)	387.8 (225.3-447.1)	351.5 (176.3-458.8)	1.001 (0.997-1.004)	.634	—	—
TLV (cm^3)	3021.6 (2283.1-3645.8)	3867.1 (3102.1-4578.2)	0.999 (0.999-1.000)	.030	—	—
Clinical factors						
Age (years)	56 (45-64)	62 (54-68)	0.932 (0.873-0.995)	.035	—	—
Sex: female vs male	—	—	3.778 (0.736-19.382)	.111	—	—
ECOG PS: 1-2 vs 0	—	—	0.783 (0.238-2.573)	.687	—	—
Pathological diagnosis: non-SCC vs SCC	—	—	0.947 (0.268-3.343)	.933	—	—
Tumor site: middle-lower vs upper lobe	—	—	1.108 (0.328-3.739)	.869	—	—
Laterality: right vs left	—	—	1.661 (0.203-2.153)	.492	—	—
Smoking status: yes vs no	—	—	0.460 (0.128-1.653)	.234	—	—
Tumor stage: IV vs III	—	—	0.188 (0.037-0.946)	.043	—	—
Concomitant chemoradiotherapy: yes vs no	—	—	1.846 (0.562-6.068)	.313	—	—

BED, biological effective dose; cGy, centigray; DVH, dose-volume histogram; MD, mean dose; OR, odds ratio; PS, performance status; PTV, planning target volume; SARP, severe acute radiation pneumonitis; SCC, squamous cell carcinoma; TLV, total lung volume; Vx, the percentage of the lung volume that received more than x Gy, respectively.
The constant in the logistic regression equation is -5.713 and the regression coefficient in the logistic regression equation is 0.089.
The logistic regression equation is: logit(p) = -5.713 + 0.089 × ipsilateral lung V_{10} (%).

FIGURE 3. **(A) ROC Curve of ilV_{10} for SARP in Present Study; (B) Kaplan–Meier Estimates for the Total Hazards for SARP (ilV_{10}-low vs ilV_{10}-high Group)**



AUC, area under the curve; ilV_{10}, ipsilateral lung V_{10}; ROC, receiver operating characteristics; SARP, severe acute radiation pneumonitis.

3 RTOG 9410 trial (NCT01134861) showed the superiority of CCRT vs sequential chemoradiotherapy for stage III NSCLC in terms of survival.[29] According to Daniel R. Gomez, MD, and colleagues, local consolidative therapy, such as radiotherapy and surgical resection, may substantially improve progression-free survival (PFS) in patients with metastatic NSCLC who have not progressed after initial systemic therapy vs maintenance therapy or observations.[30] Numerous studies have found that radiotherapy is beneficial for both locally advanced and metastatic lung cancers; radiotherapy has not been widely used to treat patients with severe pulmonary dysfunction because of the toxicity of radiotherapy.

According to Gerben R. Borst, MD, and colleagues, patients with NSCLC had a small decrease in pulmonary function after radiotherapy whereas patients with COPD had a great reduction in pulmonary function.[31] Radiotherapy can cause changes in the structure of the lungs, leading to a decrease in pulmonary function, worsening symptoms, and lower quality of life. A multicenter prospective longitudinal study of patients receiving CCRT for advanced NSCLC found substantial decreases in FEV1, total lung capacity, and FVC.[32] Despite the fact that radiotherapy has a range of toxic effects,[33,34] our research found that radiotherapy may be an independent prognostic factor for OS in patients with NSCLC and severe pulmonary dysfunction. Therefore, when selecting treatment for this population, radiotherapy should be considered.

Numerous investigators have examined the predictors for the incidence of RP. Research groups led by Yuichi Ozawa, MD, PhD,[35] and Yun Hee Lee, MD,[36] suggested an association between RP and interstitial lung disease. According to Mitsuru Okubo, MD, PhD, and colleagues, subclinical interstitial lung disease was also a significant risk factor for grade 2 or greater RP.[37] Tiziana Rancati, MS, found that the presence of COPD is associated with an increased risk of RP.[38] Given that patients with impaired pulmonary function are at a higher risk of developing RP, we should pay special attention to the development of RP in these patients following radiotherapy. Our findings showed that ilV10 is an independent predictor of SARP incidence. In a prior study, V_{10} was found to be statistically significant in relation to RP.[39] However, patients in that study received volumetric modulated arc therapy while patients in our study received IMRT; the predictive value of V_{10} was consistent with our findings. Multivariate analysis revealed a strong correlation between ilV_{10} and RP in helical tomotherapy–based lung cancer treatment.[40] A study of concurrent erlotinib and thoracic radiotherapy to treat NSCLC indicated that V_5, V_{10}, V_{15}, V_{20}, and V_{30} were significantly associated with RP.[41] These findings suggested that V_{10} may play an important role in the development of RP.

SARP was recorded in 25.4% of patients in our previous study[13] and in 30.2% of patients in this study. Poorer

baseline lung function may account for the higher incidence of SARP in this study. Additionally, our previous study found that DLCO% and MLD were associated with SARP in CCRT for patients with NSCLC affected by pretreatment moderate pulmonary dysfunction, whereas the present study showed a significant correlation between ilV_{10} and SARP. This disparity may be the result of inconsistencies between the 2 studies. First, the previous study was based on patients with NSCLC and moderate pulmonary dysfunction, while in this study, the subjects were patients with NSCLC and severe pulmonary dysfunction. A decrease in pulmonary function would increase the probability of SARP. Second, the previous study focused on stage III disease, whereas the current study included patients with disease classified as either stage III or IV. The late stage of lung cancer may have an impact on the occurrence of SARP. Third, in this study, only a small proportion of patients received concomitant chemoradiotherapy (due to their poorer performance status) and the rest received sequential chemoradiotherapy or radiotherapy alone, but all patients in the previous study received CCRT, which was proposed as an RP risk factor.[24] From our perspective, the patient characteristics in these 2 studies were quite different and thus both studies have distinct clinical significance.

The phase 3 PACIFIC study (NCT02125461) showed that consolidation therapy with durvalumab can significantly improve PFS and OS after definitive chemoradiotherapy for locally advanced unresectable NSCLC.[42] Perhaps immunotherapy administered following radiotherapy can increase OS in individuals with severe pulmonary impairment. However, because some of these individuals have preexisting lung disease, it is important to monitor them for the possible development of pneumonitis.

Several limitations to the current research should be noted. First, as it was a retrospective study, there was some selective and biased information. For example, a patient's large tumor volume could have influenced baseline pulmonary function. As the tumor shrinks with treatment, the pulmonary function may improve, resulting in prolonged survival and a reduced risk of SARP. In univariate analysis, tumor stage was an independent predictor of SARP, and patients with stage III vs stage IV disease were more likely to develop SARP (HR, 5.33; 95% CI, 1.06-26.90; $P = .043$). One possible reason was that more patients with stage III vs stage IV disease continued to be treated and followed up in our hospital after the completion of radiotherapy. There could be more patients with stage IV disease and SARP who were not treated, but we were unable to collect appropriate clinical data. Second, a relatively small sample was used; larger samples would be necessary to prove our conclusion. However, the strategies of treatment used in this study followed the recommendations of the NCCN guidelines and the conclusions can be useful for oncologists in the course of making clinical treatment decisions and evaluating radiotherapy plans. Third, only ilV_{10} was linked to the development of SARP in this study, and the best radiotherapy regimen for unresectable NSCLC with severe pulmonary dysfunction has yet to be determined. Future research is required to assess the target population's radiotherapy-related toxicity risks in order to improve the radiotherapy protocol with the greatest clinical benefit and the least radiation toxicity.

In conclusion, thoracic radiotherapy might be associated with survival benefits among patients with inoperable NSCLC and baseline severe pulmonary dysfunction. Multivariate analysis specified that ilV_{10} (>50.7%) was an independent predictor for SARP in the present cohort. While future studies are needed to verify our results, these results have value to oncologists as they make clinical treatment decisions and predict the prevalence of SARP among patients with inoperable NSCLC and baseline severe pulmonary dysfunction. ■

FUNDING: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST: There are no conflicts of interest declared by any of the contributors.

ETHICAL APPROVAL: The study was approved by the West China Hospital Research Ethics Board, Sichuan Province, China.

STATEMENT OF HUMAN AND ANIMAL RIGHTS: This article does not contain any studies with human or animal subjects.

STATEMENT OF INFORMED CONSENT: There are no human subjects in this article and informed consent is not applicable.

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For full reference list, visit cancernetwork.com/Deng_1.23

MEET OUR EXPERT

Jun J. Mao, MD, MSCE, is chief of the Integrative Medicine Service at Memorial Sloan Kettering Cancer Center and past president and liaison for the Society for Integrative Oncology, a Strategic Alliance Partner of CancerNetwork®, home of the journal *ONCOLOGY®*.

Jun J. Mao, MD, MSCE, on Updated Pain Management Guidelines for Cancer Care

"Our guidelines for pain management are not meant [to suggest use of] acupuncture and massage to cure cancer. It's more serving as an adjunctive role to help [patients with] cancer, and it will require all the disciplines to come together with a singular goal to serve the patient."

A joint guidance from the Society for Integrative Oncology (SIO) and the American Society of Clinical Oncology (ASCO) was recently released regarding pain management for an integrative care approach to treating patients with cancer.[1] These updated guidelines were created for physicians to better guide their patients with cancer on the management of pain related to their disease.

The panel consisted of clinicians from multidisciplinary settings and reviewed literature pertaining to pain management in patients with cancer. A total of 227 relevant studies were used to form the basis of the guidelines. These new recommendations focus on pain intensity, symptom relief, and adverse effects.

ONCOLOGY® recently spoke with Jun J. Mao, MD, MSCE, chief of the Integrative Medicine Service at Memorial Sloan Kettering Cancer Center in New York, New York, and past president of SIO, a strategic alliance partner of CancerNetwork®, home of the journal *ONCOLOGY®*. In the interview, Mao spoke about the updated guidelines, how to implement these into practice, and how clinicians can begin building relationships with others who specialize in these integrative approaches.

Q: What were the updated recommendations?

MAO: This is a the joint clinical guideline from the Society for Integrative Oncology and the American Society of Clinical Oncology [discussing] integrated medicine for pain in patients with cancer. A major take-home point for breast cancer survivors experiencing aromatase inhibitor–related joint pain is that acupuncture should be recommended. This is based on several smaller studies and, most importantly, [the S1200 trial (NCT01535066)] involving 227 patients recruited from the SWOG Cancer Research Network showing that acupuncture produced statistically significant and also clinically meaningful benefits compared with sham acupuncture and usual care.[2] This type of joint pain is very common for women with breast cancer who are receiving aromatase inhibitors, which not only decreases the quality of life but can also cause many women to stop lifesaving drugs that can potentially make their cancer come back. Having acupuncture as an additional tool is important for symptom control, quality of life, and well-being for breast cancer survivors.

The second recommendation is that acupuncture can be recommended for general cancer pain [management]. This was based on several systematic review meta-analyses and also a large, randomized control trial conducted by my group [SIO] which involved 360 cancer survivors with chronic musculoskeletal pain.[3] We demonstrated 2 types of acupuncture and

showed electroacupuncture and auricular acupuncture both reduced pain, improved functions and quality of life, and reduced medications. Many of the improvements also persisted for months after the treatment finished, demonstrating acupuncture is not only effective but also the 2 main effects were durable.

The third recommendation is an important take-home point that includes massage and can be used for patients with advanced cancer [undergoing] palliative care and the hospice setting. There are numerous small studies, but the largest study involves over 300 patients and is published in the journal *Annals of Internal Medicine*.[4] Relative to control, massage has improved pain control and poor quality of life. For patients living with advanced cancer, it is an incredibly challenging situation for both patients and caregivers. Acute massage can be a useful tool in the study.

Last but not least, many cancer diagnoses and procedures can be quite painful, such as a bone marrow biopsy. Hypnosis has demonstrated efficacy and may be recommended for biopsy or painful procedures to reduce acute pain. This set of clear recommendations is helpful to guide both physicians as well as patients to choose evidence-based interventions. However, we do not have clear evidence. Some of the evidence is inconclusive for mind-body treatments as well as for pain in children with cancer. Furthermore, many patients with cancer are interested in taking herbs, either orally or applied to their bodies, to help mitigate pain. Unfortunately, after an exhaustive search, we did not see a large, randomized control trial to support the use of herbs to treat pain in patients with cancer. Clearly, these are the gaps in research and require further rigorous research to build the evidence base.

Q: When working on the updated guidelines, why was it important to have a multidisciplinary team involved?

MAO: What makes these guidelines very special is we have 7 team experts. I'm an integrative medicine specialist and my cochair is Eduardo Bruera, MD, FAAHPM, who is chair of palliative care [at The University of Texas MD Anderson Cancer Center]. There's a lot of synergy between integrative oncology and palliative care because we all partake in managing symptoms and support patients with cancer, regardless of their cancer journey. Also in our panel, we not only have integrative medicine physicians but also medical oncologists, radiation oncologists, surgical oncologists, a palliative care specialist, a psychosocial oncologist, and a patient advocate. In addition, we also have international representatives because for these types of guidelines to have a balanced view and to ultimately be disseminated and hopefully implemented in diverse oncology settings, we need to have different perspectives to help us to weigh the benefit against the risks and appropriately assess the evidence base.

Q: What populations will benefit from these updated guidelines on how to manage pain?

MAO: Some of the recommendations such as the use of acupuncture for general cancer pain and massage use in the advanced cancer setting are not limited to patients with breast cancer. This is our general recommendation for patients with solid or liquid tumors. There are potentially many applications for helping patients with cancer manage pain in the context of their conventional pain management.

Q: How can clinicians begin to implement these guidelines into practice?

MAO: The first thing that is important for clinicians to know about are the basics of acupuncture massage. Acupuncture originated from traditional Chinese medicine and it has been around for about 2500 years. We use very thin, sterile, solid needles and put them in specific areas of the body to help to address symptoms and promote a sense of well-being. Often patients require a series of treatments, between 6-10, to see the initial benefit. However, after patients experienced the benefit they do seem to persist. For clinicians to talk to patients about what the therapy is, and what the evidence is [will be the most helpful in uptake]. Many people know what massage is, but oncology massage is not only manipulating the fascia, the muscle, the skin, and the tissue through touch, but also takes into consideration the patient's cancer status. In oncology, a massage therapist will put pressure on the areas of [a patient's] cancer and also where there is a medical need.

In addition to massage techniques, there is some gentle technique of the extremities, in the legs and hands, to help to induce a more general relaxation response in addition to localized pain management. It's important for clinicians who see patients with pain to not just have a knee-jerk reaction and prescribe drugs. They need to consider what patients want and refer patients [to other specialties]. We did a study [on patients with breast cancer] that found when there is a choice between pain medications and acupuncture, about 27% of patients prefer exclusive acupuncture, 26% prefer exclusive drugs, and about 40% don't have a clear preference.[5] Clearly, understanding patient preferences and guiding incorporated evidence is important for patient-centered care. ■

For references and the full interview, visit cancernetwork.com/Mao_12.22

Experts Discuss Treatment Methodologies in RCC

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In conjunction with presentations from the 2022 International Kidney Cancer Symposium, experts convened to discuss best practices for patients with renal cell carcinoma (RCC). The experts discussed recent trial updates as well as different methods for treating patients with either non–clear cell RCC or clear cell RCC. **Brian I. Rini, MD**, professor of medicine in the Division of Hematology/Oncology at Vanderbilt University in Nashville, Tennessee, led the discussion.

The panel also included **Matthew T. Campbell, MD, MS**, associate professor in the Department of Genitourinary Medical Oncology in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston; **Hans Hammers, MD, PhD**, the Eugene P. Frenkel, MD, Scholar in Clinical Medicine at UT Southwestern Medical Center in Dallas, Texas; **Moshe Ornstein, MD, MA**, a genitourinary oncologist at the Cleveland Clinic Taussig Cancer Center in Ohio; and **Ulka Nitin Vaishampayan, MBBS**, a professor of internal medicine at University of Michigan Medical School Health in Ann Arbor.

Non–Clear Cell RCC

To start the conversation, Rini asked his colleagues how they would typically treat patients with non–clear cell RCC. When given the option of an immunotherapy (IO)/tyrosine kinase inhibitor (TKI) combination or ipilimumab (Yervoy)/nivolumab (Opdivo), Hammers said he preferred to use IO monotherapy. However, he was open to a combination of a TKI and a PD-1 inhibitor, as more substantial response rates have been observed with such combinations.

Rini noted that he often chooses the TKI cabozantinib (Cabometyx) plus nivolumab, an IO agent. However, given the updated results from the phase 3 CLEAR trial (NCT02811861) of the combination of the TKI lenvatinib (Lenvima) and pembrolizumab (Keytruda), another IO agent, he may switch treatment strategies, he said.[1] "The data here [are] compelling, that papillary [disease (non–clear cell RCC)] does have a little less response than clear cell [RCC]," said Campbell. "If we have a [patient with] papillary [disease], we do like to molecularly profile and look for tumors that are potentially MET driven. Cabozantinib/nivolumab and lenvatinib/pembrolizumab are both excellent options for this patient group."

However, Rini noted that he was wary to use cabozantinib, a MET inhibitor, on patients with papillary disease. Campbell countered, saying that cabozantinib has a unique mechanism of action and has the ability to target MET. Ornstein stated that cabozantinib can be a good treatment for this population; however, in the absence of IO, patients tend to not have improved response, so he will add nivolumab to make a combination therapy.

When discussing the use of an IO/TKI combination or single-agent therapy, Vaishampayan agreed that she too

would use single-agent cabozantinib. Currently, she said she doesn't believe up front combination therapy is needed, except for those with hereditary leiomyomatosis and RCC, whom she would treat with IO as well.

Rini asked if his colleagues would choose atezolizumab (Tecentriq) over nivolumab. Vaishampayan responded that she would use nivolumab over atezolizumab, but that she would prefer pembrolizumab over nivolumab. In a combination treatment, a PD-1 inhibitor would be ideal.

Hammers noted that in some cases, a patient's insurance will not pay for a combination regimen but will allow the use of pembrolizumab monotherapy. When asked if he would use pembrolizumab to treat a patient with sarcomatoid disease, Hammers continued that he has seen effective responses to [pembrolizumab] in certain patients, so he would still lean toward the IO regimen.

Vaishampayan said that, in the future, debating the importance of IO therapy shouldn't be a conversation. Different drug combinations and/or monotherapies need to be developed to better treat various diseases and MET [inhibition], she explained, pointing out that an IO agent used in combination with a TKI has shown "suboptimal" results in non–clear RCC, particularly in patients with papillary disease.

Unclassified disease was discussed next. Rini defined it as the incidence of renal cancer when the provider can't determine what type. Ornstein said that in these situations, he treats patients as if they had sarcomatoid disease, giving IO/TKI combinations to generate those high response rates.

"A lot of these unclassified [diseases] are just clear cell [RCC] in hiding," said Hammers. "That's how I think about them, so IO tends to work better in unclassified [disease] than it does in papillary or chromophobe [RCC]." Ornstein asked Hammers if he would consider giving ipilimumab/nivolumab up front. Hammers said that the decision is determined by the tumor burden and whether a patient can afford to have continued disease progression.

On the treatment of unclassified diseases. Vaishampayan noted that she usually uses lenvatinib/pembrolizumab, which she believes helps the patient achieve the best response possible.

Next, Rini asked Ornstein about chromophobe cancer and his preferred treatment options.

"I send for next-generation sequencing, but I do give most of those patients lenvatinib and everolimus [Afinitor]," replied Ornstein.

Campbell agreed with this treatment combination. Currently, he noted, there are limited data on how to treat these patients. "Across all the different subgroups from different studies, there's always a signal that chromophobes seem to be more responsive to mTOR," Campbell said.

In conclusion, Hammers said that those with chromophobe disease need to have a VEGF inhibitor as part of their treatment, as IO cannot be relied on for [dissolution of disease].

Clear Cell RCC

Decision of Nephrectomy

For patients with clear cell RCC, debulking nephrectomy may be a viable treatment option. For a patient presenting with metastases, Vaishampayan said she might consider a nephrectomy and a lymph node removal. In addition, she said that she would add IO therapy up front. "The nephrectomy, whether it is a part of their treatment regimen or not, is sort of a secondary consideration after [it has been] established whether the patient will respond to and benefit from immune-based therapy," she explained.

Hammers considers debulking nephrectomy for those patients who are bleeding from the tumor mass and may have lung nodules, he said. He doesn't see an issue with removing the mass, as its removal can help improve the patient's quality of life.

If a patient is healthy enough to withstand debulking nephrectomy, Vaishampayan usually encourages that it be done, she said. Additionally, data from the phase 3 SURTIME trial (NCT01099423), which investigated the use of immediate or deferred cytoreductive nephrectomy in those with clear cell RCC who were receiving sunitinib (Sutent), showed an improved median overall survival of 32.4 months (95% CI, 14.5-65.3) in the immediate surgery arm with sunitinib vs 15.0 months (95% CI, 9.3-29.5) in the delayed surgery arm.[2] "Now, with our systemic therapy being so much better, are we going to only improve that exponentially? The reality that we're having so much discussion and controversy [around this]; the question needs to be answered," said Vaishampayan.

Campbell cited the phase 3 CARMENA trial (NCT00930033), which studied sunitinib alone or after nephrectomy.[3] The benefits shown in this trial included that fewer patients needed laparoscopic procedures when sunitinib was offered, which helped to defer nephrectomies.

When nephrectomy is deferred, that time can be used to conduct surveillance and to help determine the natural biology of a patient's disease, Ornstein stated. He said that he will typically delay nephrectomy for 6 to 9 months and then revisit the possibility.

Stereotactic Body Radiotherapy

The conversation then shifted to when and how to use stereotactic body radiotherapy (SBRT). Vaishampayan said she uses it if she's trying to delay systemic therapy if oligometastatic disease is involved. Hammers noted that he will use SBRT after ipilimumab/nivolumab treatment, intending it to target any breakout lesions not dismantled by therapy.

TABLE. **Leading Trials in Renal Cell Carcinoma**[1,5,6]

Trial	NCT number	Tumor type	Drugs	Efficacy
CLEAR	NCT02811861	Advanced RCC	Lenvatinib/ pembrolizumab vs sunitinib	***Median PFS*** Lenalidomide/pembrolizumab: 23.3 mo (95% CI, 20.8-27.7) Sunitinib: 9.2 mo (95% CI, 6.0-11.0) HR, 0.42 (95% CI, 0.34-0.52)
CheckMate 214	NCT02231749	Advanced or metastatic RCC	Nivolumab/ ipilimumab vs sunitinib	***Median OS*** Nivolumab/ipilimumab: 56 mo Sunitinib: 38 mo HR, 0.72 (95% CI, 0.62-0.85) ***Median PFS*** Nivolumab/ipilimumab: 12 mo Sunitinib: 12 mo HR, 0.86; 95% CI, 0.73-1.01
COSMIC-313	NCT03937219	Previously untreated advanced or metastatic RCC	Cabozantinib/ nivolumab/ ipilimumab vs placebo	***Median PFS*** Triplet arm: not reached Placebo arm: 11.3 mo (95% CI, 7.7-18.2) HR, 0.73; 95% CI, 0.57-0.94; $P = .013$

OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

Ornstein wondered if it were possible for a patient receiving IO therapy to also receive SBRT. Hammers said he hadn't seen many studies addressing toxicity in terms of IO treatment and SBRT. However, Campbell reported that SBRT could affect vertebral body metastasis, increasing risk of fracture. Such risk "must be taken very seriously when considering bone-modifying agents, because [fracture] can be devastating for patients. That's an area where we don't know how long after treatment to [give SBRT], and there are a lot of unanswered questions. That can be a complication of SBRT to the spine," said Campbell.

Frontline Treatment Options

Rini asked the panel members how they choose frontline treatment, and they responded that the International Metastatic RCC Database Consortium plays a role in how they make their choices.[4] "If [patients] have sarcomatoid features, typically I would go with IO/IO [therapy]," said Vaishampayan. "If they have any other [risk factors]—liver metastases, brain metastases, bone metastases, etc—I tend to go with [an] IO/TKI combination, because of the high response rates. [I think of] the symptomatic nature of the disease: whether a patient has symptoms, impending symptoms, or pleural effusions that are constantly filling up every week. Those things will typically drive me toward using an IO/TKI regimen."

Ornstein explained that he determines frontline therapy differently, tending to favor IO/TKI regimens but considering IO/IO if there are metastatic disease sites. If patients have pulmonary nodules, he noted that he will consider an IO/IO regimen. Currently, Ornstein said, he uses lenalidomide/pembrolizumab as his usual IO/TKI regimen, as more patients can tolerate the higher dosage. "If they can't get 20 mg [of treatment], then I don't think they should get that regimen," he noted further.

If a combination regimen is involved—no matter what the specific agents are—patients will have overlapping toxicities, according to Ornstein. He said, however, that if a patient can withstand treatment and the resounding effects for 2, 4, or even 6 months, they will likely get 3 to 6 extra years of survival. That statement is "not rooted in data, necessarily, but the idea, the concept, is there," he stressed. "I find that the first 2 to 4 months are when there are going to be more visits and more dose interruptions and modifications, but once we [get past] that time point, they're in a much better place," he said. "I wouldn't necessarily say 'cruise control,' but it's better."

Campbell takes a different approach with his patients' treatment, he said, often beginning lenalidomide at 18 mg. He explained that he likes to be flexible with the ability to increase or decrease dosages if necessary. Vaishampayan pointed out that dose intensity matters. Hammers said that in his practice, he prefers that his patients be on treatment for a certain number of days and then off treatment for a certain number as well (**Table**)[1,5,6]. ■

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Expanding Therapeutic Frontiers: CEACAM5 as a Therapeutic Target in Lung Cancer

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

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- Describe key efficacy and safety outcomes from recent clinical trials that evaluated CEACAM5-directed therapies for advanced NSCLC
- Explain approaches to mitigate/manage treatment-related adverse events observed in clinical trials of CEACAM5-targeted treatments

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This activity is supported by an educational grant from Sanofi.

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The Need for Additional Therapeutic Approaches in Lung Cancer: Rationale for Targeting CEACAM5

The therapeutic landscape in non–small cell lung cancer (NSCLC) has been transformed with targeted agents and immunotherapy becoming standard first-line approaches.[1,2] However, few therapeutic options are available for patients who progress on immunotherapy and platinum-based chemotherapy.

Antibody-Drug Conjugates in Lung Cancer

Novel therapeutic modalities, such as antibody-drug conjugates (ADCs), are being developed in lung cancer.[3] This class of therapeutics can target a cytotoxic payload directly to the tumor based on expression of a target antigen. Numerous therapeutic targets are being investigated as targets of ADCs, including carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5), HER3, trophoblast cell surface antigen 2 (TROP2), and MET. Furthermore, ADCs are becoming an established part of the therapeutic armamentarium in NSCLC with the approval of trastuzumab deruxtecan for patients with previously treated, *HER2* mutation–positive NSCLC.[4]

Targeting CEACAM5 in Lung Cancer

CEACAM5 belongs to a family of at least 12 related molecules. Many CEACAM proteins are attached to the cell membrane, but some, such as CEACAM16, are secreted.[5] In particular, CEACAM5 has demonstrated properties supporting the development of CEACAM5-targeted agents in lung cancer. CEACAM5 may play a role in allowing tumor cell proliferation by inhibiting anoikis in cells that become detached from the extracellular matrix.[6] Additionally, CEACAM5 may affect the ability of dendritic cells to present tumor antigens to T cells. The interaction between CEACAM5 on the tumor and dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) on dendritic cells may prevent maturation of the dendritic cells and stimulate production of immunosuppressive cytokines, leading to tolerance of the tumor.[6] Similarly, interaction between CEACAM5 on tumor cells and CEACAM1 on natural killer cells may lead to inhibition of tumor cell killing.[6]

Importantly, lung cancer cells have been found to express CEACAM5. In contrast, normal lung tissue has shown no or low expression of CEACAM5 when examined through immunohistochemistry.[7] This differential expression raises the possibility of CEACAM5 as a therapeutic target in NSCLC. Immunohistochemistry-based studies have found high expression (defined as at least 50% of cells at 2+ or 3+ staining intensity) in 24% of nonsquamous NSCLC tumors and higher expression in nonsquamous compared with squamous NSCLC.[8]

TABLE 1. **Phase 1/2 Trial of Tusamitamab Ravtansine in Previously Treated Nonsquamous NSCLC: Efficacy by CEACAM5 Expression[9]**

	High expression n = 64	Moderate expression n = 28
Overall response rate	20%	7%
Duration of response	5.6 months	Not calculated

CEACAM5, carcinoembryonic antigen–related cell adhesion molecule 5; NSCLC, non–small cell lung cancer.

TABLE 2. **Phase 1/2 Trial of Tusamitamab Ravtansine in Previously Treated Nonsquamous NSCLC: Selected Adverse Effects[9]**

	All grades	Grade 3 or greater
Corneal	38%	11%
Peripheral neuropathy	27%	1%
Dyspnea	22%	11%
Neutropenia	4%	0

NSCLC, non–small cell lung cancer.

Clinical Data With CEACAM5-Targeted Agents

Tusamitamab ravtansine

A phase 1/2 first-in-human study of tusamitamab ravtansine enrolled patients with previously treated, nonsquamous NSCLC and high (defined previously) or moderate (defined as at least 1% and less than 50% of cells at 2+ or 3+ staining intensity) expression of CEACAM5.[9] Data from 92 patients with a median of 3 (range, 1-10) prior lines of therapy were reported. Prior immunotherapy had been administered to 75% of the patients. In the 64 patients with high CEACAM5 expression, the overall response rate (ORR) was 20%; the ORR was 7% in the 28 patients with moderate expression (**Table 1**)[9]. In the high expressors, the duration of response was 5.6 months. Adverse effects (AEs) of note included corneal toxicity, including keratopathy and keratitis of grade 3 or greater in 11% of patients (**Table 2**)[9]. Dyspnea was also reported, although as a symptom of disease progression.

TABLE 3. **Ongoing Trials of Tusamitamab Ravtansine in NSCLC**

Study	Phase	Patients	Regimen	Reference
CARMEN-LC03	3	CEACAM5-positive nonsquamous NSCLC post chemotherapy and immunotherapy	Tusamitamab ravtansine vs docetaxel	NCT04154956
CARMEN-LC04	2	CEACAM5-positive nonsquamous NSCLC, previously treated	Tusamitamab ravtansine plus ramucirumab	NCT04394624
CARMEN-LC05	2	CEACAM5-positive nonsquamous NSCLC, no prior chemotherapy or immunotherapy	Tusamitamab ravtansine plus pembrolizumab, with or without chemotherapy	NCT04524689
CARMEN-LC06	2	Nonsquamous NSCLC, high circulating CEA post chemotherapy and immunotherapy	Tusamitamab ravtansine	NCT05245071

CEA, carcinoembryonic antigen; CEACAM5, CEA-related cell adhesion molecule 5; NSCLC, non–small cell lung cancer.

A follow-up report was presented including data from 11 patients who received treatment with tusamitamab ravtansine for at least 12 months.[10] Seven of these patients (64%) had a confirmed partial response. Among the 7 responders, 6 patients (86%) had high CEACAM expression.

Other CEACAM5-Targeted Agents

NEO-201

The antibody NEO-201 was developed to target tumor-associated CEACAM5 and CEACAM6, acting through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[11] Results were reported from a phase 1 trial of NEO-201 that included 17 patients with colorectal, pancreatic, or breast cancer. Stable disease was reported in 4 of 9 patients with colorectal cancer. The most common grade 3/4 AEs included neutropenia (94%) and febrile neutropenia (24%). Recruitment to this trial is ongoing.[12]

Cibisatamab

The bispecific agent cibisatamab was developed to target CEACAM5 on tumor cells and CD3 on T cells.[13] Initial results demonstrated single-agent activity in patients with colorectal cancer, with increased activity when combined with atezolizumab.[14]

Ongoing Trials

Several trials are ongoing with tusamitamab ravtansine in NSCLC (**Table 3**), including the phase 3 CARMEN-LC03 study comparing tusamitamab ravtansine with docetaxel in patients with nonsquamous, CEACAM5-positive NSCLC following chemotherapy and immunotherapy. Phase 2 trials are ongoing to evaluate combination therapy as well as monotherapy; among them is the CARMEN-LC06 study, evaluating the significance of high circulating CEA. ■

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