ONCOLOGY[®]

PRACTICAL, PEER-REVIEWED PERSPECTIVES

JUNE 2021 | Vol 35 • No 6

HEMATOLOGIC CANCERS

ELIAS JABBOUR, MD, ON

Friendly Competition Fosters Progress in Hematologic Malignancies

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Renal Cell Carcinoma Second-Line Therapies in the
Changing Landscape of First-Line Therapies for
Metastatic Clear Cell Renal Cell Cancer

Lung Cancer Radiotherapy for Oligometastatic Non-
Small Cell Lung Cancer: Past, Present, and Future

Gastrointestinal Cancer Mucinous Adenocarcinoma
of the Appendix With Histologic Response to
Neoadjuvant Chemotherapy: Review of Histologic
and Clinical Spectrum of Epithelial Neoplastic
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Improving Outcomes After Frontline Therapy

Thanks to rapid innovation and unmatched dedication from investigators and oncology care providers, patients with cancer are living longer than ever before, motivating further research into optimizing patient outcomes and quality of life after success with frontline therapy.

In an interview with *ONCOLOGY*[®], Elias Jabbour, MD, a professor of medicine in the Department of Leukemia, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston, discussed his contributions to the field of medicine and how innovation has paid off in spades.

"Leukemia, in particular, is really evolving at a very high speed. Every year, we see new therapies [and] a new standard of care," said Jabbour, who is also cochair of the *5th Annual Live Medical Crossfire*[®]: Hematologic Malignancies, hosted by Physicians' Education Resource, LLC (PER[®]). "It's hard to keep pace with the evolution...these are priceless accomplishments that impact the lives of people."

He went on to detail therapy advancements in pediatric and adult patients with acute lymphoblastic leukemia and how growing understanding of the disease's underlying biology has enabled better treatment selection and even cure in some cases (*see pages 304-305*).

As more and more therapies and regimens gain FDA approval for the frontline treatment of renal cell carcinoma (RCC), reexamining the standard of care in second and subsequent lines is becoming a top priority. "Treatment paradigms for first-line therapy have shifted and left an outstanding need to understand the optimal management in subsequent lines of therapy to improve patient outcomes," write Tiffany Y. Shaw, MD, and colleagues in their review of the topic. Based on available data, the authors attempt to provide guidance for oncologists treating patients with RCC following frontline therapy with an immune checkpoint inhibitor alone or in combination with antiangiogenetic tyrosine kinase inhibitors (*see pages 306-310*).

In this issue's installment of Clinical Quandaries, Mahmoud Salama, MD, PhD, and colleagues examine the case of a woman, aged 25 years, with diffuse large B-cell lymphoma who undergoes ovarian tissue cryopreservation due to concerns surrounding fertility loss with systemic therapy (*see pages 332-334*). Fertility preservation represents a significant concern of young female cancer survivors, which has motivated innovative methods for ensuring future potential for childbearing.

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

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- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

TAZVERIK, the first and only FDA-approved EZH2 inhibitor for relapsed or refractory (R/R) follicular lymphoma (FL)¹

Efficacy results*:

- **FL patients (N=95) responded** to single-agent TAZVERIK in both cohorts^{1,2}

- **Sustained response** demonstrated in patients with both MT and WT EZH2^{1,2}

(range: 0.0+ to 22.1+)
in patients with MT EZH2
(n=29/42; 95% CI: 7.2–NE)

(range: 1.0 to 22.5+)
in patients with WT EZH2
(n=18/53; 95% CI: 5.6–NE)

The data for the MT EZH2 cohort were not yet mature at the time of assessment.

*TAZVERIK was studied in an open-label, single-arm, multicenter, phase 2 trial with 6 cohorts of patients, including 2 cohorts with histologically-confirmed R/R FL. Patients received 800 mg of TAZVERIK orally twice daily until confirmed disease progression or unacceptable toxicity. The major efficacy outcome measures were ORR and DOR according to the IWG-NHL criteria as assessed by independent review committee.^{1,2}

Important Safety Information

Warnings and Precautions

• Secondary Malignancies

The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

• Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

Important Safety Information continued on back page of this insert.
Please see Brief Summary of the Prescribing Information on the adjacent pages.

TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

• TAZVERIK® (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

• TAZVERIK is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

Patient Selection - Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens [see Clinical Studies]. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: <http://www.fda.gov/CompanionDiagnostics>.

Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Swallow tablets whole. Do not cut, crush, or chew tablets. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions, and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

Dose Reduction	Dosage
First	600 mg orally twice daily
Second	400 mg orally twice daily*

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Neutropenia [see Adverse Reactions]	Neutrophil count less than $1 \times 10^9/L$	<ul style="list-style-type: none">Withhold until neutrophil count is greater than or equal to $1 \times 10^9/L$ or baseline.For first occurrence, resume at same dose.For second and third occurrence, resume at reduced dose.Permanently discontinue after fourth occurrence.
Thrombocytopenia [see Adverse Reactions]	Platelet count less than $50 \times 10^9/L$	<ul style="list-style-type: none">Withhold until platelet count is greater than or equal to $75 \times 10^9/L$ or baseline.For first and second occurrence, resume at reduced dose.Permanently discontinue after third occurrence.
Anemia [see Adverse Reactions]	Hemoglobin less than 8 g/dL	<ul style="list-style-type: none">Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.
Other adverse reactions [see Adverse Reactions]	Grade 3	<ul style="list-style-type: none">Withhold until improvement to at least Grade 1 or baseline.For first and second occurrence, resume at reduced dose.Permanently discontinue after third occurrence.
	Grade 4	<ul style="list-style-type: none">Withhold until improvement to at least Grade 1 or baseline.For first occurrence, resume at reduced dose.Permanently discontinue after second occurrence.

Dosage Modifications for Drug Interactions

Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

Current Dosage	Adjusted Dosage
800 mg orally twice daily	400 mg orally twice daily
600 mg orally twice daily	400 mg for first dose and 200 mg for second dose
400 mg orally twice daily	200 mg orally twice daily

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS

Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC_{0-45h}]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions].

Clinical Trial Experience - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in two cohorts (Cohorts 4 and 5) of Study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 87 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The median number of prior therapies was 3 (range 1 to 11). Patients were required have a creatinine clearance ≥ 40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions in $\geq 2\%$ of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in $\geq 2\%$ of patients was second primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in $\geq 3\%$ of patients were thrombocytopenia and fatigue. Dose reduction due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions ($\geq 20\%$) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions ($\geq 10\%$) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

Adverse Reaction	TAZVERIK N=99	
	All Grades (%)	Grade 3 or 4 (%)
General		
Fatigue ^a	36	5
Pyrexia	10	0
Infections		
Upper respiratory tract infection ^b	30	0
Lower respiratory tract infection ^c	17	0
Urinary tract infection ^d	11	2
Gastrointestinal		
Nausea	24	1
Abdominal pain ^e	20	3
Diarrhea	18	0
Vomiting	12	1
Musculoskeletal and connective tissue		
Musculoskeletal pain ^f	22	1
Skin and subcutaneous tissue		
Alopecia	17	0
Rash ^g	15	0
Respiratory and mediastinal system		
Cough ^h	17	0
Nervous system		
Headache ⁱ	13	0

Table 6 continues on the next page

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101 (continued)

^aIncludes fatigue and asthenia

^bIncludes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

^cIncludes bronchitis, lower respiratory tract infection, tracheobronchitis

^dIncludes cystitis, urinary tract infection, urinary tract infection staphylococcal

^eIncludes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper

^fIncludes back pain, limb discomfort, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, spinal pain

^gIncludes erythema, rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation

^hIncludes cough and productive cough

ⁱIncludes headache, migraine, sinus headache

Clinically relevant adverse reactions occurring in <10% of patients who received TAZVERIK included:

- Infection: sepsis (2%), pneumonia (2%), and herpes zoster (2%)

Table 7 summarizes select laboratory abnormalities in patients with follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 7. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

Laboratory Abnormality	TAZVERIK*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	57	18
Decreased hemoglobin	50	8
Decreased platelets	50	7
Decreased white blood cells	41	9
Decreased neutrophils	20	7
Chemistry		
Increased glucose	53	10
Increased aspartate aminotransferase	24	0
Increased alanine aminotransferase	21	2.3
Increased alkaline phosphatase	18	1.0
Increased creatinine	17	0

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

DRUG INTERACTIONS

Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A Inhibitors: Coadministration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations [see *Clinical Pharmacology*], which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose [see *Dosage and Administration*]. **Strong and Moderate CYP3A Inducers:** Coadministration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations [see *Clinical Pharmacology*], which may decrease the efficacy of TAZVERIK. Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK.

Effect of TAZVERIK on Other Drugs - CYP3A Substrates: Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates [see *Use in Specific Populations, Clinical Pharmacology*].

USE IN SPECIFIC POPULATIONS

Pregnancy - Risk Summary: Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology*], TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [AUC_{0-48h}] at the 800 mg twice daily dose (see *Data*). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data - Animal Data: In pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses of ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose). At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss,

missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

Lactation - Risk Summary: There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Females and Males of Reproductive Potential - Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK [see *Use in Specific Populations*]. **Risk Summary:** TAZVERIK can cause fetal harm when administered to pregnant women [see *Use in Specific Populations*]. **Contraception: Females -** Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective [see *Drug Interactions*]. **Males -** Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

Pediatric Use - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

Juvenile Animal Toxicity Data - In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:

- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Distended testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

Geriatric Use - Clinical studies of TAZVERIK did not include sufficient numbers of patients with relapsed or refractory follicular lymphoma aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment - No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease [see *Clinical Pharmacology*].

Hepatic Impairment - No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN). TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment [see *Clinical Pharmacology*].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs [see *Use in Specific Populations*].

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

Secondary Malignancies - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see *Warnings and Precautions*]. **Embryo-Fetal Toxicity -** Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations*]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose [see *Use in Specific Populations*]. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see *Use in Specific Populations, Nonclinical Toxicology*].

Lactation - Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose [see *Use in Special Populations*].

Drug Interactions - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, grapefruit, and grapefruit juice while taking TAZVERIK [see *Drug Interactions*].

Brief Summary [07/2020]

TZ-FL-BR-20-0129

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Important Safety Information *(continued)*

• Embryo-Fetal Toxicity *(continued)*

Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC_{0-45h}]) at the 800 mg twice daily dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions

Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.

Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.

Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation

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

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

EZH2=enhancer of zeste homologue 2; ORR=overall response rate; CI=confidence interval; CR=complete response; PR=partial response; DOR=duration of response; NE=not estimable; IWG-NHL=International Working Group Non-Hodgkin Lymphoma.

References: **1.** TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July 2020. **2.** Data on file. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.4.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 17, 2020. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.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.

The Future of Oncology: Supply and Demand for Oncology Services

Julie M. Vose, MD, MBA

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A landmark study published in 2007 by the American Society of Clinical Oncology (ASCO) predicted a major shortfall of medical oncologists by the year 2020.¹ This study, which was done in conjunction with the Association of American Medical Colleges (AAMC), surveyed hematology/oncology (hem/onc) fellows who were starting their training, fellows who had just completed their training, oncology fellowship program directors, and about 4000 practicing oncologists in the United States. The study also used National Cancer Institute (NCI) analyses of Medicare data to estimate the future demand for oncology services. According to this original study, by the year 2020 a shortfall of between 2500 and 4000 hem/onc physicians would be evident in the United States.¹ This study found a number of factors that contributed to this shortfall, including a lower supply of “pipeline” residents in internal medicine, pediatrics, surgery, and gynecology as well as hem/onc fellowship slots, while the demand for oncology services would go up by 48%.¹ Other factors in the oncology physician deficit included a high percentage of hem/onc physicians nearing retirement age, as well as physician dissatisfaction with practice/government requirements which may lead to burnout or professional modification requests.

According to the most recent “2021 ASCO Snapshot: State of the

Oncology Workforce in America,” there are 13,146 oncologists engaged in active patient care in 1638 oncology practices.² Of those oncologists, 21.1% are nearing retirement (age 64+) whereas only 14.5% are early-career oncologists (age ≤ 40); the overall median age was 53 years.² Female oncologists in practice represent 35.2% of the total while they represent approximately 45% in hem/onc fellowship programs.^{2,3} Only 11.2% of oncologists practice in areas defined as rural. The fewest oncologists practice in the West North Central and West South Central regions.⁴

How can we tackle these issues? Although the increase of pipeline residency programs can enhance the initial denominator, overall hem/onc fellowship programs will also need to be increased in volume and diversity to supply the number of hem/onc fellows who will be needed for the next several decades. Along with that increase will need to be modifications in the overall infrastructure to allow for hem/onc physician-led teams caring for the patients with advanced practice providers, oncology nurses, oncology pharmacists, and other support personnel. In some locations, this structure is not encouraged, sometimes leading to excess clinical and administrative duties for the hem/onc physicians that are unnecessary and lead to burnout. During the COVID-19 pandemic, telehealth video visits were particularly helpful

to rural and other eligible patients who would have otherwise had to drive long distances for their hem/onc care. Hopefully, the success of these visits will demonstrate that we should be allowed to continue this practice even across state lines in the future for qualifying patients. Telehealth video visits could also help with extension of care for some patients requiring hem/onc care who are in rural and other underserved areas. The use of novel programs such as oncology care at home following a hospital acute care discharge may also help to decrease readmission rates. In addition, the use of early palliative care support may enhance the quality of life for patients with cancer during their final days and allow for more quality time for the patient with their family. An added benefit of these support mechanisms includes creating less stress for the oncology team while allowing them to have more time to devote to other patients who are currently on active treatment.

The bottom line for enhancing oncology care in the future is multifactorial with an increase in availability of the oncology team members, accessibility and affordability of treatments, less unnecessary red tape, and improved support mechanisms for the oncology health care team as well as the patient and their family. ■

For full reference list, visit
cancernetwork.com/Vose_6.21

MEET OUR EXPERT

Elias Jabbour, MD, is a professor of medicine in the Department of Leukemia, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston, as well as cochair of the *5th Annual Live Medical Crossfire®: Hematologic Malignancies*, hosted by Physicians' Education Resource, LLC (PER®).

Friendly Competition Fosters Progress in Hematologic Malignancies

"These are priceless accomplishments that impact the lives of people."

Treatment selection for patients with hematologic malignancies involves a vast knowledge of variations in biology and the rapidly evolving field of systemic therapy development. With options for transplant, chimeric antigen receptor (CAR) T-cell therapy, tyrosine kinase inhibitors (TKIs), and immunotherapy in most tumor types, appropriate therapy selection for a given patient is far from straightforward or standard.

To discuss this and emerging breakthroughs, Elias Jabbour, MD, a professor of medicine in the Department of Leukemia, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston, reflected on his body of work and how competition among colleagues motivated his contributions to the field of medicine.

"I had an opportunity to work with giants in cancer. These are people who are heroes in treating cancer," Jabbour said. "Working with them, you have to be at a level [where you] work hard and you have great competition to do the best you can."

Continuing with the theme of friendly competition, Jabbour discussed the *5th Annual Live Medical Crossfire®: Hematologic Malignancies*, hosted by Physicians' Education Resource, LLC (PER®), to be held Saturday, July 17, 2021, for which he is the cochair. The annual event considers emerging topics by presenting contrasting viewpoints of key opinion leaders across a broad range of hematologic malignancies. By exploring the issues from different perspectives, clinicians may be better equipped to treat a wide range of patients.

"With leukemias and hematology [in general], these are rare diseases compared with solid tumors. People who treat hematologic malignancies have a major interest in the field," he said. "Leukemia, in particular, is really evolving at a very high speed. Every year, we see new therapies [and] a new standard of care. It's hard to keep pace with the evolution...these are priceless accomplishments that impact the lives of people."

In preparation for the meeting, Jabbour sat down with *ONCOLOGY®* to discuss emerging trends in leukemias, his area of specialty.

Q: Can you speak to some of the recent advancements in the treatment of acute lymphocytic leukemia (ALL)?

About 6000 patients [present with ALL] per year in the United States—roughly half are pediatric, and half are adult. [In children], outcomes are outstanding, with survival around 90% and above. In adult patients, outcomes are less favorable. At the 1-year [mark], survival is about 60% at MD Anderson, which is quite good compared with [what it was] 10 and 15 years ago, but we're still far away from [the survival rate seen with] pediatric ALL.

However, we have the tools to cure this disease. Why am I saying this with confidence? For 2 reasons: First, we have a better understanding of the biology of ALL, and therefore, we're able to tailor our therapy strategy based on biology. Second, we have new drugs that, after being tested, have shown promising results.

I'll give an example: TKIs in stage IV ALL. These are really potent drugs, and when combined with chemotherapy and immunotherapy, you can have great results. [We can see] a 5-year survival rate of 76%, negating the need for transplant or intensive approach. We have monoclonal antibodies, among them the CD20 antibody rituximab [Rituxan]; this, when

combined with chemotherapy, improves outcome. We have bispecific engagers like blinatumomab [Blincyto], effective in the relapsed setting and the minimal residual disease [MRD] setting. And we have an antibody-drug conjugate against CD22, inotuzumab ozogamicin [Besponsa], and this drug is available today for the refractory setting. [Plus], ongoing trials using a combination of chemotherapy with inotuzumab and blinatumomab are showing very promising results. And these drugs are moving to the fourth line.

Then we have CAR T-cell therapy, which is [among] the great innovations in science right now. I see the role of CAR T[*cell*] therapy possibly replacing transplant and being a conservative approach post chemotherapy [or following] inotuzumab or blinatumomab.

And finally, [among] the most important things to [continue looking at] in ALL is assessment for MRD. Data [indicate that] this is the principle of therapy, and it's why I'm confident we'll make progress in the next 10 to 15 years.

All patients with ALL used to have very poor outcomes because of the aggressive [nature of the] disease and, in older patients, poor tolerance to chemotherapy using normal drugs in the frontline like inotuzumab and blinatumomab. We have made huge progress, and survival has gone from 20% to 50%. In young adults, using the pediatric regimen or hyper-CVAD [cyclophosphamide, vincristine sulfate, doxorubicin

hydrochloride, and dexamethasone], we have a survival rate of 70% [at 5 years]. We did great.

These are all the principles and they're evolving. We don't have [one-size-fits-all] therapy that is good for everyone, but I think the future is to [treat] according to biology and to move away from intensive chemotherapy; [we'll go] to more of an approach that can improve the outcome without inducing a lot of toxicities.

Q: Is a chemotherapy-free treatment approach the future of ALL treatment, broadly speaking?

This is what we're aiming to accomplish, but whether we succeed or not remains to be seen.

One of the most exciting things in ALL, essentially, is to be able to stop therapy. We're able to define short-term therapy based on response. For example, if we can assess for MRD with a very sophisticated technique and identify true responders, then these patients will be spared the need for intensive chemotherapy or prolonged therapy.

Q: Can you speak to some of the recent research and strategies in the treatment of chronic myeloid leukemia (CML)?

My work in CML is [about] how we can stop therapy. [First] is novel drugs: I think there's still room for novel, potent drugs that are safer than what we had before. [Second] is how we can increase

the proportion of patients who can stop therapy and remain free of relapse. And by that I mean whether we should stick only to TKIs or explore the combination of TKIs with other drugs, such as BCL2 inhibitors.

Q: The acute myeloid leukemia (AML) landscape is exciting, with so much work going on the past few years regarding new targets and new agents. What are your goals in AML, and what do patients need now?

I'm fascinated by the role of BCL2 inhibitors in AML. Already, we have a new standard of care and the question is whether we can cure more younger patients. Are we testing combination chemotherapy plus BCL2 inhibitors? It seems that the cure rate is really improving at a very high speed, which is quite good. Of course, the subset of patients with [traditionally poor outcomes] urgently need new drugs.

We already have a standard of care, which is a combination of hypomethylating agents with BCL2 inhibitors. That is a starter, and [we need to determine] whether we can build on it by adding further targeted therapy for the improved outcomes. That is yet to be defined, but several trials are ongoing. ■

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

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Second-Line Therapies in the Changing Landscape of First-Line Therapies for Metastatic Clear Cell Renal Cell Cancer

Tiffany Y. Shaw, MD; Hannah Lee, MD, MS; and Robert A. Figlin, MD

ABSTRACT: In recent years, first-line therapies for metastatic renal cell carcinoma (mRCC) have shifted to a combination of immune checkpoint inhibitors or a combination of antiangiogenesis tyrosine kinase inhibitors (TKIs) and immunotherapy. This has led to a need to address standard-of-care treatment in the second-line setting. Our review presents an analysis of current and upcoming data to guide treatment decisions. After progression on nivolumab plus ipilimumab, current data favor monotherapy TKI with cabozantinib or axitinib. Current literature for second-line therapy given after combination TKI plus immunotherapy shows the strongest evidence for either single-agent cabozantinib or combination everolimus with lenvatinib. Investigations are ongoing for the role of TKIs with immunotherapy in the second-line setting. Novel agents, such as HIF2 α inhibitors, are currently being studied as single agents and in combination with other treatment modalities in efforts to improve patient outcomes in mRCC.

KEYWORDS: advanced renal cell carcinoma, immunotherapy, tyrosine kinase inhibitor, mTOR inhibitor, HIF2 α inhibitor

Introduction

Renal cell carcinoma (RCC) accounts for 2.2% of cancer diagnoses and 1.8% of cancer deaths across the globe and is the ninth most common cancer in the United States.¹ Approximately one-third

of cases are diagnosed as metastatic disease with poor 5-year survival rates of 12%. In recent years, first-line treatment of advanced or metastatic RCC has evolved substantially with the introduction of immune checkpoint inhibitors

PERSPECTIVE

Benjamin A. Teplý, MD considers optimal treatment on [page 308](#)

(ICIs), which have improved survival. First-line single-agent TKIs that target VEGF are quickly falling out of favor with the advent of immunotherapies. The shift in first-line treatment creates a need to readdress subsequent lines of therapies. This review presents a guide to second-line therapies based on the current evidence and highlights upcoming noteworthy studies, with a focus on clear cell histology.

First-Line Treatment Summary

In the randomized, phase 3 CheckMate 214 trial, the combination of nivolumab (Opdivo; an anti-PD-1 antibody) and ipilimumab (Yervoy; an anti-CTLA-4 antibody) was compared with single-agent sunitinib (Sutent; a first-generation VEGF TKI) in untreated patients of all risk groups with advanced clear cell RCC (ccRCC).² The primary end points were overall survival (OS), objective response rate (ORR), and progression-free survival (PFS) in intermediate- and poor-risk groups. For

the primary end points, the combination arm showed statistically significant benefit with an 18-month OS rate of 75% and an ORR of 42%, compared with 60% and 25%, respectively, in the control arm. The PFS benefit did not reach statistical significance. This pivotal trial led to FDA approval of nivolumab plus ipilimumab in first-line treatment of intermediate/poor-risk advanced ccRCC.

The randomized, phase 3 KEYNOTE-426 trial compared combination axitinib (Inlyta; a second-generation TKI against VEGF-1, VEGF-2, VEGF-3, and PDGFR) and pembrolizumab (Keytruda; an anti-PD-1 antibody) to single-agent sunitinib.³ The combination arm resulted in superior OS and PFS compared with the control arm across all risk groups. At 12 months, 89.9% of patients were alive in the pembrolizumab/axitinib arm vs 78.3% in the sunitinib arm, and median PFS was 15.1 months vs 11.1 months, respectively. The CheckMate 9ER trial led to another FDA-approved front-line ICI/TKI combination: cabozantinib plus nivolumab.⁴ Cabozantinib (Cabometyx) with nivolumab resulted in a statistically significant PFS benefit of 16.6 months vs 8.3 months with sunitinib alone. A significant OS benefit was also seen in the combination arm, with 85.7% probability of survival at 12 months vs 75.6% with sunitinib. The phase 3, randomized CLEAR trial compared lenvatinib (Lenvima) plus pembrolizumab with lenvatinib plus everolimus (Afinitor) with sunitinib alone.⁵ The lenvatinib/pembrolizumab arm had significantly longer PFS of 23.9 months, vs 9.2 months with sunitinib alone. OS at 24 months was 79.2% with

lenvatinib/pembrolizumab and 70.4% with sunitinib, a statistically significant difference. Although lenvatinib/everolimus had a significantly longer PFS compared with sunitinib, it did not have an OS benefit.

The decision to use nivolumab plus ipilimumab or a TKI/ICI combination upfront depends on several factors that include the patient's functional status, risk stratification, and extent of disease burden, as well as institutional availability. Immunotherapy has the benefit of better tolerability compared with TKIs, while TKIs have a shorter response time. In both cases, the choice of first-line regimen will significantly influence the approach to second-line therapy.

Treatment paradigms for first-line therapy [of RCC] have shifted and left an outstanding need to understand the optimal management in subsequent lines of therapy to improve patient outcomes.

Second-Line Treatment Options

The approach to second-line therapies should address the mechanisms of resistance to first-line therapies and utilize different treatment modalities. If a patient has progressed on immunotherapy, the second-line regimen should include a TKI. If a patient has progressed on combination ICI/TKI treatment, the second-line regimen should include either a different TKI alone or in combination with an mTOR inhibitor. The subsequent TKI should address escape pathways that led to treatment resistance to the prior TKI, via AKT, MET, AXL and FGF signaling.⁶ Cabozantinib is a VEGF-TKI that also targets MET and AXL. The lack of PTEN expression and aberrant AKT activation correlates with TKI resistance, and mTOR inhibitors can overcome these mechanisms to reinstate

sensitivity to TKI-mediated apoptosis.

Post-First-Line Immunotherapy

As seen in CheckMate 214, the combination of nivolumab plus ipilimumab has become one of the favored first-line treatment options in the appropriate patient population. The current standard of care after progression is a single-agent TKI, either cabozantinib or axitinib, and supportive data are extrapolated from trials of post-first-line antiangiogenesis therapy.

In the randomized, phase 2 CABOSUN trial, patients treated with cabozantinib had significantly prolonged PFS of 8.6 months vs 5.3 months with sunitinib in the up-front setting for advanced RCC.⁷ Furthermore, the phase 3 METEOR trial compared cabozantinib with everolimus (an mTOR inhibitor) after progression on VEGF-targeted therapies.⁸ Results revealed that patients who received cabozantinib achieved a superior median OS of 21.4 months vs 16.5 months with everolimus. ORR and median PFS were also statistically significantly better in the cabozantinib arm. While a retrospective analysis suggests a benefit of cabozantinib after progression on ICI-based therapies, no randomized trial data exist at this time.⁹ However, current data can be extrapolated to support the efficacy and use of single-agent cabozantinib as standard of care in the second-line setting.

Axitinib is another TKI option. The phase 3 AXIS trial compared axitinib with sorafenib (Nexavar; a multikinase inhibitor) after progression on any of these regimens: sunitinib, bevacizumab (Avastin) with interferon alfa, cytokine therapy, or temsirolimus.¹⁰ Results showed a statistically significant median PFS benefit of 8.3 months with axitinib

compared with 5.7 months with sorafenib, although no difference in median OS was seen. Axitinib thus is recognized as another appropriate second-line option.

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Current data are best established for single-agent cabozantinib or axitinib for second-line therapy after first-line combination immunotherapy. In efforts to continue to improve OS in metastatic RCC after immunotherapy, ongoing trials are examining the benefit of combination ICI/TKI therapy in the second-line setting. The recently launched phase 3 CONTACT-03 trial is exploring combination cabozantinib with atezolizumab (Tecentriq; a PD-L1 inhibitor) vs cabozantinib alone in patients who

have prior exposure to ICI therapy.¹¹ The phase 2 KEYNOTE-146 trial is studying the benefit of lenvatinib plus pembrolizumab after up-front therapy with nivolumab/ipilimumab or ICI/TKI therapy.¹² At the 2020 American Society of Clinical Oncology Virtual Annual Meeting, the reported median PFS for the RCC cohort was 11.7 months and the median duration of response was 9.9 months, which suggests benefit in sequential ICI plus TKI. Final results from these trials will help determine the role

of ICI plus TKI after immunotherapy, and they may change our approach to second-line treatments.

Post–First-Line Immunotherapy With TKIs

With multiple ICI/TKI combinations available in the first-line setting for advanced ccRCC, there is a need to standardize subsequent lines of therapy in this population.³⁻⁵ The benefit of cabozantinib as a second-line option was, again, extrapolated from the METEOR

PERSPECTIVE BY

Benjamin A. Teply, MD

Navigating an Optimal Treatment Course for Advanced Kidney Cancer

The authors of the accompanying article review the rapidly evolving treatment paradigms for renal cell carcinoma in both the first- and second-line settings. A remarkable sea change has occurred over the past 3-plus years, as the results of 5 separate positive phase 3 studies have demonstrated superiority of immunotherapy-containing regimens over monotherapy with the anti-VEGF tyrosine kinase inhibitor (TKI) sunitinib (Sutent) in the first-line setting. As a result, it is now the standard of care that most patients with advanced kidney cancer receive either combination immunotherapy or immunotherapy-TKI combinations. In fact, every eligible patient with advanced kidney cancer should receive immune checkpoint blockade during their treatment course, with the hope of deriving durable responses.

Nonetheless, the first question with regard to treatment sequencing is whether all patients with advanced/metastatic kidney cancer require *up-front* immunotherapy, rather than second- or later-line immunotherapy. Let us first examine the data for International Metastatic RCC Database Consortium (IMDC) intermediate- and poor-risk disease. In this scenario, my answer is a resounding *yes*. Four FDA-approved options—axitinib (Inlyta) plus pembrolizumab (Keytruda),¹ lenvatinib (Lenvima) plus pembrolizumab,² cabozantinib (Cabometyx) plus nivolumab (Opdivo),³ and ipilimumab (Yervoy) plus nivolumab⁴—demonstrated significantly improved overall survival (OS) in these cohorts. These regimens are all included as preferred options with category 1 evidence in the National Comprehensive Cancer Network guidelines. Axitinib plus avelumab (Bavencio)⁵ is another option, with data showing significantly improved progression-free survival. In sum, the data strongly support first-line utilization of anti-PD-1 therapy for intermediate- or poor-risk disease.

However, is the same true for patients presenting with IMDC favorable-risk

disease? The answer is less straightforward. The data for up-front immunotherapy are suggestive of survival benefit, but nearly all these patients will be able to receive a second-line therapy incorporating anti-PD-1 therapy, given the relatively indolent course of favorable-risk disease. Furthermore, with longer-term follow-up, the evidence showing an OS benefit is less clear, and toxicity is greater with combination therapy compared with sequential single-agent therapy. For example, with longer follow-up of the data for axitinib plus pembrolizumab, the early trend toward survival benefit in the first interim analysis (HR, 0.64; 95% CI, 0.25-1.68)¹ did not persist in the analysis conducted with a longer follow-up time, a median of 30.6 months (HR, 1.06; 95% CI, 0.60-1.86).⁶ Similarly, whether early strong signals of benefit with the cabozantinib/nivolumab and lenvatinib/pembrolizumab regimens in those studies' overall population persist at longer-term follow-up remains to be seen. Thus far, the reported data specifically in the IMDC favorable-risk subgroup for both cabozantinib/nivolumab (HR, 0.84; 95% CI, 0.35-1.97)³ and lenvatinib/pembrolizumab (HR, 1.15; 95% CI, 0.55-2.40)² remain immature, with few reported deaths and wide confidence intervals. It remains reasonable to treat select patients with favorable-risk disease with TKI monotherapy and to use immunotherapy as second-line therapy.

Patients who require second-line therapy after an initial immunotherapy-containing regimen may be treated with potent TKIs, such as cabozantinib, or with

and CABOSUN trials.^{7,8} Although a retrospective analysis suggests a benefit of cabozantinib after progression on ICI/TKI combination therapies, no randomized trial data exist at this time.¹³ mTOR inhibitors are current key players, but they should be used in combination, as the INTORSECT trial demonstrated a lack of benefit with single-agent temsirolimus (Torisel) when compared with sorafenib in the second-line setting.¹⁴ Study 205, a randomized phase 2 trial, compared lenvatinib plus everolimus

vs lenvatinib alone vs everolimus alone after progression on a VEGF-TKI.¹⁵ Results favored lenvatinib plus everolimus with superior PFS at 14.6 months vs 5.5 months with everolimus alone, although no statistically significant difference was seen when compared with the lenvatinib arm (PFS, 7.4 months). The study results led to the first FDA-approved combination of a TKI and an mTOR inhibitor. However, more high-grade toxicities occurred in the combination arm. Thus, newer-generation multi-TKIs, such as

vorolanib, are being studied in combination with everolimus to identify better-tolerated regimens.¹⁶ Results from the phase 1 trial of combination vorolanib/everolimus in the second-line setting were promising and have advanced to further investigation.

Lenvatinib and pembrolizumab, a different ICI/TKI combination in the second-line setting, is the subject of the current KEYNOTE-146 trial. In the RCC cohort, 65% of patients received prior ICI/TKI combination therapy, and preliminary data suggest benefit in both PFS and response rates.¹²

combinations, such as lenvatinib/everolimus (Afinitor). Thus far, the data do not support routine rechallenge with anti-PD-1 therapy after cancer progression on prior anti-PD-1 therapy. Ongoing clinical trials are exploring whether synergy between a TKI and an anti-PD-1 agent will result in resensitization to immunotherapy. However, this approach remains experimental until we have results from studies such as CONTACT-03 (NCT04338269), which is investigating second-line cabozantinib with or without atezolizumab (Tecentriq) after prior immunotherapy.

One of the most striking aspects of both first- and second-line treatment decision-making is that predictive factors or biomarkers, besides IMDC risk stratification, are absent. This lack of predictive biomarkers highlights a major unmet need in the field. In the future, we hope that a combination of factors—for example, PD-L1 status, histologic classification, or molecular profiling—will help guide treatment. Many studies, including correlative aspects of the interventional trials, are pending with this goal in mind.

In conclusion, the field of kidney cancer is evolving so rapidly that optimal therapy sequencing is a steep challenge. Ultimately, using our most effective therapies up-front will result in the most benefit in the highest numbers of patients. However, it will remain a challenge to appropriately sequence therapies to balance added toxicity of combination treatments with potential benefit.

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Discussion

In the era of a paradigm shift of first-line treatment for metastatic ccRCC, uncertainties arise in the standard of care in the second-line setting. In the setting of treatment after nivolumab plus ipilimumab, current data suggest second-line therapy with single-agent cabozantinib or axitinib.⁷⁻¹⁰ After first-line use of ICI/TKI combinations, second-line therapy options include single-agent cabozantinib or the combination of everolimus plus lenvatinib.^{7,8,15} ICI/TKI combinations are being investigated as potential second-line therapies.^{11,12} While we remain interested in the outcomes of these investigations, we recommend—given the absence of data—that patients participate in clinical trials or receive FDA-approved therapies emphasized in our review.

Efforts to improve outcomes in patients with advanced ccRCC have largely been dependent on understanding the pathophysiology of the disease, which has led to the development of novel targeted agents. Novel agents that inhibit transcription factor HIF—or hypoxia inducible factor, particularly the HIF2 α subunit—are on the horizon.¹⁷ About 90% of ccRCC cases carry mutations that result in defective von Hippel-Lindau protein, which leads to activation of hypoxia-inducible genes that activate VEGF.¹⁸ The upstream blockade effect of HIF2 α in multiple oncogenic pathways makes it an ideal target

for antitumorigenic agents in ccRCC. HIF inhibition may overcome mechanisms of resistance to mTOR inhibitors by addressing gene mutations of *TSC1*, *TSC2*, and *REDD1*.⁶ Phase 1/2 data on an oral HIF2 α inhibitor, MK-6482, after patients' progression on ICI/TKI therapy, had encouraging results, with an ORR of 24% and a disease control rate of 80% across all risk groups.¹⁸ As seen in the results of previous studies, a synergistic effect seems to emerge with the combination of different treatment modalities; therefore, HIF2 α inhibitors are being studied in combination to determine efficacy and safety. A current phase 2 study is investigating the combination of belzutifan (MK-6482/PT2977) with cabozantinib in patients who have progressed after 1 or 2 lines of therapy.¹⁹ Results from HIF2 α inhibitor trials will hopefully add novel treatment options for patients who have progressed on immunotherapy, TKIs, or mTOR inhibitors.

CONCLUSIONS

The prognosis for patients with advanced and metastatic RCC remains poor. Treatment paradigms for first-line therapy have shifted and left an outstanding need to understand the optimal management in subsequent lines of therapy to improve patient outcomes. In our review of current data, we hope to guide clinicians through FDA-approved second-line treatments, and we highlight upcoming trials of ICI/TKI combinations and of novel HIF2 α inhibitor agents that may meaningfully prolong survival in patients with advanced and metastatic RCC. ■

➤ For references, visit
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Handling Prior Authorizations Electronically May Offer Solutions for Slow Systems

BY TODD SHRYOCK

Need a mortgage approved to buy a \$400,000 house in less than an hour or specialty pet food delivered to your door by tomorrow? No problem. Need your patient to switch from warfarin (Coumadin) to enoxaparin (Lovenox) because they have surgery in 3 days? Sorry, there's no way the prior authorization will be approved in time.

Physicians continue to wonder how we can live in a world where so many transactions are handled quickly with technology, yet decisions that affect patient health can take so long to be approved even when there is only 1 clear treatment option.

Why is prior authorization so difficult?

The lack of a unified technology standard is a major obstacle to fixing the problem. Without standardization, health care vendors are left either to implement their own standards, which won't necessarily interface with those of other vendors or health systems, or to wait until a national standard is put in place.

It's up to payers whether to adopt any standards or to accept electronic prior authorizations using either third-party software or their own platform. The lack of a standard puts all the burden on the doctor, but time spent trying to navigate health plans' proprietary systems is time not spent with a patient.

Who has an incentive to change the system?

Private payers are reluctant because they have already invested in technology solutions of their own, so moving to a new system would be costly.

Some resources claim that prior authorizations are necessary for patient safety and to confirm that standards are being followed, but there is also an incentive to use them as a way to save money.

If prior authorizations are about improving outcomes and saving money, then there's a possibility that data-driven value-based care contracts could render them moot. In value-based care, physicians are constantly measured on costs, utilization, and outcomes. This would provide both physicians and health plans with incentives to reach the same goals.

Where will prior authorizations be in 5 years?

The only thing that's certain about the future of prior authorizations is that they aren't going away.

Prior authorizations are "really an important tool to promote patient safety, quality, and care that is more affordable," said Kate Berry, senior vice president of America's Health Insurance Plans. "But hopefully in the next 5 years, electronic prior authorizations will grow and make [the situation] less burdensome for everybody, and people can get safe, effective care that's affordable without having to worry about so many phone calls and faxes."

To read the full article, visit <https://bit.ly/3hkge6v>

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Radiotherapy for Oligometastatic Non–Small Cell Lung Cancer: Past, Present, and Future

Neal S. McCall, MD; and Kristin A. Higgins, MD

ABSTRACT: Historically, patients with stage IV non–small cell lung cancer (NSCLC) have been treated with chemotherapy alone, reserving local therapies for symptom palliation. However, evidence has accumulated that a subset of patients with oligometastatic NSCLC (OM-NSCLC) may benefit from local ablative therapies (LATs). In this article, we review the data that have formed the rationale for LAT, specifically radiotherapy, and the prospective trials that support its use in this population. Finally, we examine the evolving role of LAT in patients with OM-NSCLC in the context of immunotherapy and targeted therapies, as well as discuss ongoing clinical trials incorporating LAT in these patients.

KEYWORDS: Non–small cell lung cancer, oligometastatic, stereotactic body radiotherapy, local ablative therapy.

Introduction

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the United States, with approximately 57% of patients presenting with distant metastases at the time of diagnosis.^{1,2} Until recently, the prognosis for these patients had been dismal, with 5-year overall survival (OS) rates of just 5%.³ Historically, stage IV NSCLC had been regarded as a disseminated, fundamentally incurable disease. As such, chemotherapy alone formed the prevailing treatment

paradigm; local therapies were reserved to palliate symptoms, rather than alter disease trajectory. However, as stereotactic body radiation therapy (SBRT), improved diagnostics, and dramatic improvements in systemic therapy have all emerged, ablative local therapies are being increasingly employed for patients with oligometastatic (ie, limited metastatic) disease (OMD).

Hellman and Weichselbaum first coined the term oligometastatic in 1995, referring to a subset of patients with limited metastases from solid

tumors.⁴ They proposed that such a state could be associated with more indolent disease biology that had not yet acquired the ability to develop diffuse metastases. The clinical implication of the oligometastatic state is that treatment with aggressive LAT, most often either surgery or radiotherapy, may eliminate resistant clones that are responsible for the transition to a polymetastatic state—this would prolong survival in patients, if not cure them. Notably, they proposed that the OMD state would be increasingly prevalent and relevant with increasing efficacy of systemic therapy in controlling micrometastatic disease.⁵

Since the introduction of this theory, considerable efforts have been made to both prove the existence of the OMD and to establish a role for LAT. The first proof of concept of the OMD theory, among all solid tumors, came from long-term follow-up of patients who had undergone surgical metastectomies. Among patients with colorectal cancer, Tomlinson et al⁶ demonstrated that 10-year disease control and survival had been achievable in 16.7% of patients who had undergone liver metastectomy between 1985 and 1994. Similarly, a report of 5206 cases from the International Registry of Lung Metastases described an actuarial survival rate of 22% at 15 years following lung

TABLE 1. Completed Single-Arm Phase 2 Trials of LAT in OM-NSCLC

Study	Trial design	N	Setting	Number of lesions
De Ruysscher 2012, 2018 ^{27,28}	LAT in OM-NSCLC	39	S: 100%	≤5 (excluding locoregional disease)
Collen 2014 ²⁹	SBRT to primary tumor and metastases for patients with OM-NSCLC	26	S: 73%, M: 27%	≤5 (including primary tumor and lymph nodes)
Iyengar 2014 ³⁰	SBRT + erlotinib after progression on first-line systemic therapy	24	NR	≤6
Blake-Cerda 2021 ³¹	Consolidative SBRT to pulmonary lesions	47	S: 100%	≤5 (including primary tumor)
Baumli 2019 ⁵²	Pembrolizumab after LAT in OM-NSCLC	45	S: 31% M: 69%	≤4 before LAT
Chan 2020 (ATOM) ⁵⁸	LAT (surgery or SBRT) in patients with oligoresidual <i>EGFR</i> -mutated NSCLC after 3 months of first-line TKI	16	NR	≤4 after TKI

CMT, chemotherapy; LAT, local ablative therapy; M, metachronous disease presentation; NR, not reported; OM-NSCLC, oligometastatic non-small cell lung cancer;

metastectomy.⁷ These studies, along with others, collectively proved that long-term survival or cure was possible with aggressive LAT, even in patients with metastatic disease. With advances in treatment techniques, radiotherapy has become increasingly used as a LAT, with several early randomized trials supporting its use in patients with oligometastatic NSCLC (OM-NSCLC).⁸⁻¹⁰

A fundamental challenge associated with introducing LAT into the management of patients with OM-NSCLC has been patient selection, as metastatic disease exists on a spectrum.⁴⁻⁵ In 2017, the American Joint Committee on Cancer adopted the M1b designation for patients with a single site of extrathoracic metastatic disease.¹¹ Organizational guidelines, in general, currently consider 1 to 5 metastatic lesions to constitute OMD, although a number of important

nuances exist.¹² Joint American Society for Radiation Oncology and European Society for Radiotherapy and Oncology guidelines, for example, emphasize the importance of the method used to count lesions as well as consideration of the time course of OMD, distinguishing between patients with metachronous OMD or oligorecurrence vs synchronous OMD.

In this review, we will summarize the rationale for LAT, specifically radiotherapy, in OM-NSCLC, as well as discuss prospective trials that have begun to establish this paradigm. We will also present nuances of OMD for which data are limited, including the precise definitions of OMD.¹² Finally, we will discuss the dramatic improvements in the efficacy of systemic therapy¹³⁻¹⁷ and how these will affect future research into LAT for patients with OM-NSCLC.

Rationale for LAT in OM-NSCLC

For patients with OM-NSCLC, patterns of failure analyses formed the rationale for employing LAT. In the era before immunotherapy, upon receiving 4 to 6 cycles of a platinum-doublet regimen, about 70% to 80% of patients with stage IV NSCLC would have either a partial response or stable disease.¹⁸⁻²⁰ Adding maintenance chemotherapy provided minimal OS benefit of 1 to 2 months at most.^{18,19,21} Further, after first-line chemotherapy, 64% of patients progressed locally or at sites of initial disease involvement, 27% progressed both locally and distantly, and 9% of patients progressed distantly only.²² The rational implication of these data is that LAT may prolong time to progression and potentially OS.

Early reports of LAT for patients with OM-NSCLC came primarily from the surgical literature, most often regarding patients with a single site of OMD.

Dose/ fractionation	Systemic therapy	Median PFS (months)	Median OS (months)	Toxicity
<ul style="list-style-type: none"> ■ Brain: 18-24 Gy in 1-3 fractions ■ All other sites: 54 Gy in 3 fractions ■ Variety of non-SBRT regimens also used 	95% received first-line CMT	12.1	13.5	<ul style="list-style-type: none"> ■ Grade 3: 18% ■ Grade 4/5: 0%
50 Gy in 10 fractions	65% induction CMT	11.2	23	<ul style="list-style-type: none"> ■ Grade 3: 8% (pulmonary only) ■ Grade 4/5: 0%
<ul style="list-style-type: none"> ■ 19-24 Gy in 1 fraction ■ 27-33 Gy in 3 fractions ■ 35-40 Gy in 5 fractions 	Prior first-line CMT (100%); erlotinib (100%)	14.7	20.4	<ul style="list-style-type: none"> ■ Grade 3: 8% ■ Grade 4/5: 0%
45-60 Gy in 3-5 fractions	61.7% received 4 cycles of first-line CMT and 38.3% received TKI for 2 months prior to SBRT	34.3	Not reached	<ul style="list-style-type: none"> ■ Grade 3 (pulmonary): 7.7% ■ Grade 4/5: 0%
NR; LAT included surgery, SBRT, concurrent chemoradiation +/- consolidative CMT	53% received chemotherapy prior to enrollment; 100% received pembrolizumab after LAT	18.7	41.6	<ul style="list-style-type: none"> ■ Grade 3: 11.1% ■ Grade 4: 2.2% ■ Grade 5: 0%
<ul style="list-style-type: none"> ■ Vertebrae: 35 Gy in 5 fractions ■ All other sites: 50 Gy in 5 fractions 	100% received 3 months of induction TKI (gefitinib, erlotinib, afatinib)	15.2	44.3	Grade 3/4/5: 0%

OS, overall survival; PFS, progression-free survival; S, synchronous disease presentation; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.

Downey et al²³ conducted a phase 2 trial of induction chemotherapy and radical resection in 23 patients with NSCLC who had a solitary extrathoracic metastatic lesion. Median OS was 11 months, and 2 of the 8 patients who underwent resection were alive at 5 years. By the early 2000s, however, SBRT was being increasingly utilized for the treatment of stage I NSCLC among patients who were medically inoperable.²⁴ SBRT utilizes high-quality image guidance, immobilization, and target motion management along with nonoverlapping beams to safely deliver ablative doses of radiation with steep dose gradients, often over 5 fractions or less. The tolerability and convenience of SBRT made it an attractive alternative to surgical metastectomy.

A series of phase 1/2 dose-escalation studies demonstrated that standard SBRT doses for patients with stage

I NSCLC were also safe for patients with OMD from all solid tumors.^{25,26} Single-arm, nonrandomized phase 2 trials of radiotherapy for patients with OM-NSCLC are summarized in **Table 1**. De Ruysscher et al²⁷ conducted a phase 2 trial of metastasis-directed radiotherapy (orchemoradiotherapy) for patients with 5 or fewer sites of synchronous OMD, in addition to treatment of the primary tumor and regional lymph nodes. Median OS was 13.5 months with 3 patients alive at 5 years on long-term follow up without evidence of disease.²⁸ Another phase 2 study treated patients with 5 or fewer metastatic lesions (inclusive of primary tumor and regional lymph nodes) with a dose of 50 Gy in 10 fractions, either alone or following induction cytotoxic chemotherapy, delivered to all sites of disease.²⁹ While the primary end point in this study was metabolic response rate, median OS with this approach again

appeared favorable at 23 months. Iyengar and colleagues³⁰ completed another phase 2 study of SBRT with erlotinib in patients with limited metastatic disease (≤ 6 metastases) whose disease had progressed after at least 1 line of systemic therapy. Median OS was 20.4 months, impressive results for a heavily pretreated population. None of these 3 studies reported any cases of grade 4 or 5 toxicities. Finally, Blake-Cerda et al³¹ reported results of their phase 2 trial of SBRT (45-60 Gy in 3-5 fractions) to only the primary and pulmonary metastatic disease sites in patients with 5 or fewer total lesions. Despite not treating extrapulmonary metastases, median progression-free survival (PFS) was 34.1 months, and median OS was not reached.

Ashworth et al³² published a systematic review of studies in the literature that described surgery (55%), stereo-

Table 2. Completed Randomized Phase 2/3 Trials of LAT in Patients With OM-NSCLC

Study	N	Setting	OMD definition and evaluation		
			Number of lesions	Primary tumor	Lymph nodes*
SABR-COMET 2019, 2020 ^{9,36}	99 (NSCLC, n = 18)	M: 100%	■ ≤5 per protocol ■ 1: 42% ■ 2-3: 51% ■ 4-5: 7%	■ Not treated ■ Required controlled primary tumor for 3 months	■ Excluded per protocol ■ 3% of patients had a lymph node as SBRT target (protocol violation)
Iyengar 2018 ⁸	29	NR	■ ≤6 prior to induction per protocol ■ Number of lesions NR	Included in OMD count	■ Included in OMD count but did not specify how ■ 17.2% had involved N1 nodes ■ 50% had involved N2 or N3 nodes
Gomez 2016, 2019 ^{10,37}	49	S: 94% M: 6%	■ ≤3 post induction, per protocol ■ 1: 6.1% ■ 2-3: 93.9%	Included in OMD count	■ Included in OMD count. Each level (N1-N3) counted as a site of OMD ■ Involved N1 nodes: 24.5% ■ Involved N2/3 nodes: 53%
SINDAS 2020 ⁵⁹	133 (EGFR-mutant)	S: 100%	■ ≤5 per protocol ■ 1-2: 48.6% ■ 3-4: 28.6% ■ 5: 12.8%	Included in OMD count	■ Included in OMD count. Each involved node counted separately ■ Number of patients with involved nodes NR

CMT, chemotherapy; LAT, local ablative therapy; M, metachronous disease presentation; NR, not reported; NSCLC, non-small cell lung cancer; OM-NSCLC, oligometastatic NSCLC; OMD, oligometastatic disease; S, synchronous disease presentation; SBRT, stereotactic body radiotherapy.

tactic radiosurgery (SRS; 35%), and SBRT (10%) as definitive local therapy in patients with NSCLC and 1 to 5 sites of OMD. Five-year OS rates ranged between 8.3% and 86.0% (median, 42%). In another meta-analysis of data on individual patients, Ashworth et al³³ reported the outcomes of patients with NSCLC, primarily with 1 to 2 sites of OMD, who were treated with LAT for both the primary and metastatic disease. More recently, data were reported from a large United Kingdom-based prospective registry of 1422 patients with OMD (defined as 1-3 sites of extracranial disease), including 64 patients with OM-NSCLC, who were treated with SBRT to doses of 24 to 60 Gy in 3 to 8 fractions.³⁴ Median 2-year OS was 65.4% among patients with OM-NSCLC, and no treatment-related deaths were reported in the entire cohort. Despite the heterogeneity of patients on which these analyses were based, the results reinforce the potential for long-term survival following LAT in select patients with OM-NSCLC.

Randomized Trials of LAT

Despite the accumulated data for LAT in OM-NSCLC, immortal time bias and other selection biases could easily account for favorable outcomes with LAT in comparison with historical or retrospective controls.³⁵ To date, 3 published phase 2 randomized trials have included OM-NSCLC; they are summarized in Table 2 and their outcomes are depicted in the Figure. The landmark SABR-COMET study randomized 99 patients (18 with NSCLC) with or fewer metastatic lesions to receive either standard palliative therapy or SBRT in a 1:2 ratio with an end point of OS.³⁶ The experimental group received SBRT immediately after registration followed by standard-of-care systematic therapy. Median OS in the SBRT group was 50 months, compared with 28 months in the control group (P = .006); 42.3% of patients in the SBRT group survived 5 years.⁹ However, this came at the cost of 3 (4.5%) treatment-related deaths. Another trial conducted by Gomez et al^{10,37} randomized patients with 3 or

fewer metastatic lesions after 4 cycles of first-line, standard-of-care systemic therapy to receive either maintenance therapy alone or maintenance therapy plus local consolidative therapy, which was either hypofractionated RT, SBRT, or surgery (Table 2). The primary end point was PFS, and the trial was halted early after an interim analysis demonstrated improved median PFS with local consolidative therapy (18.7 vs 11.9 months; P = .005; Figure). On long-term follow-up, this translated to a significant OS benefit (41.2 vs 18.9 months; P = .017). Finally, a trial was conducted by Iyengar et al⁸ in patients with NSCLC who had 6 or fewer sites of extracranial metastatic disease (including primary tumor) prior to therapy, who then had received 4 to 6 cycles of induction systemic therapy. The patients were randomized either to consolidative radiotherapy (SBRT or hypofractionated RT) plus maintenance therapy or to maintenance therapy alone (Table 2). This trial also was terminated early after meeting

Brain metastases	Timing of LAT	Systemic therapy	Dose and number of fractions	Toxicity
<ul style="list-style-type: none"> ■ Included in OMD count ■ 4% of patients affected 	After registration	NR	<ul style="list-style-type: none"> ■ Lung: 54-60 Gy in 3-8 fractions ■ Bone: 35 Gy in 5 fractions ■ Vertebrae: 16-20 Gy in 1 fraction or 30 Gy in 3 fractions. ■ Liver: 45-60 Gy in 3-8 fractions ■ Adrenal: 60 Gy in 8 fractions 	<ul style="list-style-type: none"> ■ Grade ≥ 2: 29% vs 9% ■ Grade 5: 5% (2 pulmonary, 1 gastrointestinal) vs 0%
<ul style="list-style-type: none"> ■ Not included in A ■ Required treatment prior to enrollment 	After 4-6 cycles of CMT	Cytotoxic CMT, bevacizumab, or erlotinib	<ul style="list-style-type: none"> ■ 21-27 Gy in 1 fraction ■ 26.5-33.0 Gy in 3 fractions ■ 30.0-37.5 Gy in 5 fractions ■ 45 Gy in 15 fractions (for bulky lymphadenopathy) 	Grade ≥ 3 : 0% vs 0%.
<ul style="list-style-type: none"> ■ Included in OMD count ■ 27% of patients affected 	<ul style="list-style-type: none"> ■ After 4-6 cycles of CMT ■ LAT could be surgery or radiotherapy 	Cytotoxic CMT, bevacizumab, or erlotinib	<ul style="list-style-type: none"> ■ Brain: 15-20 Gy in 1 fraction ■ Lung: variety of SBRT, hypofractionated, and conventional regimens ■ Bone: 18-45 Gy in 1-15 fractions ■ Adrenal: 60 Gy in 8 fractions 	<ul style="list-style-type: none"> ■ Grade 3: 20% vs 8.3% ■ Grade 4/5: 0%
Brain metastases excluded	After registration	Erlotinib, gefitinib, or icotinib	25-40 Gy in 5 fractions	<ul style="list-style-type: none"> ■ Grade 3/4 pneumonitis (7.3% vs 2.9%) ■ Grade 3/4 esophagitis (4.4% vs 3.0%)

^aN1, N2, and N3 refer to nodal group staging as defined by the American Joint Committee on Cancer, 8th edition.

its primary end point at interim analysis: The median PFS was 9.7 months in the group receiving consolidative radiotherapy compared with 3.5 months in the group receiving maintenance therapy alone ($P = .01$; Figure). OS results are not yet mature.

Despite each of these 3 trials having convincingly met their primary end points, subtle differences in their designs disclose clinically relevant questions. The majority of patients in the 3 trials had 3 or more sites of distant metastatic disease. For example, only 7 patients on the SABR-COMET trial had 4 or 5 sites of OMD.³⁶ The Iyengar trial reported a median of 3 sites of OMD in each group, but it did not report additional descriptive data.⁸ The number of metastatic lesions has been shown to be inversely associated with survival in retrospective series.^{33,38} Consequently, it is unclear how generalizable the results of these trials are to patients with 4 or 5 sites of OMD.

Further, definitions of OMD and how

metastatic lesions were counted varied significantly among trials. For example, brain metastases were considered sites of OMD in the SABR-COMET and Gomez trials.^{10,36} Conversely, the Iyengar study permitted treatment prior to enrollment but did not include intracranial lesions as OMD, as the role for SRS for limited brain metastases is already well established.^{8,39-41} The burden of thoracic, especially mediastinal, lymph node involvement introduces another layer of complexity in extrapolating these studies to real-world patients, as hilar and mediastinal nodal involvement has been correlated with worse OS in several retrospective analyses of patients receiving LAT for OMD.^{33,38} One explanation for this finding is that central location tends to be the dose-limiting factor with respect to lung SBRT, and attenuated or more fractionated courses may be needed to safely treat the hila or mediastinum.⁴² Indeed, central thoracic metastases were SBRT targets in both of the patients who developed grade

5 pulmonary toxicity on the SABR-COMET study.³⁶ The Iyengar trial did not specify how involved lymph nodes were counted.⁸ However, patients receiving consolidative radiation to the hilum or mediastinum received either lower-dose SBRT (30 Gy in 5 fractions) or hypofractionated radiotherapy (45 Gy in 15 fractions). In the Gomez trial, each nodal group (ie, left or right hilar [N1], mediastinal [N2], or supraclavicular [N3]) was counted as a site of OMD.¹⁰ These patients were treated with either hypofractionated radiotherapy or concurrent chemoradiation. Despite the majority of patients in the Iyengar and Gomez trials having nodal involvement, the absence of high-grade toxicities in these trials, in contrast with the SABR-COMET trial, argues for greater fractionation and/or dose reduction for nodal oligometastases.

Also, the disease presentations of the patients included in these 3 trials also had fundamental differences. For example, the SABR-COMET study

Table 3. Ongoing Randomized Phase 3 Trials of LAT in Patients With OM-NSCLC

Study	Patient population	Treatment arms	Key eligibility criteria	Design	N	Primary outcome
NRG-LU002 (NCT03137771) ⁶⁸	OM-NSCLC	Local consolidative therapy (SBRT or surgery) with maintenance therapy vs maintenance therapy alone	<ul style="list-style-type: none"> ■ ≤3 sites of extracranial OMD (defined by isocenter) ■ Excludes patients receiving first-line targeted therapy (<i>EGFR/ALK</i>) 	Phase 2/3	378 (2:1)	<ul style="list-style-type: none"> ■ Phase 2: PFS ■ Phase 3: OS
SARON (NCT02417662) ⁷⁵	OM-NSCLC	Radiotherapy to the primary tumor and SBRT to metastases vs noninvestigational platinum doublet	<ul style="list-style-type: none"> ■ ≤5 sites of OMD (including primary tumor and regional lymph nodes) ■ Excludes <i>EGFR/ALK</i> 	Phase 3	340	OS
LONESTAR (NCT03391869) ⁷⁶	Metastatic and OM-NSCLC	Induction ipilimumab/nivolumab followed by local consolidative therapy (SBRT, surgery, radiofrequency ablation for 3 lesions) with continued immunotherapy vs continued immunotherapy	<ul style="list-style-type: none"> ■ No eligibility criteria based on number of sites of OMD. OM-NSCLC (3 lesions) to be analyzed as a subgroup ■ Patients must be naive to immunotherapy ■ Excludes <i>EGFR/ALK</i> 	Phase 3	270	OS
OITROL (NCT02076477) ⁷⁷	OM-NSCLC	Concurrent chemoradiation followed by cytotoxic chemotherapy vs neoadjuvant cytotoxic chemotherapy (2 cycles) followed by concurrent chemoradiation	<ul style="list-style-type: none"> ■ ≤5 sites of OMD (not including primary tumor and regional lymph nodes) ■ Excludes patients receiving immunotherapy and targeted therapy 	Phase 3	420	ORR at 3 months
SABR-COMET-3 (NCT03862911) ⁶⁷	OMD	SBRT to all sites of OMD followed by SOC therapy vs SOC therapy alone	<ul style="list-style-type: none"> ■ Any histology included ■ ≤3 sites of OMD ■ Controlled primary tumor for at least 3 months 	Phase 3	297 (2:1)	OS
SABR-COMET-10 (NCT03721341) ⁶⁶	Metastatic cancer	Comprehensive SBRT to all sites of disease + SOC therapy vs SOC therapy alone	<ul style="list-style-type: none"> ■ Any histology included ■ Total number of metastases: 4-10 ■ Controlled primary tumor for at least 3 months 	Phase 3	159 (2:1)	OS

LAT, local ablative therapy; OM-NSCLC, oligometastatic non-small cell lung cancer; OMD, oligometastatic disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiotherapy; SOC, standard of care.

population included only patients with metachronous OMD, rather than synchronous, as the protocol mandated that the primary tumor be controlled for at least 3 months prior to randomization. While the Gomez and Iyengar trials did not exclude patients with metachronous presentation, they were both more representative of patients with synchronous disease presentation (Table 2). Retrospective studies have demonstrated the improved outcomes among patients with metachronous OMD, and the duration of the preceding disease-free interval further determines prognosis.³³

Additionally, the timing of LAT in these trials varied considerably. The SA-

BR-COMET trial treated patients prior to any maintenance/systemic therapy, whereas Gomez and Iyengar both delivered LAT following 4 to 6 cycles of systemic therapy, most often cytotoxic chemotherapy. Such an approach allows for chemoselection, assuming that patients who are nonresponders to first-line therapy would be less likely to benefit from local consolidative therapy.⁴³ Patients enrolled on the Iyengar trial had 6 or fewer sites of OMD, but this was determined prior to induction systemic therapy. The OMD burden on the Gomez study, however, was determined following 4 cycles of systemic therapy. While the burden of disease prior to induction therapy was

not reported, this study may be most notable for its proof of concept that OMD is inducible with systemic therapy.⁵

It should be noted that the 2 trials for OM-NSCLC were conducted prior to the FDA approvals for multiple immunotherapeutic agents that have now become the standard of care for frontline therapy in stage IV NSCLC. Given the improvements in OS seen in the era of immunotherapy, LAT for OM-NSCLC may have potential even greater than what has been seen in published trials thus far.

OMD and Immunotherapy

The prevalence of OMD, as hypothesized by Hellman and Weichselbaum, is directly

related to the effectiveness of systemic therapy in controlling or eliminating micrometastatic disease.⁵ In recent years, immunotherapy and targeted therapies have dramatically improved the efficacy of systemic therapy for patients with metastatic NSCLC. Indeed, the induction and maintenance regimens used in the Gomez or Iyengar trials are no longer considered standard-of-care first-line therapy by today's standards.^{8,10} The PD-L1/PD-1 axis is the most well-characterized pathway of immune evasion, and PD-1/PD-L1 inhibitors have drastically increased

the survival of patients with advanced NSCLC. For example, immunotherapies such as pembrolizumab (Keytruda) have replaced chemotherapy among patients with PD-L1 >50%, and pembrolizumab has been added to standard chemotherapy regimens among patients without PD-L1 expression or *EGFR/ALK* mutations.^{13,44-46}

How to best integrate LAT, specifically radiotherapy, with immunotherapy is an active area of investigation. Interestingly, progression outside of initial sites of disease involvement may be more common with immunotherapy in comparison with cytotoxic chemotherapy, although results of patterns-of-failure analyses have been mixed.⁴⁷ Nevertheless, preclinical evidence suggests that radiotherapy may enhance responses to PD-1/PD-L1 inhibitors by acting as an in situ vaccine, garnering out-of-field (ie, abscopal) responses.⁴⁸⁻⁵⁰ The clinical implication of this synergy in patients with OMD is that SBRT could enhance a patient's response to immunotherapy both locally and systemically. While clinical data on this phenomenon have been mixed, a secondary analysis of the KEYNOTE-001 trial found improved OS among patients treated with pembrolizumab who had received prior radiotherapy.⁵¹ Bauml and colleagues⁵² reported results from a phase 2, single-arm study in which patients with ≤4 oligo-

metastatic foci received pembrolizumab for 4 to 12 weeks following LAT (Table 1). The majority of patients received a combination of LAT modalities, includ-

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ing resection, chemoradiation, and radiofrequency ablation, although treatment details such as dose and fractionation were not reported. Median PFS from LAT and OS both compared very favorably with historical controls at 19.1 and 41.6 months, respectively. Finally, the phase 2 PEMBRO-RT trial randomized patients with met-

astatic (not necessarily oligometastatic) NSCLC to receive pembrolizumab with or without SBRT (24 Gy in 3 fractions) to a single site.⁵³ SBRT numerically improved response rates (18% without SBRT; 36% with SBRT; $P = .07$), although the predefined threshold of clinical significance was not reached. Notably, the dose and fractionation of radiotherapy has been hypothesized to play a role in whether systemic immune responses are generated; higher doses may cause obliteration of the immune infiltrates that are responsible for generating antitumor immunity.⁵⁴ It is therefore possible that the optimal dose-fractionation of SBRT or hypofractionated radiotherapy may depend upon the systemic therapy received.

OMD and Targeted Therapy

Cases of NSCLC with genetic driver mutations or alterations, including those with *EGFR* mutations or *ALK* rearrangements, exhibit unique disease biology. These alterations confer sensitivity to targeted tyrosine ki-

nase inhibitors (TKIs), which can induce profound and durable responses. Despite this, resistance to targeted therapy invariably develops, with few effective salvage or second-line options. Similar to patients without targetable genetic alterations, progression most often occurs in the sites of initial disease involvement in patients with *EGFR* variants.⁵⁵⁻⁵⁷ Further, complete responses are uncommon, and nearly all patients have residual disease at the time of best response. This has led some investigators to hypothesize that LAT, either upfront or at the time of best response, may eliminate resistant clones and prolong responses, if not survival.

Among the oncogene-driven subtypes of NSCLC, *EGFR* mutations have been the most closely studied with respect to OMD. The nonrandomized phase 2 ATOM trial studied the effect of consolidative SBRT on oligoresidual (defined as ≤4 sites of OMD) *EGFR*-mutant NSCLC after 3 months of induction TKI.⁵⁸ Median OS was 43.3 months among the 16 patients enrolled and analyzed, and no grade 3 or greater toxicities were observed. When the enrolled patients were compared with a cohort of patients

who had failed screening for inclusion on this trial, consolidative SBRT reduced the risk of progression (HR, 0.41; $P = .0097$; Table 1). At the 2020 American Society of Clinical Oncology Virtual Annual Meeting, Wang et al presented results of the phase 3 SINDAS trial that randomized patients with untreated oligometastatic (≤5 sites of OMD) *EGFR*-mutated NSCLC without brain metastases to TKI alone (ge-

fitinib [Iressa], erlotinib [Tarceva], icotinib) or TKI plus SBRT. The addition of SBRT prolonged PFS (20.2 vs

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Figure. **Outcomes of Completed Phase 2/3 Trials of LAT in OM-NSCLC^a**

LAT, local ablative therapy; OM-NSCLC, oligometastatic non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

^aPFS and OS are plotted for each of the 4 trials involving LAT. Of note, values plotted in the SABR-COMET trial reflect the entire cohort (N = 99) rather than those with OM-NSCLC; N = 18. OS in the Iyengar trial was not reached and is therefore not shown.

12.5 months; $P < .001$) and OS (25.5 vs 17.4 months; $P < .001$).⁵⁹ Notably, *EGFR* 20 insertion, an alteration that confers TKI resistance, was more frequent in the TKI-alone arm, and full publication of results are forthcoming. Despite the low overall rates of toxicity on the SINDAS trial, LAT to sites of residual OMD (as on the ATOM trial) rather than de novo OMD would reduce treatment volumes and potentially reduce toxicity without compromising disease control, as few patients progress within the first few months of therapy.^{58,60} Further studies

are needed to define the optimal timing of LAT in patients with *EGFR*-mutated OM-NSCLC.

Another challenge of defining a role for LAT in patients with *EGFR*-mutant NSCLC is the rapidly evolving landscape of first-line therapies. Osimertinib (Tagrisso), a third-generation *EGFR* TKI with activity against the T790M resistance mutation, was shown to improve PFS and OS in the FLAURA trial.^{17,61} Interestingly, nearly 80% of patients still have residual disease at the time of

best response, and initial sites of disease involvement remain the most common sites of progression.^{17,60,61} To date, no prospective trials of LAT in combination with osimertinib have been reported. Osimertinib is distinguished from earlier-generation TKIs by its robust intracranial activity, with central nervous system (CNS) response rates of 64% and CNS disease control rates of 90%.^{62,63} With osimertinib's intracranial disease control rates approaching those of extracranial disease control, up-front intracranial radiotherapy is being increasingly deferred for patients with asymptomatic *EGFR*-mutant brain metastases. This shifting paradigm calls into question whether there could be a role for stereotactic radiosurgery to oligoresidual brain metastases after induction osimertinib.

While *EGFR* remains the most common and best studied mutational subtype in the setting of OM-NSCLC, others deserve mention. Patients with *ALK*-rearranged NSCLC have also seen recent dramatic improvements in therapy. The next-generation *ALK* inhibitors—alelectinib (Alecensa), ceritinib (Zykadia), lorlatinib (Lorbrena), and brigatinib (Alunbrig)—have all outperformed crizotinib in the first-line setting.^{16,64,65} Data for LAT in patients with *ALK*-rearranged OM-NSCLC are much more limited, although retrospective studies suggest a potential role for LAT in these patients as well. Furthermore, targeted therapies are now approved for patients with sensitizing *BRAF*, *ROS1*, *NTRK*, *MET*, and *RET* alterations.^{3,15} As these therapies are increasingly being utilized, further research regarding a role for LAT in patients receiving these agents will be warranted.

Ongoing Clinical Trials and Future Directions

Based on the data available, multiple groups have recommended delivery of radical LAT for patients with OM-NSCLC when it is safe and feasible, typically in the

setting of 1 to 5 sites of OMD.¹² Several prospective, randomized clinical trials that are under way to confirm these findings are summarized in **Table 3**. Among patients with all solid tumor histologies, SABR-COMET-3 is a phase 3 trial designed to confirm the findings of the initial SABR-COMET trial in patients with ≤ 3 sites of OMD.^{66,67} The NRG-LU002 trial randomizes patients with OM-NSCLC who have 1 to 3 sites of OMD to receive either maintenance therapy or local consolidative therapy (surgery or radiotherapy) plus continued maintained therapy.⁶⁸ While patients receiving first-line targeted therapy are excluded, all FDA-approved first-line regimens containing immunotherapy are permitted. Given the success of LAT in OM-NSCLC, studies are under way to understand if LAT can improve outcomes in polymetastatic disease. Radiation technologies have improved over time, making treatment of multiple lesions more feasible in the clinic. The ongoing SABR-COMET-10 trial is evaluating SBRT in patients with 4 to 10 sites of OMD.

Aside from confirming a benefit with LAT in patients with OM-NSCLC, these trials may also provide additional guidance on the optimal dose and fractionation for LAT. As previously noted, the importance of balancing local control with safety was highlighted by the grade 5 toxicities seen on the SABR-COMET trial.³⁶ The SABR-COMET-3 and SABR-COMET-10 trials are

employing the same SBRT regimens as their phase 2 predecessor; however, the NRG LU-002 trial, for example, is using attenuated radiation doses: 24 Gy in 1 fraction, 30 Gy in 3 fractions, or 34 Gy in 5 fractions.⁶⁶⁻⁶⁸ For the treatment of primary and regional nodal disease, hypofractionated radiation (45 Gy in 15 fractions) is recommended. To date, the SAFFRON-II trial is the only randomized study to directly compare SBRT dosing schedules (28 Gy in 1 fraction vs 48 Gy in 4 fractions) for patients with OMD who have peripheral lung metastases. No differences in local control or safety were identified in SAFFRON-II.⁶⁹ Following the publication of the results of the trials listed in Table 3, further studies of this type will likely be needed.

Finally, ongoing translational research is also needed to better define OMD biology, and the importance of translational

end points in these ongoing trials should not be overlooked. Some investigators hypothesize that the presence of circulating tumor cells (CTCs) or mutational burden detected by circulating tumor DNA (ctDNA) may be better than conventional imaging in approximating metastatic disease burden and responses to systemic therapy.⁷⁰ In 2 small studies, detection of CTCs has tended to correlate with shorter OS and PFS after SBRT

for patients with OMD.^{71,72} The NRG LU002 trial will be correlating ctDNA in each arm after induction therapy with

PFS and OS. Among patients with stage I to III NSCLC, ctDNA mutation burden has been shown to predict relapse up to 5 months before conventional imaging.^{70,73} In a correlative translational analysis of the Gomez trial,⁷⁴ there was no association between ctDNA mutation kinetics and outcome, although the analysis was limited by a small sample size. Local consolidative therapy, however, did appear to numerically decrease ctDNA mutations. Interestingly, ctDNA burden appeared to increase 6 months prior to radiographic progression, also suggesting that ctDNA may indeed reflect tumor burden. These early results offer a glimpse into the potential of how blood-based biomarkers could better identify and quantify OMD, and how they could either supplement or replace conventional imaging as a tool for counting the number of metastatic sites in a patient.

Conclusions

In summary, the accumulated evidence indicates that LAT may improve outcomes for patients with OM-NSCLC. Several early randomized clinical trials have demonstrated improved PFS or even OS with its use. Nevertheless, larger, well-powered phase 3 trials are needed to confirm these findings in the context of modern systemic therapies. Subgroup and correlative translational analyses will help to better define both the oligometastatic state in patients with OM-NSCLC and the optimal timing for LAT. ■

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➤ For full reference list, visit cancernetwork.com/McCall_6.21

Early results offer a glimpse into the potential of how blood-based biomarkers could better identify and quantify [oligometastatic disease].

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Routine Breast Cancer Screening in Average-Risk Women Younger Than 50 Years: Current Paradigms Based on National Guidelines

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ABSTRACT: Approximately 270,000 women are diagnosed with breast cancer each year in the United States alone. While there is consensus among national organizations including the US Preventive Services Task Force, the American Cancer Society, and the American College of Radiology that routine mammography screening should be performed in women 50 years and older, there is debate about the benefit-to-harm ratio of routine screening in average-risk women aged between 40 and 49 years. In this review, we examine risks and benefits of routine breast cancer screening starting at age 40 at the individual level, followed by evaluation of the role of advanced imaging techniques in screening women on a population level.

Introduction

Breast cancer poses a large health care burden. More than 270,000 women are diagnosed with breast cancer every year in the United States alone, and more than 40,000 women will die from the disease over the same period.¹ Advances in routine screening and curative treatment options have led to mean 5-year survival rates for localized and regional disease of 98.9% and 85.7%, respectively.¹ Diagnosis at an early stage, often due to routine screening, represents one of the most

important prognostic factors for survival.

Routine mammography screening in average-risk women 50 years and older has reduced the age-adjusted mortality rate from breast cancer by 34% just over the past 20 years.^{2,3} While there is consensus among national health organizations regarding the benefits of routine mammographic screening in women 50 years and older, screening recommendations for average-risk women aged between 40 and 49 years vary.

Differences in screening recommendations among national organizations large-

ly reflect variations in assessment of the benefit-to-harm ratio of screening women aged between 40 and 49 years who are less likely to develop breast cancer, compared with older women. Women who do develop breast cancer in this age group, however, are more likely to develop more aggressive disease.^{4,5} Over the past decade, this has become an increasingly important topic of discussion as breast cancer shifts to a younger age of onset.¹ In this review, we examine the risks and benefits of routine breast cancer screening starting at age 40 at the individual level, followed by an evaluation of the role of advanced imaging techniques in screening women on a population level.

Current Breast Cancer Screening Guidelines

National health organizations update breast cancer screening recommendations primarily using pivotal, large-scale, multi-institutional randomized controlled trials (RCTs).^{2,6-12} RCTs inform meta-analyses and/or systematic reviews by stakeholder organizations for guideline formation. Updates to these recommendations are presented as new and long-term follow-up data become available.

In 2009, the US Preventive Services Task Force (USPSTF) recommended biennial mammographic screening for women aged between 50 and 74 years and updated these recommendations in 2016.^{13,14} In women aged between 40 and 49 years, the decision of periodic screening is based on individual self-assessment and risk profile; however, the USPSTF recommends against routine screening for average-risk women in this age group. The 2003 American Cancer Society (ACS) guidelines, updated in 2015, strongly recommend routine mammography screening for average-risk women annually (when aged between 45 and 54 years) or every 2 years (when 55 years or older).^{15,16} Women aged between 40 and 44 years should have the opportunity to begin annual screening based on individual risk, but there is less certainty about the balance of benefits relative to harms in this age group. The American College of Radiology (ACR) recommendations, made in collaboration with the Society of Breast Imaging (SBI), were published in 2010 and updated in 2017,^{17,18} and they include additional information to cover gaps in the previously issued USPSTF and ACS guidelines. The ACR/SBI recommends annual screening for women 40 years and older. The ACR/SBI also recommend annual screening for high-risk women younger than 40 years. There is considerable agreement among ACR/SBI screening recommendations and those of the American Society of Breast Surgeons,¹⁹ the National Comprehensive Cancer Network (NCCN),²⁰ and the National Consortium of Breast Centers.²¹

In contrast to the USPSTF's process for making recommendations, the ACS and the ACR/SBI also incorporate large observational study designs, those that evaluate breast cancer mortality, into their method for creating guidelines; the latter organizations also use modeling and simulation studies to supplement pivotal trial data. Using such studies in addition to RCTs allows for better reflection of current practice and a more robust representation

of patient demographics throughout the treatment landscape in the United States. ACR/SBI guidelines also outline additional benefits of screening when it begins for average-risk women at age 45 years: reduction in the use of chemotherapy, earlier detection of high-risk disease, less aggressive forms of surgery, and improvements in life-years gained.¹⁸

Risk Stratification and Existing Guidelines

The USPSTF, ACR/SBI, and ACS agree that women with a strong familial history of breast cancer and/or ovarian cancer or a prior personal history of chest radiation therapy, or who are carriers of mutated *BRCA1* or *BRCA2* genes, have a higher cumulative lifetime risk of developing breast cancer. Therefore, different screening recommendations are warranted.¹³⁻²¹ High-risk women may be offered mammographic screening at ages younger than 40 years, more frequent screening, and/or supplemental imaging, such as ultrasound and MRI.¹⁵ Among average-risk women, there is significant heterogeneity in further risk stratification used to define both the age of initiation and the frequency of screening, and age remains the primary variable in screening recommendations for women younger than 50 years.¹⁵

Benefits and Harms of Breast Cancer Screening for Younger Women

The consensus among national health organizations is that mammographic screening in average-risk women is overall beneficial in reducing breast cancer mortality.³ However, key differences exist among organizations related to (1) recommended age to initiate screening and (2) frequency of routine screening.

Benefits

Across all organizations, the primary benefit of breast cancer screening is a reduction in breast cancer–specific mortality as outlined in pivotal RCT data. Overall breast cancer mortality as reported in a

pooled analysis in women aged between 35 and 85 years was reduced between 11% and 36% in women screened with mammography compared with those who were not screened.²² Estimates quoted by the ACR/SBI meta-analysis similarly show a 26% to 39% reduction in breast cancer mortality with mammographic screening in women aged between 40 and 74 years.^{23,24} When incorporating the ACS meta-analyses, the breast cancer mortality reduction was 22% for the ACS and ACR/SBI groups, in comparison with 15% in the USPSTF groups.²⁵ The difference in overall mortality reduction can potentially be attributed to the larger pool of studies included in the ACS and ACR/SBI analyses that represents more recent practice not captured in core RCT data. While the benefits of screening in women aged between 40 and 49 years is commonly referenced between ACR/SBI and ACS, these societies diverge in their recommendations in terms of when screening should commence. This is primarily due to ACR/SBI's choice to incorporate factors such as a particular risk-benefit model that prioritizes life-years gained, racial disparities, and the impact of advanced imaging technologies.

When stratifying by age groups, there is a clear benefit when screening women aged between 40 and 49 years, although the magnitude of this benefit appears less than that of screening women 50 years and older due to overall lower incidence. The age-adjusted mortality reduction in the pivotal RCTs is lower than those presented in updated, large observational studies. Data from meta-analyses of RCTs showed a 15% to 35% mortality reduction with up to 18 years of follow-up in women 40 to 49 years of age,²⁶ compared with 26% to 48% in large observational studies.²⁷ The Swedish Mammography Screening in Young Women cohort study showed a 29% reduction in breast cancer mortality with 16-year follow-up after recommendations for invitation to screen in this younger age group.²⁸

Breast cancer screening in women starting at age 40 has the potential to reduce

Risk-based screening using more accurate tools appears to represent a viable solution for health care providers to determine which women require earlier and more frequent screening.

mortality significantly and to lead to longer potential life spans (a 42% to 47% increase in the number of life-years gained) relative to when women are screened between ages 50 and 74 years.^{18,29,30} RCT data may not fully capture additional benefits of screening in this group; to do so may necessitate the incorporation of more recent, observational studies.

Harms

The benefits of routinely screening average-risk women aged between 40 and 49 years must be balanced with the harms associated with screening women who experience a lower incidence of breast cancer.³¹

False positive (FP) mammographic screening examinations that result in women being subsequently recalled for additional imaging or biopsy—but are eventually found to not have cancer—represent the primary harm of screening women in this younger age group. The incidence rate of FP findings has been estimated to be as high as 7% to 12% among women aged 40 to 59 years.^{14,23} In comparison, women aged 40 to 49 years have higher FP rates than women aged 50 to 59 years, with an odds ratio of 1.25 (95% CI, 1.23-1.26) due to denser breast tissue that impacts mammographic imaging sensitivity.³²⁻³⁴ Overall, an inverse relationship exists between age and FP and biopsy rates per 1000 screening exams for women older than 40 years.^{14,31} Anywhere from 80.0% to 87.3% of women with FP findings, however, undergo only additional imaging and not biopsy.^{36,37} A large retrospective cohort study of more than 200,000 women aged 50 to 69 years showed a low cumulative 20-year risk of

20.0%, 4.1%, and 2.0% for FP results, subsequent invasive procedures, and subsequent core biopsies, respectively.³⁸

An early systematic review showed that women in the United States older than 40 years with FP screening findings are more likely than women of the same age who do not get FP screening findings to report greater psychological distress, anxiety about breast cancer, and worry over perceived risk of future breast cancer.³⁹ While these exams have not been shown to lead to generalized anxiety or depression, breast cancer-specific distress related to FP results can persist for up to 3 years post screening mammogram.⁴⁰ Despite these findings, up to 98% of adults in a United States survey who said that they were recalled following FP cancer screening examinations were satisfied that they had undergone the subsequent recommended test.⁴¹

The larger-scale economic harms of FP screening mammograms may be substantial. Each subsequent examination following FP screening findings ranged from \$134.80 USD for follow-up imaging to \$1374.69 USD for more invasive testing; this equates to an additional \$5.26 million USD per 1000 women screened.^{42,43} In a 2015 study examining US health care expenditure data of more than 700,000 women, an 11% annual FP rate among screened women aged 40 to 49 years was estimated to cost an additional \$2.8 billion annually (range, \$1.2-\$5.0 billion).³⁴ Because FP findings incur such large additional costs, the individual benefits of annual screening for women aged 40 to 49 years need to be carefully balanced with the higher economic costs.

Overdiagnosis refers to screen-detected breast cancer that would not have progressed to clinical presentation during an individual's lifetime nor would it have caused that individual harm in the absence of screening. This is a potential harm of increasing breast cancer screening examinations based on age and screening frequency; however, data are sparse. Estimates of overdiagnosis range from 5% to 50%,^{16,44-45} requiring significant assumptions that may overinflate results.⁴⁶ Significant uncertainty still surrounds the magnitude of risks related to overdiagnosis, and further evaluation of this risk is necessary before informing action.⁴⁵ Transitioning the focus of future studies to preventing overtreatment rather than overdiagnosis may represent a more prudent way of addressing management of more indolent tumors.

Advances in Imaging Technology

Mammography remains the gold standard for breast cancer screening but has well-established limitations. Use of advanced techniques purport improved cancer detection over full-field digital (2D) mammography alone. Appropriate use of advanced imaging technologies for screening may help maximize the overall benefit-to-harm ratio of screening average-risk women. We review these advanced imaging technologies here.⁴⁷

Advances in Mammographic Imaging

Many of the pivotal RCTs informing guideline recommendations were completed with film-screen mammography. However, digital mammography is now widely used across the United States. The Digital Mammographic Imaging Screening Trial found no significant difference between film-screen and digital mammography in imaging sensitivity across more than 49,000 women in the United States and Canada.⁴⁸ However, digital mammography had significant benefit over film-screen mammography when used in pre- and perimenopausal

women, women younger than 50 years,⁴⁹ and women with dense breasts.⁴⁸

Digital breast tomosynthesis (DBT) or “3D” imaging is a recent advancement that demonstrates improved screening interpretation performance when combined with 2D digital mammography, compared with 2D digital mammography alone.^{49,50} Evidence is accumulating that shows recall rates and cancer detection are improved with the use of DBT.⁵¹⁻⁵³ In a comparative effectiveness study in women aged 40 to 79 years, recall rates decreased from 24 of 1000 exams to 204 of 1000 exams, and cancer detection rates increased from 5.9 to 8.8 per 1000 exams.⁵⁴

Contrast-enhanced screening mammography (CESM) provides the ability to identify angiogenesis induced by breast tumors. The examination involves a double exposure, using both low and high-energy x-rays. The result is a low-energy image, analogous to digital mammography, as well as recombined images demonstrating areas of enhancement with subtraction of background breast parenchyma, analogous to contrast-enhanced subtraction breast MRI images following contrast administration. CESM demonstrates improved diagnostic performance characteristics compared with digital mammography alone with better lesion detection and improved sensitivity and specificity.⁵⁵ As practice evolves and advanced mammographic techniques become widely available, these techniques can be used to overcome limitations of 2D digital mammography.

Screening Breast Ultrasound

Screening breast ultrasound has shown additional benefits, particularly in women who have dense breast tissue that may obscure tumors on mammography. Incremental cancer detection rates of nearly 4.5 per 1000 women have been reported.^{56,57} Whole-breast ultrasound demonstrates a higher additional breast cancer detection rate than DBT, but increased FP examination rates associated with its use are not insignificant. High FP and biopsy rates

as high as 8.8% have been reported.⁵⁸ In addition, whole-breast ultrasound is largely a time-consuming, operator-dependent examination requiring technical expertise, which may limit utilization.

Breast MRI

Compared with digital mammography alone, supplemental breast MRI screening has been shown to increase diagnostic yield of small, node-negative tumors. Currently, it is the most sensitive supplemental screening technique, with an additional cancer detection rate of 15.5 per 1000 women screened. In addition, it has been shown to reduce interval cancer rates.⁵⁹ While the ACS recommends an annual breast MRI in women with a lifetime risk of breast cancer that is greater than 20%,⁶⁰⁻⁶² other women, including those with dense breasts and those at intermediate risk, may benefit from this technology. However, MRI screening is not routinely recommended for patients with average risk due to the increased risk of FP results and increased costs.⁶³ In women who may derive benefit from breast MRI but who are not considered high risk, a viable option may be abbreviated breast MRI, which has been associated with shortened imaging time and decreased costs, offering the potential to widen its availability to more patients. Overall, abbreviated breast MRI has been shown to achieve a cancer detection rate similar to that of full multiparametric MRI protocols without sacrificing diagnostic accuracy.^{64,65}

Conclusions and Future Directions

While national organizations differ in their recommendations related to initiation age and frequency of screening, there is consensus that, overall, routine mammography screening is beneficial in reducing breast cancer–specific mortality for average-risk women. While national organizations have not yet reached con-

sensus about screening in younger women, improvement in advanced imaging techniques will, clearly, further support efforts to increase the benefit-to-harm ratio of routine mammographic screening in women younger than 50 years. Technological advances, including those in artificial intelligence, may eventually improve risk stratification and further refine recommendations. Risk-based screening using more accurate tools appears to represent a viable solution for health care providers to determine which women require earlier and more frequent screening; these tools can also contribute to reducing the anxiety and FP results often associated with increased screening frequency in women at low risk.

Recently, the USPSTF published a draft research plan to be used to update their breast cancer screening recommendations; it will include study designs in addition to RCTs. The evaluation of racial disparities on breast cancer screening and outcomes will also be included in the updated USPSTF plan and marks an important step in consideration of additional risk factors in future screening recommendations.⁶⁶ This may be an indicator of eventual convergence of national screening recommendations; however, collaboration among stakeholders, with continued reassessment of data, will be needed to achieve true consensus among organizations. In turn, this will lead to improvements in clinical management of preventive care as well as reductions in patient confusion related to breast cancer screening.

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CARD Trial: JEV TANA combined with prednisone demonstrated improved efficacy outcomes when compared with a second androgen-signaling-targeted inhibitor (ASTI) (abiraterone or enzalutamide), in mCRPC patients who had previously received a docetaxel-containing regimen.¹

CARD Trial Design: A randomized, open-label, multicenter trial in patients (N=255) with mCRPC who previously received docetaxel and had progressed within 12 months on an androgen-signaling-targeted inhibitor—either abiraterone or enzalutamide. These patients were randomized 1:1 to JEV TANA (n=129) or abiraterone or enzalutamide (n=126); patients received abiraterone if they were previously treated with enzalutamide, or enzalutamide if they were previously treated with abiraterone.^{1,2}

Indication

JEV TANA is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing treatment regimen.

Important Safety Information

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. JEV TANA is contraindicated in patients with neutrophil counts of $\leq 1,500$ cells/mm³. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m².

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEV TANA infusion and administration of appropriate therapy. Patients should receive premedication. JEV TANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

CONTRAINDICATIONS

JEV TANA is contraindicated in patients with neutrophil counts of $\leq 1,500$ /mm³, patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80, and patients with severe hepatic impairment (total bilirubin $>3\times$ upper limit of normal (ULN)).

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression (BMS): BMS manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported. Monitor blood counts frequently to determine if initiation of G-CSF and/or dosage modification is needed. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. Caution is recommended in patients with hemoglobin <10 g/dl.

Increased Toxicities in Elderly Patients: Patients ≥ 65 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely.

Hypersensitivity Reactions: Severe hypersensitivity reactions can occur. Premedicate all patients with antihistamines, corticosteroids and H₂ antagonists prior to JEV TANA. Observe patients closely, especially during the first and second infusions. Discontinue JEV TANA immediately if severe hypersensitivity occurs and treat as indicated.

Gastrointestinal (GI) Adverse Reactions: Nausea, vomiting, and severe diarrhea may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials and mortality related to diarrhea has been reported. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Rehydrate and treat with antiemetics and antidiarrheals as needed. If experiencing grade ≥ 3 diarrhea, dosage should be modified.

GI hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants, and prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding. Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious GI toxicity and should be evaluated and treated promptly. JEV TANA treatment delay or discontinuation may be necessary.

HEAD-TO-HEAD CARD DATA MAY CHANGE HOW YOU SEE JEVTANA

2X

rPFS

(median 8.0 months [95% CI: 5.7-9.2] with JEVTANA [n=129] vs 3.7 months [95% CI: 2.8-5.1] with abiraterone or enzalutamide [n=126]; HR=0.54; 95% CI: 0.40-0.73; $P<0.0001$).¹

36%

relative reduction in risk of death

(median OS, 13.6 months [95% CI: 11.5-17.5] with JEVTANA [n=129] vs 11.0 months [95% CI: 9.2-12.9] with abiraterone or enzalutamide [n=126]; HR=0.64; 95% CI: 0.46-0.89; $P=0.008$).^{1,2}

At the cutoff date, 153 deaths were noted, with 70 (54.3%) in the JEVTANA group and 83 (65.9%) in the abiraterone or enzalutamide group.²

Renal Failure: Cases, including those with fatal outcomes, have been reported. Identify cause and manage aggressively.

Urinary Disorders including Cystitis: Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

Respiratory Disorders: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection. Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

Use in Patients with Hepatic Impairment: JEVTANA dose should be reduced for patients with mild (total bilirubin >1 to ≤ 1.5 x ULN or AST >1.5 x ULN) and moderate (total bilirubin >1.5 to ≤ 3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients. Administer JEVTANA 20 mg/m² for mild hepatic impairment. Administer JEVTANA 15 mg/m² for moderate hepatic impairment. Monitor closely.

Embryo-Fetal Toxicity: JEVTANA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA.

ADVERSE REACTIONS (ARs)

The most common all grades adverse reactions and laboratory abnormalities ($\geq 10\%$) with JEVTANA 20 mg/m² or 25 mg/m² are neutropenia, anemia, diarrhea, nausea, fatigue, asthenia, vomiting, hematuria, constipation, decreased appetite, back pain, and abdominal pain.

DRUG INTERACTIONS

Avoid coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the drug-associated risk.
- **Lactation:** The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of JEVTANA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.
- **Females and Males of Reproductive Potential:** Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA.

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

mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; rPFS=radiographic progression-free survival.

1. JEVTANA Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC. 2. de Wit R, de Bono J, Sternberg CN, et al; for the CARD Investigators. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381(26):2506-2518.

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SANOFI GENZYME

JEVTANA®
(cabazitaxel) injection, for intravenous use

Rx Only

Brief Summary of Prescribing Information

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. JEV TANA is contraindicated in patients with neutrophil counts of $\leq 1,500$ cells/mm³. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m² [see **Contraindications (4)** and **Warnings and Precautions (5.1, 5.2)**].

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEV TANA infusion and administration of appropriate therapy. Patients should receive premedication. JEV TANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see **Dosage and Administration (2.1)**, **Contraindications (4)**, and **Warnings and Precautions (5.3)**].

1 INDICATIONS AND USAGE

JEVTANA® is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of JEV TANA is based on calculation of the Body Surface Area (BSA), and is 20 mg/m² administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEV TANA treatment.

A dose of 25 mg/m² can be used in select patients at the discretion of the treating healthcare provider [see **Warnings and Precautions (5.1, 5.2)**, **Adverse Reactions (6.1)**, and **Clinical studies (14)** in the full prescribing information].

Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m² [see **Contraindications (4)** and **Warnings and Precautions (5.1, 5.2)**]. Premedicate at least 30 minutes prior to each dose of JEV TANA with the following intravenous medications to reduce the risk and/or severity of hypersensitivity [see **Warnings and Precautions (5.3)**]:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H₂ antagonist.

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed [see **Warnings and Precautions (5.3)**].

JEVTANA injection single-dose vial requires **two** dilutions prior to administration [see **Dosage and Administration (2.5)**].

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue JEV TANA dosing for adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEV TANA

Toxicity	Dosage Modification
Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriate medication including granulocyte-colony stimulating factor (G-CSF)	Delay treatment until neutrophil count is $>1,500$ cells/mm ³ , then reduce dosage of JEV TANA by one dose level. Use G-CSF for secondary prophylaxis.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is $>1,500$ cells/mm ³ , then reduce dosage of JEV TANA by one dose level. Use G-CSF for secondary prophylaxis.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of JEV TANA by one dose level.
Grade 2 peripheral neuropathy	Delay treatment until improvement or resolution, then reduce dosage of JEV TANA by one dose level.
Grade ≥ 3 peripheral neuropathy	Discontinue JEV TANA.

Patients at a 20 mg/m² dose who require dose reduction should decrease dosage of JEV TANA to 15 mg/m² [see **Adverse Reactions (6.1)**].

Patients at a 25 mg/m² dose who require dose reduction should decrease dosage of JEV TANA to 20 mg/m². One additional dose reduction to 15 mg/m² may be considered [see **Adverse Reactions (6.1)**].

2.3 Dose Modifications for Hepatic Impairment

- Mild hepatic impairment (total bilirubin >1 to $\leq 1.5 \times$ Upper Limit of Normal (ULN) or AST $>1.5 \times$ ULN): Administer JEV TANA at a dose of 20 mg/m².
- Moderate hepatic impairment (total bilirubin >1.5 to $\leq 3 \times$ ULN and AST = any): Administer JEV TANA at a dose of 15 mg/m² based on tolerability data in these patients; however, the efficacy of this dose is unknown.
- Severe hepatic impairment (total bilirubin $>3 \times$ ULN): JEV TANA is contraindicated in patients with severe hepatic impairment [see **Warnings and Precautions (5.8)** and **Clinical Pharmacology (12.3)** in the full prescribing information].

2.4 Dose Modifications for Use with Strong CYP3A Inhibitors

Concomitant drugs that are strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEV TANA with these drugs. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEV TANA dose reduction [see **Drug Interactions (7.1)** and **Clinical Pharmacology (12.3)** in the full prescribing information].

2.5 Preparation and Administration

JEVTANA is a cytotoxic anticancer drug. Follow applicable special handling and disposal procedures [see **References (15)** in the full prescribing information]. If JEV TANA first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin or mucous, immediately and thoroughly wash with soap and water.

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of JEV TANA infusion solution.

JEVTANA should not be mixed with any other drugs.

Preparation

Read this **entire** section carefully before mixing and diluting. JEV TANA requires **two** dilutions prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to overdose [see **Overdosage (10)**].

Note: Both the JEV TANA injection and the diluent vials contain an overflow to compensate for liquid loss during preparation. This overflow ensures that after dilution with the **entire contents** of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL JEV TANA.

Inspect the JEV TANA injection and supplied diluent vials. The JEV TANA injection is a clear yellow to brownish-yellow viscous solution.

Step 1 – first dilution

Each vial of JEV TANA (cabazitaxel) 60 mg/1.5 mL must first be mixed with the **entire contents** of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of JEV TANA.

When transferring the diluent, direct the needle onto the inside wall of JEV TANA vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam dissipate prior to continuing the preparation process.

The resulting initial diluted JEV TANA solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2.

Step 2 – second (final) dilution

Withdraw the recommended dose from the JEV TANA solution containing 10 mg/mL as prepared in Step 1 using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of JEV TANA is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL JEV TANA is not exceeded. The concentration of the JEV TANA final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Fully prepared JEV TANA infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion), or for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions.

Discard any unused portion.

Administration

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the JEV TANA first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

Use an in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) during administration.

The final JEV TANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

4 CONTRAINDICATIONS

JEVTANA is contraindicated in patients with:

- neutrophil counts of $\leq 1,500$ /mm³ [see **Warnings and Precautions (5.1)**]
- history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see **Warnings and Precautions (5.3)**]
- severe hepatic impairment (total bilirubin $>3 \times$ ULN) [see **Warnings and Precautions (5.8)**]

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

JEVTANA is contraindicated in patients with neutrophils $\leq 1,500$ /mm³ [see **Contraindications (4)**]. Closely monitor patients with hemoglobin <10 g/dL.

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported.

TROPIC Trial (JEVTANA 25 mg/m²)

In the TROPIC trial with G-CSF administered only at the investigator's discretion, 5 patients (1.3%) died from neutropenic infection (sepsis or septic shock); 4 of these patients died in the first 30 days of treatment. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. Grade 3–4 neutropenia occurred in 82% of patients treated with JEVTANA in the randomized trial [see *Adverse Reactions* (6.1)].

PROSELICA Trial (comparison of JEVTANA 20 mg/m² versus 25 mg/m²)

In the PROSELICA trial comparing two doses of JEVTANA, primary prophylaxis with G-CSF was not allowed, but could be administered after development of neutropenia at investigators' discretion. Eight patients (1%) on the 20 mg/m² arm and 15 patients (3%) on the 25 mg/m² arm died from infection; of these, 4 deaths on the 20 mg/m² arm and 8 deaths on the 25 mg/m² arm occurred within the first 30 days of treatment. Clinically important neutropenia-related events occurred and included febrile neutropenia (2.1% on 20 mg/m² arm and 9.2% on 25 mg/m² arm), neutropenic infection/sepsis (2.1% on 20 mg/m² arm and 6.4% on 25 mg/m² arm), and neutropenic deaths (0.3% on 20 mg/m² arm and 0.7% on 25 mg/m² arm).

Fewer patients receiving JEVTANA 20 mg/m² were reported to have infectious adverse reactions. Grade 1–4 infections were experienced by 160 patients (28%) on the 20 mg/m² arm and 227 patients (38%) on the 25 mg/m² arm. Grade 3–4 infections were experienced by 57 patients (10%) on the 20 mg/m² arm and 120 patients (20%) on the 25 mg/m² arm. Noninferiority for overall survival was demonstrated between these two arms [see *Adverse Reactions* (6.1)].

CARD Trial (JEVTANA 25 mg/m² + primary prophylaxis G-CSF)

In the CARD trial where JEVTANA 25 mg/m² was administered with primary prophylaxis of G-CSF, 1 patient (0.8%) died from sepsis within the first 30 days of treatment. Grade 1–4 neutropenia-related adverse reactions were experienced in 33 patients (26%). Grade 3–4 neutropenias were experienced by 26 patients (21%). Clinically important neutropenia-related events occurred and included febrile neutropenia (3.2%), neutropenic infection/sepsis (0.8%) and neutropenic deaths (0.8%) [see *Adverse Reactions* (6.1)].

Based on guidelines for the use of G-CSF and the adverse reactions profile of JEVTANA, primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features (older patients, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. Consider primary prophylaxis with G-CSF in all patients receiving JEVTANA 25 mg/m².

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed [see *Dosage and Administration* (2.2)].

5.2 Increased Toxicities in Elderly Patients

In a randomized trial (TROPIC), 2% of patients (3/131) <65 years of age and 6% (15/240) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. Patients ≥65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia. The incidence of the following grade 3–4 adverse reactions was higher in patients ≥65 years of age compared to younger patients; neutropenia (87% vs 74%), and febrile neutropenia (8% vs 6%).

In a randomized clinical trial (PROSELICA) comparing two doses of JEVTANA, deaths due to infection within 30 days of starting JEVTANA occurred in 0.7% (4/580) patients on the 20 mg/m² arm and 1.3% (8/595) patients on the 25 mg/m² arm; all of these patients were >60 years of age.

In PROSELICA, on the 20 mg/m² arm, 3% (5/178) of patients <65 years of age and 2% (9/402) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. On the 25 mg/m² arm, 2% (3/175) patients <65 years of age and 5% (20/420) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose [see *Adverse Reactions* (6) and *Use in Specific Populations* (8.5)].

In CARD, a death due to infection within 30 days of starting JEVTANA occurred in 0.8% (1/126) patient who was >75 years of age. There were 2.4% (3/126) of patients who died of causes other than disease progression within 30 days of the last JEVTANA dose; all of these patients were >75 years of age.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm.

Premedicate all patients prior to the initiation of the infusion of JEVTANA [see *Dosage and Administration* (2.1)]. Observe patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. JEVTANA is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see *Contraindications* (4)].

5.4 Gastrointestinal Adverse Reactions

Nausea, vomiting and severe diarrhea, at times, may occur. Deaths related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Antiemetic prophylaxis is recommended. Treat patients with rehydration, antidiarrheal or antiemetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥3 diarrhea [see *Dosage and Administration* (2.2)].

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with JEVTANA [see *Adverse Reactions* (6.2)]. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants,

JEVTANA[®]

(cabazitaxel) injection, for intravenous use

and patients with a prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding.

Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.

The incidence of gastrointestinal adverse reactions is greater in the patients who have received prior radiation. In PROSELICA, diarrhea was reported in 41% (297/732) of patients who had received prior radiation and in 27% (118/443) of patients without prior radiation. Of the patients who had previously received radiation, more patients on the 25 mg/m² arm reported diarrhea, compared to patients on the 20 mg/m² arm.

5.5 Renal Failure

In the randomized clinical trial (TROPIC), renal failure of any grade occurred in 4% of the patients being treated with JEVTANA, including four cases with fatal outcome. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy [see *Adverse Reactions* (6.1)]. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

5.6 Urinary Disorders Including Cystitis

Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation [see *Adverse Reactions* (6.2)]. In PROSELICA, cystitis and radiation cystitis were reported in 1.2% and 1.5% of patients who received prior radiation, respectively. Hematuria was reported in 19.4% of patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

5.7 Respiratory Disorders

Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome [see *Adverse Reactions* (6.2)]. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection.

Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

5.8 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.

JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) [see *Contraindications* (4)]. Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN) and moderate (total bilirubin >1.5 to ≤3.0 × ULN and any AST) hepatic impairment, based on tolerability data in these patients [see *Dosage and Administration* (2.3) and *Use in Specific Populations* (8.7)]. Administration of JEVTANA to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety.

5.9 Embryo-Fetal Toxicity

Based on findings in animal reproduction studies and its mechanism of action, JEVTANA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1) in the full prescribing information]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose (approximately 0.06 times the C_{max} in patients at the recommended human dose). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression [see *Warnings and Precautions* (5.1)]
- Increased Toxicities in Elderly Patients [see *Warnings and Precautions* (5.2)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.3)]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.4)]
- Renal Failure [see *Warnings and Precautions* (5.5)]
- Urinary Disorders Including Cystitis [see *Warnings and Precautions* (5.6)]
- Respiratory Disorders [see *Warnings and Precautions* (5.7)]
- Use in Patients with Hepatic Impairment [see *Warnings and Precautions* (5.8)]

6.1 Clinical Trials Experience

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

TROPIC Trial (JEVTANA 25 mg/m² compared to mitoxantrone)

The safety of JEVTANA in combination with prednisone was evaluated in 371 patients with metastatic castration-resistant prostate cancer treated in the randomized TROPIC trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA-treated patients and 3 (<1%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVTANA-treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single

dose of JEV TANA. Other fatal adverse reactions in JEV TANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common ($\geq 10\%$) grade 1–4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

The most common ($\geq 5\%$) grade 3–4 adverse reactions in patients who received JEV TANA were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Treatment discontinuations due to adverse reactions occurred in 18% of patients who received JEV TANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEV TANA group were neutropenia and renal failure. Dose reductions were reported in 12% of JEV TANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEV TANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2: Adverse Reactions* and Hematologic Abnormalities in $\geq 5\%$ of Patients in TROPIC

Adverse Reactions	JEV TANA 25 mg/m ² every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m ² every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
Blood and Lymphatic System Disorders				
Anemia [†]	98	11	82	5
Leukopenia [†]	96	69	93	42
Neutropenia [†]	94	82	87	58
Thrombocytopenia [†]	48	4	43	2
Febrile Neutropenia	7	7	1	1
Gastrointestinal Disorders				
Diarrhea	47	6	11	<1
Nausea	34	2	23	<1
Vomiting	22	2	10	0
Constipation	20	1	15	<1
Abdominal Pain [‡]	17	2	6	0
Dyspepsia [§]	10	0	2	0
General Disorders and Administration Site Conditions				
Fatigue	37	5	27	3
Asthenia	20	5	12	2
Pyrexia	12	1	6	<1
Peripheral Edema	9	<1	9	<1
Mucosal Inflammation	6	<1	3	<1
Pain	5	1	5	2
Renal and Urinary Tract Disorders				
Hematuria	17	2	4	<1
Dysuria	7	0	1	0
Musculoskeletal and Connective Tissue Disorders				
Back Pain	16	4	12	3
Arthralgia	11	1	8	1
Muscle Spasms	7	0	3	0
Metabolism and Nutrition Disorders				
Anorexia	16	<1	11	<1
Dehydration	5	2	3	<1
Nervous System Disorders				
Peripheral Neuropathy [¶]	13	<1	3	<1
Dysgeusia	11	0	4	0
Dizziness	8	0	6	<1
Headache	8	0	5	0

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Table 2: Adverse Reactions* and Hematologic Abnormalities in $\geq 5\%$ of Patients in TROPIC (continued)

Adverse Reactions	JEV TANA 25 mg/m ² every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m ² every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	12	1	4	<1
Cough	11	0	6	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	10	0	5	0
Investigations				
Weight Decreased	9	0	8	<1
Infections and Infestations				
Urinary Tract Infection [#]	8	2	3	1
Cardiac Disorders				
Arrhythmia ^P	5	1	2	<1
Vascular Disorders				
Hypotension	5	<1	2	<1

*Graded using NCI CTCAE version 3.

[†]Based on laboratory values, JEV TANA: n=369, mitoxantrone: n=370.

[‡]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

[§]Includes gastroesophageal reflux disease and reflux gastritis.

[¶]Includes peripheral motor neuropathy and peripheral sensory neuropathy.

[#]Includes urinary tract infection enterococcal and urinary tract infection fungal.

^PIncludes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.

PROSELICA Trial (comparison of two doses of JEV TANA)

In a noninferiority, multicenter, randomized, open-label study (PROSELICA), 1175 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were treated with either JEV TANA 25 mg/m² (n=595) or the 20 mg/m² (n=580) dose.

Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m² and 32 (5.4%) patients in the 25 mg/m² arm. The most common fatal adverse reactions in JEV TANA-treated patients were related to infections, and these occurred more commonly on the 25 mg/m² arm (n=15) than on the 20 mg/m² arm (n=8). Other fatal adverse reactions in JEV TANA-treated patients included cerebral hemorrhage, respiratory failure, paralytic ileus, diarrhea, acute pulmonary edema, disseminated intravascular coagulation, renal failure, sudden death, cardiac arrest, ischemic stroke, diverticular perforation, and cardiorenal syndrome.

Grade 1–4 adverse reactions occurring $\geq 5\%$ more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, decreased appetite, nausea, diarrhea, asthenia, and hematuria.

Grade 3–4 adverse reactions occurring $\geq 5\%$ more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, and febrile neutropenia.

Treatment discontinuations due to adverse reactions occurred in 17% of patients in the 20 mg/m² group and 20% of patients in the 25 mg/m² group. The most common adverse reactions leading to treatment discontinuation were fatigue and hematuria. The patients in the 20 mg/m² group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m² group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m² group, 128 patients (22%) had a dose reduced from 25 to 20 mg/m², 19 patients (3%) had a dose reduced from 20 to 15 mg/m² and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m². In the 20 mg/m² group, 58 patients (10%) had a dose reduced from 20 to 15 mg/m², and 9 patients (2%) had a dose reduced from 15 to 12 mg/m².

Table 3: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in PROSELICA

Adverse Reactions	JEVTANA 20 mg/m ² every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m ² every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
Blood and Lymphatic System Disorders				
Anemia [†]	99.8	10	99.7	14
Leukopenia [†]	80	29	95	60
Neutropenia [†]	67	42	89	73
Thrombocytopenia [†]	35	3	43	4
Febrile Neutropenia	2	2	9	9
Gastrointestinal Disorders				
Diarrhea	31	1	40	4
Nausea	25	0.7	32	1
Constipation	18	0.3	18	0.7
Vomiting	15	1.2	18	1
Abdominal pain	6	0.5	9	1
Stomatitis	5	0	5	0.3
General Disorders and Administration Site Conditions				
Fatigue	25	3	27	4
Asthenia	15	2	20	2
Edema peripheral	7	0.2	9	0.2
Pyrexia	5	0.2	6	0.2
Renal and Urinary Disorders				
Hematuria	14	2	21	4
Dysuria	5	0.3	4	0
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.7	19	1
Musculoskeletal and Connective Tissue Disorders				
Back pain	11	0.9	14	1
Bone pain	8	2	8	2
Arthralgia	8	0.5	7	0.8
Pain in extremity	5	0.2	7	0.5
Nervous System Disorders				
Dysgeusia	7	0	11	0
Peripheral sensory neuropathy	7	0	11	0.7
Dizziness	4	0	5	0
Headache	5	0.2	4	0.2
Infections and Infestations				
Urinary tract infection [‡]	7	2	11	2
Neutropenic infection [§]	3	2	7	6
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	5	0.9	8	0.7
Cough	6	0	6	0
Investigations				
Weight decreased	4	0.2	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	3	0	6.1	0

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Table 3: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in PROSELICA (continued)

Adverse Reactions	JEVTANA 20 mg/m ² every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m ² every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
Injury, Poisoning and Procedural Complications				
Wrong technique in drug usage process	0.3	0	5	0

*Grade from NCI CTCAE version 4.03.

†Based on laboratory values, JEVTANA 20 mg/m²: n=577, JEVTANA 25 mg/m²: n=590.

‡Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and urosepsis.

§Includes neutropenic sepsis.

CARD Trial (JEVTANA 25 mg/m² + primary prophylaxis with G-CSF)

The safety of JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis G-CSF was evaluated in a randomized, open-label study (CARD) in patients with metastatic castration-resistant prostate cancer who progressed after receiving prior docetaxel-containing regimens and abiraterone acetate or enzalutamide [see *Clinical Studies 14.3 in the full prescribing information*]. This study compared JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis with G-CSF to either abiraterone acetate 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily. Among patients receiving JEVTANA, 35% remained on treatment at 6 months and 4.7% remained on treatment at 12 months.

Serious adverse reactions occurred in 39% of patients receiving JEVTANA. Serious adverse reactions in ≥3% of patients included neutropenia (6%), infections (4.8%), and diarrhea, fatigue, pneumonia, and spinal cord compression (3.2% each). Deaths due to causes other than disease progression were reported in 2.4% of JEVTANA treated patients. Fatal adverse reactions in JEVTANA-treated patients were septic shock, urinary tract infection (UTI), and aspiration (0.8% each).

Treatment discontinuations due to adverse drug reactions occurred in 20% of patients who received JEVTANA and 8% of patients who received abiraterone acetate plus prednisone/prednisolone or enzalutamide. The adverse reactions leading to treatment discontinuation in >1% of patients in JEVTANA arm were nervous system disorders, infections/infestations, and gastrointestinal disorders.

Dose interruptions (alone or in combination with dose reduction) due to an adverse reaction occurred in 31% of patients receiving JEVTANA. Dose reductions were reported in 18% of JEVTANA-treated patients. The most frequent adverse reactions leading to dose interruption of JEVTANA were fatigue (7%) and hypersensitivity reaction (3.2%); the most frequent adverse reaction leading to reduction of JEVTANA were neutropenia and peripheral neuropathy (3.9% each).

Table 4 summarizes the adverse reactions and laboratory hematologic abnormalities in patients in CARD.

The most common (≥10%) adverse reactions were fatigue, diarrhea, musculoskeletal pain, nausea, infections, peripheral neuropathy, hematuria, constipation, abdominal pain, decreased appetite, vomiting, dysgeusia, edema peripheral and lower urinary tract symptoms.

The most common (≥10%) hematologic abnormalities were anemia, lymphopenia, neutropenia and thrombocytopenia.

Table 4: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in CARD Trial

Adverse Reactions	JEVTANA 25 mg/m ² + prednisone/ prednisolone + G-CSF (N=126)		Abiraterone + prednisone/ prednisolone or Enzalutamide (N=124)	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
Blood and Lymphatic System Disorders				
Anemia [†]	99	8	95	4.8
Lymphopenia [†]	72	27	55	17
Neutropenia [†]	66	45	7	3.2
Thrombocytopenia [†]	41	3.2	16	1.6

Table 4: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in CARD Trial (continued)

Adverse Reactions	JEVTANA 25 mg/m ² + prednisone/ prednisolone + G-CSF		Abiraterone + prednisone/ prednisolone or Enzalutamide	
	(N=126)		(N=124)	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
General Disorders and Administration Site Conditions				
Fatigue [†]	53	4	36	2.4
Edema peripheral [§]	11	0.8	10	1.6
Pyrexia	6	0	7	0
Pain	6	0	6	0.8
Gastrointestinal Disorders				
Diarrhea [¶]	40	4.8	6	0
Nausea	23	0	23	0.8
Constipation	15	0	11	0
Abdominal pain [#]	14	1.6	6	0.8
Vomiting	13	0	12	1.6
Stomatitis	8	0	1.6	0
Dyspepsia	4.8	0	2.4	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain [‡]	27	1.6	40	6
Pain in extremity	4.8	0	11	2.4
Bone fracture [§]	3.2	1.6	8	2.4
Infections and Infestations				
Infections [‡]	19	4	14	6
Nervous System Disorders				
Peripheral neuropathy [‡]	18	1.6	4.8	0
Dysgeusia	11	0	4	0
Polyneuropathy	6	1.6	0	0
Dizziness	0.8	0	4.8	0
Renal and Urinary Disorders				
Hematuria [‡]	16	0.8	6	1.6
Lower urinary tract symptoms [‡]	10	0	9	0
Acute kidney injury [‡]	5	2.4	10	4
Metabolism and Nutrition Disorders				
Decreased appetite	14	0.8	15	2.4
Hypokalemia	3.2	0	6	0
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)				
Cancer pain	8	1.6	9	2.4
Cardiac disorders[‡]	6	0.8	6	3.2
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonia [‡]	6	1.6	3.2	0.8
Dyspnea	6	0	2.4	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	6	0	0	0
Injury, Poisoning and Procedural Complications				
Fall	4.8	0	0	0
Vascular Disorders				
Hypertension [‡]	4	2.4	8	2.4

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Table 4: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in CARD Trial (continued)

Adverse Reactions	JEVTANA 25 mg/m ² + prednisone/ prednisolone + G-CSF		Abiraterone + prednisone/ prednisolone or Enzalutamide	
	(N=126)		(N=124)	
	Grade 1–4 %	Grade 3–4 %	Grade 1–4 %	Grade 3–4 %
Investigations				
Weight decreased	4	0	6	0
Psychiatric Disorders				
Insomnia	3.2	0	4.8	0

*Grade from NCI CTC version 4.0.

†Based on laboratory values - % calculated using the number of patients with at least one event(n) over the number of patients assessed for each parameter during the on-treatment period.

‡includes asthenia, fatigue, lethargy, malaise.

§includes lymphoedema, edema peripheral, peripheral swelling.

¶includes colitis, diarrhea, diarrhea hemorrhagic, gastroenteritis.

#includes abdominal pain, abdominal pain lower, abdominal pain upper, flank pain, gastrointestinal pain.

‡includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain.

§includes femoral neck fracture, pathological fracture, rib fracture, spinal compression fracture, sternal fracture, thoracic vertebral fracture.

¶includes bacteremia, bacteriuria, cellulitis, device related sepsis, Enterobacter sepsis, erysipelas, furuncle, influenza, influenza like illness, localized infection, oral fungal infection, perineal cellulitis, pulmonary sepsis, pyelocaliectasis, pyelonephritis, pyelonephritis acute, respiratory tract infection, respiratory tract infection viral, sepsis, septic shock, subcutaneous abscess, upper respiratory tract infection, urethritis, urinary tract infection, urinary tract infection bacterial, urosepsis, viral infection.

‡includes neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy.

§includes hematuria, cystitis hemorrhagic.

¶includes lower urinary tract symptoms, micturition urgency, nocturia, pollakiuria, urinary incontinence, urinary retention, dysuria.

‡includes acute kidney injury, blood creatinine increased, renal failure, renal impairment.

§includes aortic valve incompetence, aortic valve stenosis, atrial fibrillation, atrial flutter, atrioventricular block complete, atrioventricular block second degree, bradycardia, sinus bradycardia, tachycardia, cardiac failure, acute coronary syndrome, angina pectoris.

¶includes lower respiratory tract infection, lung infection, lung infiltration, pneumonia.

‡includes hypertension, hypertensive crisis.

Clinically relevant ≥ Grade 3 adverse reactions in <5% of patients who received JEVTANA in combination with prednisone and primary prophylaxis G-CSF: febrile neutropenia (3.2%), pulmonary embolism (1.6%), and neutropenic infection (0.8%). Hematuria

In study TROPIC, adverse reactions of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.

In study PROSELICA, hematuria of all grades was observed in 18% of patients overall.

In CARD, hematuria of all grades was observed in 16% of patients receiving JEVTANA.

Hepatic Laboratory Abnormalities

The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤1%.

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Gastrointestinal: Gastritis, intestinal obstruction.

Respiratory: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome.

Renal and urinary disorders: Radiation recall hemorrhagic cystitis.

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Cabazitaxel is primarily metabolized through CYP3A [see *Clinical Pharmacology* (12.3) in the full prescribing information]. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider

a 25% JEV TANA dose reduction [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3) in the full prescribing information].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of JEV TANA have not been established in females. There are no human data on the use of JEV TANA in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose [see *Data*].

Data

Animal data

In an early embryonic developmental toxicity study in rats, cabazitaxel was administered intravenously for 15 days prior to mating through day 6 of pregnancy, which resulted in an increase in pre-implantation loss at 0.2 mg/kg/day and an increase in early resorptions at ≥ 0.1 mg/kg/day (approximately 0.06 and 0.02 times the C_{max} in patients at the recommended human dose, respectively).

In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and embryo-fetal toxicity consisting of increased postimplantation loss, embryolethality, and fetal deaths when administered intravenously at a dose of 0.16 mg/kg/day (approximately 0.06 times the C_{max} in patients at the recommended human dose). Decreased mean fetal birthweight associated with delays in skeletal ossification was observed at doses ≥ 0.08 mg/kg. Cabazitaxel crossed the placenta barrier within 24 hours of a single intravenous administration of 0.08 mg/kg to pregnant rats at gestational day 17. A dose of 0.08 mg/kg in rats resulted in a C_{max} approximately 0.02 times that observed in patients at the recommended human dose. Administration of cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.

8.2 Lactation

Risk Summary

The safety and efficacy of JEV TANA have not been established in females. There is no information available on the presence of cabazitaxel in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats [see *Data*].

Data

Animal data

In a milk excretion study, radioactivity related to cabazitaxel was detected in the stomachs of nursing pups within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the C_{max} in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEV TANA [see *Use in Specific Populations* (8.1)].

Infertility

Males

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

8.4 Pediatric Use

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

JEV TANA was evaluated in 39 pediatric patients (ages 3 to 18 years) receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m² intravenously over 1 hour on Day 1 of a 21 day cycle in pediatric patients with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One patient had a partial response among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid premedication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearances by body surface area were comparable to those in adults.

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with JEV TANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients [see *Warnings and Precautions* (5.2)]. The incidence of grade 3–4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater compared to younger patients. The following grade 1–4 adverse reactions were reported at rates $\geq 5\%$ higher in patients 65 years of age or older compared to younger patients: fatigue (40% vs 30%), neutropenia (97% vs 89%), asthenia (24% vs 15%), pyrexia (15% vs 8%), dizziness (10% vs 5%), urinary tract infection (10% vs 3%), and dehydration (7% vs 2%), respectively.

In the PROSELICA study, the grade 1–4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients

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were diarrhea (43% vs 33%), fatigue (30% vs 19%), asthenia (22% vs 13%), constipation (20% vs 13%), clinical neutropenia (13% vs 6%), febrile neutropenia (11% vs 5%), and dyspnea (10% vs 3%).

In the CARD study, the grade 1–4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients were decreased appetite (16% vs 7%), hypertension (5% vs 0), constipation (18% vs 7%), paresthesia (6% vs 0), stomatitis (10% vs 3%), musculoskeletal pain (5% vs 0), fatigue (31% vs 23%), asthenia (30% vs 19%), and edema peripheral (11% vs 0). Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients < 65 years ($n=100$) and older ($n=70$).

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance $CL_{CR} < 15$ mL/min/1.73 m²), should be monitored carefully during treatment [see *Clinical Pharmacology* (12.3) in the full prescribing information].

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin > 1 to $\leq 1.5 \times$ ULN or AST $> 1.5 \times$ ULN) should have JEV TANA dose of 20 mg/m². Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety [see *Clinical Pharmacology* (12.3) in the full prescribing information]. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin > 1.5 to $\leq 3.0 \times$ ULN and AST = any) was 15 mg/m², however, the efficacy at this dose level was unknown. JEV TANA is contraindicated in patients with severe hepatic impairment (total bilirubin $> 3 \times$ ULN) [see *Contraindications* (4)].

10 OVERDOSAGE

There is no known antidote for JEV TANA overdose. Overdose has resulted from improper preparation [see *Dosage and Administration* (2.5)]. Read the entire section *Dosage and Administration* (2) carefully before mixing or diluting. Complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. Overdose has led to fatal outcome.

In case of overdose, the patient should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

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Emergency Fertility Preservation in a Young Woman With Non-Hodgkin Lymphoma

Mahmoud Salama, MD, PhD; Evgenia Isachenko, PhD; Gohar Rahimi, MD; Peter Mallmann, MD; and Vladimir Isachenko, PhD

THE CASE

A nulliparous woman, age 25 years, had received a diagnosis of non-Hodgkin lymphoma (NHL) and now presented with stage IIA diffuse large B-cell lymphoma (DLBCL). According to her hematological oncologist's treatment plan, chemotherapy had to start immediately (within 1 week), with the patient receiving 6 courses of the standard R-CHOEP21 regimen (rituximab 375 mg/m², cyclophosphamide 750 mg/m², hydroxydaunorubicin 50 mg/m², vincristine 1.4 mg/m², etoposide 100 mg/m², prednisone 40 mg/m²).

Due to potential risks of chemotherapy-induced gonadotoxicity and subsequent iatrogenic premature ovarian failure (POF) and fertility loss, the patient was referred to the reproductive medicine department for fertility preservation counseling and further management.

With the aforementioned findings, what should be recommended for fertility preservation in this patient?

- A. Embryo cryopreservation
- B. Oocyte cryopreservation
- C. Ovarian tissue cryopreservation
- D. Ovarian protection

TURN TO PAGE 333 for the answer and a discussion of this case by experts.

FIGURE. Surgical Technique of Laparoscopic Orthotopic Autotransplantation of Cryopreserved-Thawed Ovarian Tissue
(a, b, c, d) Formation of 2 separated peritoneal windows. **(e, f, g)** Insertion of 2 thawed ovarian fragments into 2 peritoneal windows. **(h)** Two ovarian fragments in 2 separated peritoneal windows at the end of autotransplantation. Bar = 5.0 mm

Discussion

NHL is the most common type of lymphoma, representing 88% of lymphoma cases, and typically occurs in adolescents and young adults more than in children.¹⁻³ In this patient, several challenges are raised regarding fertility preservation, including that:

(1) the patient is a young adult who wants to have children in the future. Overall survival (OS) in NHL has increased dramatically in recent years, especially in young adults (5-year OS, 69%; 10-year OS, 64%), giving the patient reason to look forward to her survivorship and possible parenthood. Still, OS is not 100%;

(2) the chemotherapy regimen R-CHOP21 includes the alkylating agent cyclophosphamide. Cumulative doses of aggressive alkylating agents can lead to gonadotoxicity and subsequent iatrogenic POF and fertility loss in most cases;

(3) if the patient's disease becomes relapsed or refractory, hematopoietic stem cell transplant (HSCT) may be indicated, in which case pre-HSCT myeloablative conditioning regimens will be used to induce immunosuppression. These regimens, including total body irradiation (TBI) and/or high-dose alkylating chemotherapy, lead to severe gonadotoxicity and subsequent iatrogenic POF and fertility loss in almost 100% of cases;

(4) DLBCL, the most aggressive (and most common) form of NHL, requires immediate chemotherapy initiation, leaving not enough time to apply several fertility preservation options;

(5) the traditional options of embryo cryopreservation and oocyte cryopreservation (*answer choices A & B*) need prior ovarian stimulation for some weeks to retrieve mature oocytes that are ready for in vitro fertilization, and that is not feasible in this patient due to lack of time;

(6) the innovative option of ovarian tissue cryopreservation and further autotransplantation (*answer choice C*) is suitable for emergency fertility preservation, but it is also risky due to possible contamination of ovarian tissue with lymphoma cells; and

CORRECT ANSWER: C. Ovarian tissue cryopreservation

(7) ovarian protection options (*answer choice D*), which include oophorectomy, pelvic shielding, and gonadotropin-releasing hormone (GnRH) analogues, are not reliable. Oophorectomy and pelvic shielding do not protect ovaries when systemic chemotherapy is used, while GnRH analogues have not been proven to protect the ovaries in patients with lymphoma, and they do not protect ovaries if TBI is used.¹⁻³

Management

To overcome the aforementioned challenges, we discussed options with the patient and decided that ovarian tissue extraction and cryopreservation (*answer choice C*) was the most suitable emergency fertility preservation option.⁴ The first step involved routine ovarian function tests; results were satisfactory and informed consent was obtained from the patient prior to the surgical procedure.

After coordinating with her hematological oncologists, the patient was admitted to our department and her right ovary was excised via laparoscopy 3 days before chemotherapy initiation. The excised ovarian tissue was transported to our laboratory within 10 minutes of extraction for further processing. As previously described by our group,⁵ the basal medium used for transport and dissection was composed of Leibovitz L-15 Medium supplemented with 5% dextran serum substitute. The temperature of the sample was maintained between 32 °C and 34 °C. Afterward, ovarian cortex was dissected into small medulla-containing strips, each measuring 0.5 to 1 cm square and 1 to 2 mm thick.

The ovarian tissue strips were then cooled at 5 °C for 24 hours, followed by cryopreservation using a slow freezing protocol. Cryopreservation began with placing the ovarian tissue strips for 30 minutes at room temperature in 20 mL of freezing medium, composed of basal medium supplemented with 6% dimethyl sulfoxide, 6% ethylene glycol, and 0.15 M sucrose. Then, each strip was placed into a standard 5-mL

cryovial previously filled with 4.5 mL freezing medium and frozen in an 14S freezer. The slow cooling profile began at -6 °C, then the cryovials were cooled from -6 °C to -34 °C at a rate of -0.3 °C/min. This slow-freezing protocol included an auto-seeding step at -6 °C. Finally, at -34 °C, the cryovials were plunged into liquid nitrogen (-196 °C) and stored for future use.

Prognosis

The patient plans to complete her anti-cancer therapy and become fit in recovery. When she would like to become pregnant, a new assessment of her endocrine and reproductive ovarian functions will be performed. If it is found that she has POF induced by the anticancer therapy, she can then use her cryopreserved ovarian tissue to attempt to restore her fertility. The success rate of ovarian tissue cryopreservation and further autotransplantation has been reported recently at around a 25% live birth rate per transplant.⁶ This success rate is promising but not conclusive; it seems to be case dependent and should be extrapolated with caution to the patient during counseling.

Technically, autotransplantation of cryopreserved-thawed ovarian tissue can be performed orthotopically into the remaining ovary, ovarian fossa, or broad ligament, or heterotopically into the subcutaneous space of the anterior abdominal wall or forearm. So far, the most successful method seems to be laparoscopic orthotopic autotransplantation of cortical ovarian tissue that was slowly cryopreserved then rapidly thawed.⁷ In the **Figure**, we show the standard surgical technique of laparoscopic orthotopic autotransplantation of cryopreserved-thawed ovarian tissue as performed in the Department of Obstetrics & Gynecology at the University of Cologne.⁸

To date, autotransplantation of cryopreserved-thawed ovarian tissue has resulted in more than 120 live births worldwide.⁹ Due to its promising results, ovarian tissue cryopreservation and fur-

Key Points

- NHL is the most common type of lymphoma (88%), usually occurring in adolescents and young adults more than in children.
- Unfortunately, most chemotherapy regimens for NHL, such as CHOP and R-CHOP, include alkylating agents (ie, cyclophosphamide) that are highly gonadotoxic.
- Each female fertility preservation option has both advantages and disadvantages; one may be more suitable than another for any given patient with lymphoma. A fertility preservation strategy should be individualized for each patient to have the best chance of being effective.
- Overall, ovarian tissue extraction and cryopreservation is the best emergency fertility preservation option available for lymphoma patients.
- Extracted ovarian tissue can be frozen for future autotransplantation or, alternately, processed in vitro for development of artificial ovary when autotransplantation is contraindicated due to high risk of ovarian tissue contamination with hematological malignant cells or MRD.

ther autotransplantation was announced in 2019 as an established option for female fertility preservation by the American Society for Reproductive Medicine.¹⁰

However, the possible contamination of ovarian tissue with hematological malignant cells or minimal residual disease (MRD) remains a significant, serious concern regarding autotransplantation of cryopreserved-thawed ovarian tissue in patients with hematological malignancies. According to the results of several studies, systematic reviews, and meta-analyses designed to assess the risk of reintroducing hematological malignant cells, autotransplantation of cryopreserved-thawed ovarian tissue should be strongly contraindicated in all types of leukemia (high risk), although it may be performed in Hodgkin lymphoma (mild risk) and in non-Hodgkin lymphoma (moderate risk). Although that recommendation is reassuring for patients with lymphoma, autotransplantation of cryopreserved-thawed ovarian tissue should still be considered with caution for fertility restoration. To reduce the risk of reintroducing malignant cells, several tests should be performed in advance, including histological examination, in vitro culture, immunohistochemistry, polymerase chain reaction, multicolor flow cytometry, and long-term xenografting of ovarian tissue portion.^{11,12}

When autotransplantation of cryopreserved-thawed ovarian tissue is contraindicated, that tissue could instead be processed in vitro for developing an artificial ovary; it would be an experimental option for fertil-

ity preservation and restoration. Artificial ovary is a novel experimental technology that aims to produce mature oocytes ready for in vitro fertilization through an ex vivo multistep strategy that includes sequential in vitro cultures of ovarian tissue, follicles, and oocytes.¹³⁻¹⁵ Artificial human ovary could be the safest option to preserve and restore fertility of young women and girls with hematological malignancies, especially when other fertility preservation options are not feasible or are contraindicated. Although artificial ovary has been successful in producing mature oocytes only in mice, to date, further research advances are likely to improve results and help to establish it successfully in humans.

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Mucinous Adenocarcinoma of the Appendix With Histologic Response to Neoadjuvant Chemotherapy: Review of Histologic and Clinical Spectrum of Epithelial Neoplastic Mucinous Lesions of the Appendix

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ABSTRACT: Appendiceal mucinous neoplasms are a rare and heterogeneous group of diseases with challenging clinical management decisions. They account for less than 1% of all cancers but their incidence is on the rise. Treatment is based on their stage and histology. Appendiceal neoplasms frequently metastasize inside the abdomen; this leads to tumor cell growth in the abdominal cavity, known as peritoneal carcinomatosis, and buildup of mucinous material, known as pseudomyxoma peritonei. While low-grade, early-stage tumors can be effectively treated with limited surgical resection, patients with low-grade, advanced-stage disease require peritoneal debulking and hyperthermic intraperitoneal chemotherapy. Therapeutic options for high-grade, advanced-stage mucinous tumors of the appendix have not been well established. Debulking surgery with hyperthermic intraperitoneal chemotherapy preceded and/or followed by systemic chemotherapy has been utilized based on some prospective but not randomized data. We present a case of mucinous adenocarcinoma of the appendix treated with neoadjuvant chemotherapy followed by cytoreductive surgery/hyperthermic intraperitoneal chemotherapy and adjuvant chemotherapy. Preoperative chemotherapy provided a favorable histologic response by converting initial mucinous appendiceal adenocarcinoma histology to a high-grade mucinous appendiceal neoplasm.

KEY WORDS: Appendiceal epithelial neoplasms, peritoneal carcinomatosis, hyperthermic intraperitoneal chemotherapy.

Case

A White woman, aged 65 years, presented with pain and fullness in her lower abdomen. Initial evaluation, including gynecologic exam and a CT scan of the abdomen and pelvis, showed a heterogeneous centrally located uterus with a possible semisolid hematoma, submucosal fibroid, or a polyp. Further evaluation with a transvaginal ultrasound reported a 3.5 × 3.8 × 2.7-cm uterine mass. Endometrial biopsy was negative for hyperplasia or malignancy. She was scheduled for a laparoscopic hysterectomy, which was delayed due to COVID-19 infection and patient nonadherence. Six months from the original presentation, she was taken to the operating room for laparoscopic hysterectomy. During the procedure, she was noted to have carcinomatosis throughout the abdomen with findings of omental caking. The procedure was changed to a diagnostic laparoscopy. The appendix appeared to be obliterated on the tip with inflammatory tissue and inflamed fat around the tip. The base of the appendix and cecum was visualized and looked normal. Peritoneal and omental biopsies were taken. Postprocedure restaging CT

scan of the abdomen and pelvis showed induration within the anterior peritoneal fat, representing peritoneal carcinomatosis and prominence of the appendix (**Figure 1A, 1B**). Upper and lower endoscopies were negative. Pathology of the left peritoneal wall and omentum biopsy was consistent with moderately differentiated adenocarcinoma with mucin present intracellularly. Immunohistochemical stains for pankeratin, cytokeratin 20, and CDX2 were positive (**Figure 2A, 2B, 2C**), whereas stains for synaptophysin, cytokeratin 7, calretinin, and PAX8 were negative. MLH1, PMS2, MSH2, and MSH6 protein expression was retained. A next-generation sequencing companion diagnostic assay showed no FDA-approved targetable alteration but 1 genomic finding of a pathogenic *BRAF* p.D594G mutation. PD-L1 immunohistochemistry analysis revealed tumor proportion score of 0% (FoundationOne CDx).

Based on the multidisciplinary tumor board consensus, she was treated with

neoadjuvant chemotherapy of 5-fluorouracil (5-FU), folinic acid, and oxaliplatin (FOLFOX) and bevacizumab (Avastin) for 6 cycles, to be followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). After neoadjuvant therapy, restaging CT scans revealed decreased omental fat stranding and a mildly dilated appendix. She underwent CRS with right hemicolectomy, small bowel resection, cholecystectomy, peritonectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy followed by HIPEC. Pathology revealed no evidence of tumor in the ileum or colon but high-grade appendiceal mucinous neoplasm (HAMN) involving the distal half of the appendix with invasion through the muscle wall into the adjoining periappendiceal fibroadipose tissue with extensive acellular mucin areas and focal signet-ring cell differentiation. Twenty-eight regional lymph nodes were negative. There was no lymphovascular or perineural invasion.

Uterus revealed focal adenomyosis and atypical hyperplasia of the endometrium but no evidence of mucinous neoplasm. Ovaries showed focal acellular mucin and focal low-grade mucinous neoplasm on the surface without penetration into the ovarian stroma. Pathologic stage was pT4a (tumor invades through the visceral peritoneum), pN0 (no regional lymph node metastasis), pM1b (intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells).

Introduction

Cancers of the appendix are extremely rare, with an estimated incidence of 0.15 to 0.9 per 100,000 people. Appendiceal mucinous neoplasms comprise 0.2% to 0.3% of appendectomy specimens. Affecting men and women equally, the average age of onset is between 50 and 55 years.^{1,2} Clinical presentation can be an appendicitis, a hernia filled with mucin, an abdominal/pelvic mass, or an incidental finding on some form of imaging study or during a surgical procedure for an unrelated indication. In women, these neoplasms often spread to the ovaries and can easily be confused with ovarian cancer. A majority (65%) of appendiceal tumors are of neuroendocrine origin. Adenocarcinomas (mucinous, nonmucinous, or signet-ring) constitute approximately 20% of these tumors.³ Treatment of appendiceal tumors depends on the extent and the histology of the disease. Systemic chemotherapy and cytoreductive surgery have long been used to treat macroscopic disease. Addition of HIPEC to CRS has become a novel approach to eradicate both macroscopic and microscopic residual tumor tissue in the abdomen. The treatment of appendiceal mucinous neoplasms has not been well defined, with controversies regarding pre- and postoperative chemotherapy, extent of surgery, role of early postoperative intraperitoneal chemotherapy, and HIPEC. Here, we present a review of the histologic and clinical spectrum of epithelial neoplastic mucinous lesions of the appendix.

TABLE. Epithelial Neoplastic Appendiceal Mucinous Lesions

Lesion	Characteristics
Hyperplastic polyp	Straight crypts with serration limited to luminal aspect of the crypt
Sessile serrated lesion without dysplasia	Distorted crypts with serration and crypt dilatation extending to crypt bases without cytological dysplasia
Sessile serrated lesion with dysplasia	Distorted crypts with serration and crypt dilatation extending to crypt bases with cytological dysplasia
Low-grade appendiceal mucinous neoplasm	Dysplastic epithelium that produces abundant mucin and characteristically exhibits expansile growth with a “pushing” border, which may or may not cause loss of the muscular components of the wall and mural fibrosis
High-grade appendiceal mucinous neoplasm	Cribriform growth, nuclear stratification to the surface of the epithelium, piling up of epithelial cells with high-grade features enlarged, hyperchromatic and pleomorphic nuclei, and abundant atypical mitotic activity
Adenocarcinoma	Infiltrative invasion pattern, typically with a marked desmoplastic stromal reaction
Mucinous adenocarcinoma	Extracellular mucin composing >50% of the cross-sectional area of lesion under the microscope
Signet-ring adenocarcinoma	Mucinous adenocarcinoma with signet-ring cells >50%

Histopathology

The appendix can be home to several distinctive benign and malignant pathologies with variable histologic classifications. Accurate histologic diagnosis of appendiceal neoplasms can be quite challenging. A complete examination of the entire specimen and rigorous evaluation of the appendiceal wall for any evidence of epithelial invasion are crucial to distinguish between adenocarcinomas and all other types of mucinous lesions. In 2016, an international panel of pathologists and clinicians—the Peritoneal Surface Oncology Group

International (PSOGI)—came together to categorize noncarcinoid epithelial tumors of the appendix.⁴ The current pathological classification schemes for neoplastic lesions of the appendix take into account both the variations of the histopathological appearance and the pattern of mural involvement in the epithelium. Neoplastic appendiceal mucinous lesions consist of serrated polyps (hyperplastic lesions with or without dysplasia), hyperplastic polyps, low-grade appendiceal mucinous neoplasms, high-grade appendiceal mucinous neoplasms, and mucinous adenocarcinomas with or without signet-ring cell carcinomas (**Table**).⁴⁻⁶

Historically, hyperplastic lesions have been considered to be reactive in nature. Most of them lack cytological atypia/dysplasia and typically involve the mucosa circumferentially. Serrated polyps of the appendix, with or without dysplasia, remain incompletely studied and are not always classified as neoplasms. Due to the lack of certainty about their biological nature, it has been suggested that these lesions should be classified as serrated polyps, either with or without epithelial dysplasia, rather than using the term adenoma, a term that would more specifi-

cally classify them as benign neoplasms.⁴ Low-grade appendiceal mucinous neoplasms (LAMNs) are true neoplasms,

Mucinous neoplasms of different anatomic sites can present with very similar histomorphologic appearances and frequently metastasize.

with dysplastic epithelium and expansile growth, but they lack overt infiltrative epithelial invasion of the appendiceal wall.⁵ They remain mostly confined to the muscularis propria. Due to their expansile growth pattern, however, they may push and cause the thinning and rupture of the appendiceal wall; this can result in spillage of cellular or acellular mucin, leading to pseudomyxoma peritonei (PMP). HAMNs are defined by the degree of epithelial

dysplasia, including cribriform growth, nuclear stratification to the surface of the epithelium, and hyperchromatic and pleomorphic nuclei with ample atypical mitotic activity.⁵ Mucinous adenocarcinomas of the appendix are described as infiltrative lesions with invasive pattern, and they typically have a marked desmoplastic stromal reaction. They can be mucinous or nonmucinous.⁶ Similar to other adenocarcinomas, they are categorized into well-, moderately, or poorly differentiated histologies. The presence of signet-ring cells denotes the poorly differentiated category. While well-differentiated mucinous adenocarcinomas are more likely to produce peritoneal spread with a clinical picture of PMP, the higher-grade tumors present with peritoneal carcinomatosis and distant metastasis.⁷

Immunohistochemistry and Molecular Diagnostics

Published in 2019, the 5th edition of current World Health Organization classification of appendiceal tumors is largely based on the tumors' histologic appearance and does not include their immunohistochemistry features or molecular pathology.⁸ Mucinous neoplasms of various sites,

including gastrointestinal, breast, lung, pancreas, and gynecologic, all can present with very similar histomorphologic appearances and frequently metastasize to the peritoneal surface, ovary, liver, or lung, which makes the identification of the primary site rather difficult.^{9,10} All mucinous neoplasms express low-molecular-weight cytokeratins (CKs), such as CK7, CK8, CK18, and CK20.^{10-12,13} While most mucinous neoplasms of the lower gastrointestinal tract express CK20, and most nongastrointestinal mucinous neoplasms express CK7, the reverse can be true: CK20 can be expressed in 47% to 83% of ovarian mucinous neoplasms, and CK7 can be expressed in 37% of appendiceal mucinous neoplasms.¹³⁻¹⁵ CDX2, a transcription factor regulating intestinal epithelial cell differentiation, is strongly expressed in gastrointestinal epithelial tumors, including appendiceal mucinous neoplasms.^{16,17} PAX8, a very specific ovarian mucinous neoplasm marker, is not commonly expressed in appendiceal neoplasms.¹⁸ SATB2, a 733-amino acid human DNA-binding protein involved in transcriptional regulation and chromatin remodeling, has been shown to have highly restricted expression to glandular cells lining the lower gastrointestinal tract, including appendiceal mucinous neoplasms.^{19,20}

Hyperplastic polyps and serrated lesions with or without dysplasia often have *KRAS* mutations but rarely *BRAF* mutations. LAMNs and HAMNs share high rates of *KRAS* and *GNAS* mutations but are usually wild-type for *BRAF*, *APC*, and *TP53*. Acquisition of *TP53* or *ATM* mutations may drive progression to a more advanced phenotype.^{21,22} Appendiceal adenocarcinomas frequently harbor mutations in *KRAS*, *GNAS*, *TP53*, *PIK3CA*, and *APC*. They can also have significant nuclear expression of β -catenin, loss of nuclear or nuclear and cytoplasmic expression of SMAD4, and loss of cytoplasmic membranous expression of E-cadherin. Recent identification of heterozygous *CTNNB1*, *NOTCH1*, and

FIGURE 1A. Induration within the anterior peritoneal fat representing peritoneal carcinomatosis

FIGURE 1B. Prominence of appendix possible underlying lesion

NOTCH4 germline mutations in LAMNs and HAMNs suggest a hereditary predisposition; however, microsatellite instability does not seem to have a role in the pathogenesis of epithelial appendiceal neoplasms and is rarely detected in these tumors.²³⁻²⁵ This patient's tumor contained a *BRAF* p.D594G pathogenic mutation. This *BRAF* mutation occurs within the highly conserved DFG motif of the kinase domain of the *BRAF* protein and is a class 3 inactivating mutation (kinase impaired). It is likely insensitive to vemurafenib (Zelboraf).^{26,27} However, it leads to increased activation of ERK signaling through CRAF-RAS pathways and has been postulated to be potentially responsive to receptor tyrosine kinase or MEK inhibition, although more studies are required.^{26,27} This mutation has been shown to occur somatically in a diverse set of tumors, including lung, melanoma, and colorectal cancers.²⁸

Clinical Presentation

Clinical presentation is usually asymptomatic or with rather nonspecific symptoms. Acute or chronic right lower quadrant abdominal pain, occasionally a palpable abdominal mass, or, less commonly, intermittent colicky abdominal pain and/or gastrointestinal bleeding associated

with intussusception of a mucocoele, can be initial presenting symptoms. Intestinal obstruction from mass effect, genitourinary symptoms, or acute abdomen from mucocoele rupture or sepsis are other possible presentations.²⁹⁻³¹ At the time of diagnosis, appendiceal cancer can be either localized to the appendix or may have already spread to the abdominal cavity and peritoneum. Because of the appendix's thin-wall anatomy, these neoplasms are more likely to have spread at the time of initial diagnosis. Mucinous lesions due to hyperplasia (serrated polyps) or retention cysts (simple mucocoeles) are not associated with recurrence once they rupture. However, when mucinous lesions due to LAMNs, HAMNs, or mucinous adenocarcinomas rupture, they usually present with progressive intraperitoneal spread, resulting in accumulation of both mucinous ascites and neoplastic cells—a clinical syndrome referred to as PMP.²

PMP was originally described as intraperitoneal mucinous spread from a ruptured cystadenoma (now called LAMN), seeding the peritoneum with mucus-producing cells and leading to progressive accumulation of copious amounts of mucinous fluid.³² The recent PSOGI pathologic classification redefined PMP as a complex syndrome with unique bio-

logical behavior and described 3 categories: low grade, high grade, and high grade with signet-ring cells. However, acellular mucin was classified separately.^{4,33} Appendiceal cancers rarely spread outside the abdominal cavity, and when they do, they are most commonly seen in poorly differentiated or signet-ring cell cancers.

Management

Surgical resection is the mainstay of treatment for all localized appendiceal mucinous neoplasms. Depending on the surgeon's experience, an open or laparoscopic standard appendectomy procedure with the inclusion of the cuff of the cecum, without intruding on the ileocecal valve, is preferable. If the base of the appendix is involved, a partial resection of cecum with preservation of the ileocecal valve, resection of the ileocecal valve, or resection of the entire right colon may be necessary to enable clear surgical margins. While by some groups right hemicolectomy has been proposed for tumors that involve the periappendiceal area, measure 2 cm or larger, have high-grade histology, or present with perforation, we prefer to reserve right colectomy for tumors with high-grade histology or documented lymph node involvement.³⁴ In patients presenting with clinically evident peritoneal

disease, a diagnosis can be established by percutaneous biopsy of a peritoneal lesion, and appendectomy can be deferred to the time of definitive cytoreductive surgery.

The initial surgery for ruptured but localized appendiceal mucinous lesions can be limited to an appendectomy/right hemicolectomy with careful inspection of the abdominal cavity and biopsy of any suspicious peritoneal lesions. During the surgery, the goal should be to minimize tumor cell implantation of the abdomen and surgical wounds by thorough washing, cleaning, and irrigation.³⁵ Advanced-stage, ruptured, and/or metastatic appendiceal mucinous neoplasms require additional surgical treatment with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at a specialized center.

Radical surgical removal of all abdominopelvic disease combined with administration of heated intraperitoneal chemotherapy has been developed as a comprehensive treatment approach for curative intent and has been utilized at centers with expertise in this disease.³⁶ Efficacy of this approach depends on the ability to accomplish minimal residual disease, described as tumor deposits smaller than 2 to 2.5 mm after the cytoreductive surgery. The 2 most commonly used intraperitoneal chemotherapeutic agents have been mitomycin and oxaliplatin. The results of the only randomized trial comparing these 2 chemotherapeutic agents showed no difference in efficacy: 3-year survival was 73% in both groups, with similar postoperative complications and long-term adverse effects.³⁷

Neoadjuvant Therapy

The role of preoperative chemotherapy in appendiceal mucinous neoplasms has been evaluated in nonrandomized studies with controversial results. This is mostly likely due to the retrospective nature of these studies, limitations of current imaging modalities, and lack of standard response criteria to assess peritoneal disease involvement.³⁸ Retrospective studies suggest that optimal CRS and HIPEC treatment without preoperative systemic chemotherapy is appropriate for low-grade appendiceal neoplasms. However, for high-grade appendiceal adenocarcinomas, systemic preoperative chemotherapy should be considered.³⁹ A potential advantage of neoadjuvant chemotherapy can be tumor volume reduction, which may lead to less extensive surgical procedures with improved organ preservation. Due to less-than-ideal accuracy of preoperative clinical exam and imaging studies, it has been difficult to assess the impact of neoadjuvant chemotherapy on the extent of cytoreductive surgery. Thus, surgical exploration offers the best approach to accurately evaluate this effect. In the results of one study, systemic chemotherapy administered prior to CRS/HIPEC for peritoneal mucinous adenocarcinoma of appendiceal origin showed a significant rate of histological response.⁴⁰ The results of another study showed that neoadjuvant treatment utilizing systemic 5-FU-based chemotherapy produced complete or near-complete pathologic responses in patients with peritoneal

FIGURE 2A. Omentum biopsy showing neoplastic cells dissecting through fibroadipose tissue (hematoxylin and eosin, 400x magnification)

FIGURE 2B. Immunoperoxidase stain for CDX2 (400x magnification)

FIGURE 2C. Immunoperoxidase stain for CK20 (400x magnification)

mucinous carcinomatosis, making limited surgical resections possible.⁴¹

Adjuvant and Systemic Therapy

Similarly, the impact of adjuvant chemotherapy following CRS/HIPEC in appendiceal mucinous neoplasms has not been well established due to rareness of this disease and lack of randomized trials. In the advanced-disease setting, available retrospective data suggest beneficial effect from systemic chemotherapy in moderate- to high-grade appendiceal mucinous tumors but not in low-grade mucinous neoplasms.⁴² In a large National Cancer Database study of 639 patients with metastatic low-grade mucinous appendiceal adenocarcinoma, systemic chemotherapy did not show beneficial effect on overall survival (OS).⁴³ However, in moderate- to high-grade mucinous tumors, signet-ring cell tumors, and all nonmucinous tumors of appendiceal origin, systemic chemotherapy has been shown to be beneficial.⁴⁴⁻⁴⁶ Similarly, in earlier studies from a small group of 17 patients with PMP, adjuvant therapy following cytoreductive surgery reported no OS benefit.⁴⁷ However, in patients with moderate- to high-grade or signet-ring cell appendiceal tumors, ad-

juvant chemotherapy following complete cytoreductive surgery provided significant OS benefit.⁴⁸ The molecular profile of this case does not match to any current FDA targeted therapy; however, the presence of the kinase-impaired *BRAF* mutation highlights the need for additional clinical trials targeting specific hotspot mutations in highly mutated oncogenes, especially in the setting of basket trials for rare diseases.

Conclusions

Appendiceal mucinous lesions are rare and have considerable heterogeneity and a rising incidence. They can be nonneoplastic (simple mucocoeles/retention cysts) or neoplastic (serrated polyps; low-grade or high-grade appendiceal mucinous neoplasms; mucinous adenocarcinomas with or without signet-ring cell features). Treatment is based on a lesion's histology and extent. While early-stage, low-grade tumors can be effectively treated with surgical resection of the primary site, advanced-stage disease requires peritoneal debulking surgery and intraperitoneal chemotherapy. Treatment of advanced-stage and high-grade tumors requires further prospective trials evaluating the role of pre- and postoperative chemotherapy as

an addition to CRS/HIPEC. Prospective randomized trials evaluating the impact of established chemotherapeutic agents, as well as the novel therapeutic agents targeting pathways involving *KRAS*, *p53*, *GNAS*, *SMAD4*, *APC*, *ATM*, *PIK3CA*, *FBXW7*, and *BRAF*, are desperately needed.

Outcome of the Case

After 6 cycles of neoadjuvant FOLFOX/bevacizumab systemic therapy, the patient underwent cytoreductive surgery; it revealed a histologic response mostly consisting of HAMN findings with focal signet-ring cell differentiation on her surgical debulking specimen. Following her recovery from CRS/HIPEC, she received 6 more cycles of adjuvant systemic therapy with FOLFOX/bevacizumab. Currently, she has no evidence of disease recurrence. ■

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

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placebo + trastuzumab + capecitabine¹**

Reduced risk of disease progression or death by 46%

Median PFS: 7.8 months (95% CI: 7.5–9.6) vs 5.6 months
(95% CI: 4.2–7.1); HR = 0.54 (95% CI: 0.42–0.71); $P < 0.00001$

Extended median OS by 4.5 months

Median OS: 21.9 months (95% CI: 18.3–31.0) vs 17.4 months
(95% CI: 13.6–19.9); HR = 0.66 (95% CI: 0.50–0.87); $P = 0.0048$

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

TUKYSAhcp.com

Indication

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

Select Safety Information

Warnings and Precautions

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

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

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

Please see full Important Safety Information on the following pages.

TUKYSA[®]
tucatinib
50 mg | 150 mg tablets

RAISING THE STANDARD FOR SURVIVAL

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*¹

4.5
MONTH
IMPROVEMENT
IN MEDIAN OS

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

Important Safety Information

Warnings and Precautions

- Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
- Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase $>5 \times$ ULN, 6% had an AST increase $>5 \times$ ULN, and 1.5% had a bilirubin increase $>3 \times$ ULN (Grade ≥ 3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

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

Adverse Reactions

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

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

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

In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

PRIMARY ENDPOINT*

PFS

46% reduction in the risk of disease progression or death¹

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

EXPLORATORY ANALYSIS*†

PFS AT 12 MONTHS

~3x as many patients were progression-free²

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

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

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

BICR = blind independent central review; CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; PPE = palmar-plantar erythrodysesthesia; RECIST = Response Evaluation Criteria in Solid Tumors.

Lab Abnormalities

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

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

Drug Interactions

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

- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

Use in Specific Populations

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

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. TUKYSA [Prescribing Information]. Bothell, WA: Seagen Inc. April 2020.
2. Murthy RK, Loi S, Okines A, et al. Supplemental appendix for: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382:597-609.

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TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA® (tucatinib) tablets, for oral use

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

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

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

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions

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

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

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

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

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

Severity	TUKYSA Dosage Modification
Diarrhea¹	
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.
Hepatotoxicity^{1,2}	
Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> 3 to 10 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)	Permanently discontinue TUKYSA.
ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN	Permanently discontinue TUKYSA.
Other adverse reactions¹	
Grade 3	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

Clinical Trials Experience

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

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

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

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

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates,

where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

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

Females and Males of Reproductive Potential

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

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

Contraception:

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

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

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

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

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

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

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

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EXPERT COMMENTARY ON THE PRODUCT PROFILE OF

Tazemetostat for Follicular Lymphoma

Product Profile

Drug name: Tazemetostat (Tazverik)

Date of approval: Initial approval, January 23, 2020 (unresectable epithelioid sarcoma); supplemental approval for follicular lymphoma, July 18, 2020

Initial indication: Accelerated approval for the treatment of adult patients with relapsed or refractory follicular lymphoma harboring *EZH2* mutation as detected by an FDA-approved test following at least 2 prior systemic therapies and for those who have no satisfactory alternative treatment options for their disease¹

Dosage and administration: 800 mg taken orally twice daily with or without food.

How supplied: 200-mg tablets

Pivotal clinical trial: Phase 1/2 study E7438-G000-101 (NCT0189757), cohorts 4 and 5

Companion diagnostic: cobas *EZH2* Mutation Test

Design of Study E7438-G000-101²

IWG-NHL, International Working Group, non-Hodgkin lymphoma.

REFERENCES

1. Tazverik. Prescribing information. Epizyme; 2020. Accessed May 21, 2021. <https://bit.ly/3oBelE6>
2. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(11):1433-1442. doi:10.1016/S1470-2045(20)30441-1
3. Epizyme announces the U.S. Food and Drug Administration lifts partial clinical hold on tazemetostat clinical program. News release. Epizyme; September 24, 2018. Accessed May 20, 2021. <https://bit.ly/3oAwnpZ>

COMMENTARY BY

Kelly Valla, PharmD, BCOP

Emory Healthcare
Winship Cancer Institute
Atlanta, GA

Q: Can you briefly describe the mechanism of action of tazemetostat?

Tazemetostat is a novel, first-in-class EZH2 inhibitor that is approved for follicular lymphoma. EZH2 is a histone methyltransferase that is abundant in the germinal center where follicular lymphoma originates. In about 20% of follicular lymphoma cases, *EZH2* is mutated. Tazemetostat is known to inhibit this mutated form of *EZH2*. What's unique is that tazemetostat can also inhibit the wild-type form, which is abundantly prevalent in the germinal center, as well, so we found that there is activity in both mutated *EZH2* as well as wild-type [disease]. It's worthwhile to note that response rates are higher in those with mutated *EZH2*.

Q: What are some of the biggest concerns with the drug's toxicity profile? Have any new safety concerns become more apparent with its use in the real-world treatment setting as opposed to what was seen in clinical trials?

In the clinical trial that garnered its approval by the FDA, tazemetostat was really well tolerated. Most toxicities were low-grade to grade 1/2—things like nausea and abdominal pain, [along with] some upper respiratory tract infections and other gastrointestinal disturbances. Overall, there were low rates of grade 3/4 toxicities, so this is a well-tolerated agent. [However, because] this agent

was [just] approved [about] a year ago, we still have a lot of information to gather about what some of its long-term toxicities may be in the real-world setting.

Q: How does tazemetostat's toxicity profile compare with those of other available agents?

In comparison with other treatment options—primarily other oral treatment options, such as the PI3K inhibitors, including idelalisib [Zydelig], duvelisib [Copiktra], copanlisib [Aliqopa], and even umbralisib [Ukoniq]—tazemetostat has a pretty favorable safety profile. We don't have to worry as much about immune-mediated adverse effects [AEs] as we do with the PI3K inhibitors; those AEs can really limit their use in patients with follicular lymphoma. Additionally, the efficacy of tazemetostat compares favorably with these agents, showing high overall response rates. What's interesting is that even though patients may first achieve a partial response, and it may take a while [to do so], we can see deepening of the response with tazemetostat over time.

Q: Can you discuss the risk of secondary malignancies with this agent?

In early phases of investigation of tazemetostat, the FDA did halt, or pause, investigation of this agent due to a case of T-cell lymphoblastic lymphoma [T-LBL] in a pediatric patient.³ Secondary malignancies are of concern, [but] they did lift

the halt. [The label of tazemetostat] has a note that it can cause secondary malignancies, including T-LBL and T-cell acute lymphoblastic leukemia, as well as myelodysplastic syndrome [MDS], and acute myeloid leukemia [AML].

In younger patients, we're more concerned about those T-cell malignancies due to the active thymus. In adults, these really haven't been seen to date, but cases of MDS and AML have been, although at very low rates. A few questions still need to be answered regarding whether or not tazemetostat is the sole contributor to the secondary malignancy or if prior treatment history was at play at all. Also, there may be a link [between] a longer duration of treatment with tazemetostat and the risk of secondary malignancies. Needless to say, the loss of function of *EZH2* [due to] long-term inhibition can be pathogenic for MDS or myeloproliferative neoplasms.

Q: Are dosing modifications common with this agent?

Dosing modifications are not required [or] incredibly common. From an AE standpoint, patients require dose modification at very low rates. Only about 9% of patients in the trial that [supported the] FDA approval required dose modification [and] only about 8% discontinued due to treatment-related toxicities. However, almost a third of patients did need some sort of treatment pause, and that is something to watch out for. However, overall, modifications are not common and are clearly outlined in the prescribing information.

Q: What major drug interactions, if any, should clinicians be aware of with tazemetostat?

Tazemetostat is a CYP3A4 substrate, so worrying about strong and moder-

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In comparison with other treatment options—primarily other oral treatment options, such as the PI3K inhibitors... tazemetostat has a pretty favorable safety profile.

ate CYP3A4 inhibitors is of importance here. Strong CYP3A4 inhibitors should be avoided at all costs. However, moderate CYP3A4 inhibitors, if absolutely necessary, can be given with tazemetostat by following dose modification guidelines that are found in the package insert. Tazemetostat is also a weak inducer of CYP3A4, so it may affect agents that are substrates of this same enzyme.

You would also want to counsel patients about some food products and herbal supplements: Exotic citrus fruits such as grapefruit, pomegranate, and

Seville oranges might affect the metabolism of tazemetostat, as might herbal supplements like St John's wort.

Q: Have any barriers to administration or receipt of this drug come up since the agent's approval that would get in the way of prescribing this to a patient?

In the age of specialty medications and oncology, these are concerns for patients [who are] thinking about access to medications. Use of a specialty pharmacy here is paramount, [as is] making sure that pri-

or authorizations and any sort of questionnaires are completed accurately so that we can get insurance approval—this many include documentation based on whether or not the patient has *EZH2* mutated vs wild-type [disease]. Making sure we're following the FDA label indication is essential to rapid payer approval.

Also, Epizyme, the manufacturer, has a pretty robust and multifaceted program for patient assistance. That includes co-pay cards for commercially insured patients as well as other patient-assistance [arrangements] for uninsured or underinsured patients. [This program may] bridge therapy for patients who lose or change coverage and may be under financial hardship. ■

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

Kelly Valla, PharmD, BCOP, Discusses Tazemetostat for Follicular Lymphoma

...on Comparing Tazemetostat With Other Available Agents for Follicular Lymphoma
[Cancernetwork.com/Valla_tazemetostat1](https://cancernetwork.com/Valla_tazemetostat1)

...on Drug Interactions of Tazemetostat
[Cancernetwork.com/Valla_tazemetostat2](https://cancernetwork.com/Valla_tazemetostat2)

In an interview with *ONCOLOGY*®, Kelly Valla, PharmD, BCOP, offers a comprehensive review of real-world treatment considerations of tazemetostat as therapy for adult patients with relapsed or refractory follicular lymphoma harboring *EZH2* mutation after 2 or more prior systemic therapies or with no satisfactory alternative treatment options for their disease. She discusses toxicities associated with the agent, its mechanism of action, dosing modifications, drug interactions, and barriers to therapy administration.

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The National Comprehensive Cancer Network® (NCCN®) now recognizes Breast Cancer Index (BCI) as the only test that predicts benefit from extended endocrine therapy in early-stage, HR+ breast cancer.¹ That means avoiding overtreatment for the patients for whom endocrine therapy beyond 5 years has no impact.²⁻⁷ And informing treatment for the patients it can help.²⁻⁷

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Breast Cancer Index Intended Uses and Limitations

The Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test is indicated for use in women diagnosed with hormone receptor-positive (HR+), lymph node-negative (LN-) or lymph node-positive (LN+; with 1-3 positive nodes) early-stage, invasive breast cancer, who are distant recurrence-free. The BCI test provides: 1) a quantitative estimate of the risk for both late (post-5 years from diagnosis) distant recurrence and of the cumulative distant recurrence risk over 10 years (0-10y) in patients treated with adjuvant endocrine therapy (LN- patients) or adjuvant chemoendocrine therapy (LN+ patients), and 2) prediction of the likelihood of benefit from extended (>5 year) endocrine therapy. BCI results are adjunctive to the ordering physician's workup; treatment decisions require correlation with all other clinical findings. This test was developed and its performance characteristics determined by Biotheranostics, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration. This test is used for clinical purposes. It should not be regarded as investigational or for research. How this information is used to guide patient care is the responsibility of the physician. Biotheranostics is certified under the Clinical Laboratory Improvement Amendments of 1988 to perform high complexity clinical laboratory testing.

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Individualizing Extended Adjuvant Therapy in HR+ Breast Cancer

Vijayakrishna (V.K.) Gadi, MD, PhD

University of Illinois, Chicago

Reshma L. Mahtani, DO

University of Miami Health System,
Deerfield Beach, FL

Gadi and Mahtani shared clinical experiences and perspectives on adjuvant therapy in HR+ breast cancer. This article provides highlights of the discussion.

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In the setting of hormone receptor-positive (HR+), HER2-negative, lymph node-negative (pN0) breast cancer, postsurgical antiestrogen therapy (ie, adjuvant endocrine therapy) with tamoxifen or an aromatase inhibitor is recommended for at least 5 years to reduce the risk of recurrence and extend the disease-free survival (DFS) interval.¹ However, some patients benefit from extending adjuvant endocrine therapy beyond 5 years.¹ Identifying which patients are most likely to benefit from extended therapy while sparing others from prolonged drug exposure may become easier with a new recommendation from the National Comprehensive Cancer Network (NCCN). This was the topic of discussion in a recent *OncView*TM, which featured insights and perspectives from Vijayakrishna (V. K.) Gadi, MD, PhD, professor and director of medical oncology, Department of Medicine, associate director, translational oncology, University of Illinois, Chicago; and Reshma L. Mahtani, DO, associate professor of clinical medicine, Division of Hematology/Oncology; coleader of the Breast Cancer Program; director of community outreach, Sylvester Comprehensive Cancer Center, University of Miami Health System, Deerfield Beach, Florida.

NCCN-Recommended Assays

In the April 2021 version of its breast cancer guidelines, the NCCN endorsed the Breast Cancer Index (BCI) assay as one that can be treatment predictive in the HR+ setting.¹ Individualized precision medicine continues to gain traction in

breast cancer because of several commercially available bioassays, including the 21-gene (Oncotype Dx), 70-gene (MammaPrint), 50-gene (Prosigna), 12-gene (EndoPredict), and BCI gene expression assays.¹ Although all these assays are recommended in NCCN guidelines as prognostic indicators to complement the TNM (tumor, node, metastasis) staging system and biomarker information, not all are predictive of treatment benefit associated with the pursuit of a particular therapeutic course.¹

“Genomic assays really aim to give us a more in-depth understanding of the biology of the individual’s tumor by looking at various levels of gene expression,” explained Mahtani. “The information can aid in further prognostication beyond clin[ical]-path[ological] factors alone, and most importantly, [it] can help us predict the benefit, or sometimes the lack of benefit, of our treatments such as chemotherapy and endocrine therapy.”

In the realm of bioassays, Gadi explained that, if a test is prognostic, it provides information about “the chance the cancer could come back,” but if it is predictive, it provides “the chance that an intervention...works versus doesn’t work.” Tests with predictive ability refer to whether adjuvant chemotherapy should be recommended after surgery, but in the case of the BCI assay, its predictive ability references whether adjuvant endocrine therapy should be extended beyond 5 years. This makes

the BCI unique among currently recommended bioassays used for those with HR+ breast cancer.

“Many of us forget that not too long ago, we were giving chemotherapy to the majority of women with localized breast cancer regardless of lymph node status, menopausal status, or [hormone] receptor status,” said Mahtani. “[However], the availability of genomic assays...has really allowed us to tailor our treatments much better and...spare women the toxicities for those who are...not benefiting from our treatments.”

Adjuvant Endocrine Therapy

Gadi explained that adjuvant endocrine therapy consists of either an agent that blocks estrogen receptors directly or an agent that blocks the enzyme responsible in the final step of converting pre-estrogens into active estrogens. The specific agents that can accomplish these goals are tamoxifen and aromatase inhibitors, respectively.¹ To provide protection against early-stage recurrence (defined as disease recurrence ≤ 5 years after diagnosis), patients should receive one of these agents for at least 5 years following surgery. However, because some patients are at risk for late-stage disease recurrence (defined as disease recurrence > 5 years after diagnosis), these patients should continue receiving endocrine therapy for an additional 5 years to extend their DFS interval.² Because only 3% to 5% of women with early-stage HR+ disease benefit from extended endocrine therapy, identifying these patients is important. Not only can doing so protect this small subset of patients, but it can also help to avoid overtreatment in the remaining 95%.²

“The thinking...in considering [extended adjuvant hormonal therapy] is that, for some patients, the risk of recurrence continues well beyond the 5 years post diagnosis,” explained Mahtani. She went on to state, “We typically make [the]

Although many studies are being done with novel drugs, “in terms of diagnostics, it’s a little bit different. We still don’t have a good sense of who really benefits.”

— Vijayakrishna (V. K.) Gadi, MD, PhD

decision on whether to extend...based on clinical-pathological features such as nodal status and tumor size. [Certainly] this information can be prognostic, but the challenge is that [clinical-pathological factors are] not always reliable, and that’s where we really need an additional piece of information.”

Extending Adjuvant Endocrine Therapy in Early-Stage HR+ Breast Cancer

In the April 2021 edition of the NCCN breast cancer guidelines, the BCI assay consensus statement was changed from having undetermined predictive value to being affirmatively predictive of benefit for extending adjuvant endocrine therapy in those with early-stage HR+ breast cancer, and it was assigned a category 2A recommendation.¹ Mahtani and Gadi both pointed out that the BCI assay is currently the only gene expression assay that has consensus from the NCCN for being able to predict the benefit of extending endocrine therapy.

The nature of cancers that recur early (within the first 5 years after diagnosis) is that they tend to be highly proliferative, explained Gadi. Thus, the treatment approach has been to maximize therapy within that 5-year window to prevent recurrence by utilizing multiple layers of systemic therapy up front, including chemotherapy, novel biologics, and antiestrogen therapies. Conversely, Gadi

noted how cancers that recur later (10-25 years after diagnosis) tend to be “lurking,” “slumber[ing],” or “hibernating” in the background for 1 or more decades, until they are “turn[ed] on again.” Extending endocrine therapy past the initial 5 years may be of benefit to prevent cancers that recur later.

The “benefit [of extending endocrine therapy] really should be balanced against the toxicities that many women who are on extended therapy face,” said Mahtani. “Many of these women are suffering with [adverse] effects...[that] significantly impact quality of life... and it’s a very frequent discussion I have in my clinic about how to manage the toxicities of endocrine therapy.”

The BCI can inform treatment decisions by identifying the subset of patients who should continue receiving adjuvant endocrine therapy past 5 years, which spares the remaining patients from extended drug exposure.

The Utility of the BCI Assay

The BCI assay is a combination of 2 genomic profiles: the *HOXB13:IL17BR* expression ratio (known as the H:I ratio) and the Molecular Grade Index (known as MGI).¹ Those with a BCI score of 5.1 to 10 are considered high risk, and extending endocrine therapy has demonstrated significant improvement in DFS according to a retrospective analysis of data collected from 3 major trials: the MA.17, Trans-aT-

Tom, and IDEAL trials.¹ In patients in the low-risk category, “there was minuscule benefit [of] extend[ing] therapy,” explained Gadi. “[The] benefits were so low, yet there were all these risks from being on therapy for longer.” On the other hand, for patients with high-risk disease who extended therapy, “there was a 65% reduction in the risk of disease [recurrence].”

Gadi noted that, although these retrospective analyses have been highly insightful, these results need to be proved in prospective trials moving forward. He explained, “The hope is that if we can more carefully select patients who are going to benefit from being on the therapy for longer, then...we can lower the burden of women recurring later” by sparing them from toxic and harmful therapies needed to treat the late-stage recurrence down the road.

Mahtani added, “The [BCI] assay has been shown to provide an individualized risk of distant recurrence from years 5 to 10, and this information really can help inform the patients’...[and] physicians’ perception of their risk of recurrence above and beyond clinical-path[ological] features. I’d say that I’ve been really surprised in my practice to see some of the assumptions that I’ve made using clinical-path[ological] features be challenged by the results of the BCI, which have shown some patients with N1 disease to have a low rate of distant recurrence, while at the same time, [there have been] some patients where I expected their prognosis would be quite good...[because they were] N0, ... [but they came] back with higher risk of distant recurrence. So I think [the BCI] has been very useful in my practice to help patients make this decision.”

Although the NCCN guidelines state that there are currently limited data regarding the utility of BCI in HR+, HER2-negative, lymph node-positive disease (pN+) disease, secondary anal-

yses of the MA.17, Trans-aTTom, and IDEAL trials showed that patients who had a high BCI score and pN+ disease experienced significant improvements in DFS when adjuvant endocrine therapy was extended.¹ “This [NCCN] recommendation [to use the BCI expression assay to predict benefit of extended endocrine therapy] includes both node-negative and node-positive patients,” clarified Mahtani.

When asked about how he utilizes genomic assays in his clinical practice, Gadi responded that he typically orders the 70-gene or the 21-gene assay around the time of surgery because these are predictive of whether adjuvant (postsurgical) chemotherapy is likely to provide benefit.¹ Near the 5-year mark post surgery, Gadi then adopts a shared decision-making approach with regard to ordering the BCI assay. “I have a personal preference to practice medicine in a shared decision-making model. So that, for me, means going through the pros and cons of the [BCI] test and saying, ‘OK, this is the information we are going to unearth,’ and ‘Are you going to be comfortable knowing that and acting upon that?’ And if a patient says to me... ‘I don’t care what the test says—I’m not doing those things,’ then I’m not going to burden them with that information.”

Unmet Needs

When queried about unmet needs in the treatment of early-stage HR+ breast cancer, Gadi noted that “we need better

“[Although] we’ve made considerable progress, we still have quite a bit of work to do.”

— Reshma L. Mahtani, DO

[antiestrogen] drugs.” He explained that there are already some novel antiestrogen therapies that are being developed and tested in the metastatic realm. The hope is that they will also prove their utility in treatment of early-stage disease as well. Gadi also noted that, although many studies are being done with novel drugs, “in terms of diagnostics, it’s a little bit different. We still don’t have a good sense of who really benefits.” This is why tests specifically designed to provide information about these things are needed, he explained. Even with the BCI assay, Gadi commented, there is still a subset of patients “[for whom] we know that the risk is a little higher, ...but the test predicts no benefit from therapy,... [so] what do we do for these patients, and how can we keep them out of harm’s way with recurrences?”

Given that the NCCN endorses the BCI, Mahtani concluded by saying, “I think it will have a big impact in that patients [who] are not really benefiting from [extended] endocrine therapy may choose not to continue that treatment and not suffer those [adverse] effects.” She added that, although “we’ve made considerable progress, we still have quite a bit of work to do.” ■

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Advances in Later-Line Management of Relapsed/Refractory Follicular Lymphoma

The goal of this **CancerNetwork® OncView™** program, “Advances in Later-Line Management of Relapsed/Refractory Follicular Lymphoma,” was to discuss treatment options for relapsed or refractory follicular lymphoma.

Clinical experiences and perspectives were shared by faculty panelist Sameh Gaballa, MD. This article provides highlights of the discussion.

Sameh Gaballa, MD
Moffitt Cancer Center
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For more information, watch the full program at <https://www.cancernetwork.com/oncview/management-of-r-r-follicular-lymphoma>.

Follicular lymphoma (FL) is an indolent B-cell lymphoproliferative disease that accounts for approximately 20% of all cases of non-Hodgkin lymphoma.¹ CancerNetwork® met with Sameh Gaballa, MD, of Moffitt Cancer Center in Tampa, Florida, to discuss the management of relapsed/refractory (R/R) FL. Gaballa said that patients with FL are not expected to be cured after frontline therapy. Most patients relapse, although he noted that approximately 80% of patients remain in remission for 2 or more years after chemoimmunotherapy and have a very good prognosis. Patients who experience progression of disease within 2 years after frontline (POD24) have a worse prognosis.

Treatment of Relapsed/Refractory Follicular Lymphoma

The treatment goal with R/R FL is to control symptoms, said Gaballa. “You’re not going to cure [patients with R/R FL],” he said. “If they have bulky disease, if they have symptomatic disease, then those are the patients who you would consider treatment for. Otherwise, you could just observe them.”

Regarding first-line treatment of R/R FL, Gaballa favors chemoimmunotherapy, such as rituximab and bendamustine, for most patients. He typically reserves R-CHOP (a chemotherapy regimen including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for patients who he thinks may have transformed disease, and he may offer monotherapy rituximab monotherapy to those who have low bulky disease.

Selection of second-line therapy and beyond may not be so straightforward. “Beyond first line, there is not a 1-standard-of-care regimen,” Gaballa said, noting that the rituximab plus lenalidomide combination is now commonly used in the second line. For third line, there are now several options, including PI3K inhibitors (eg, idelalisib, copanlisib, duvelisib, umbralisib), an EZH2 inhibitor (tazemetostat), and chimeric antigen receptor T-cell therapy, which was just recently FDA approved for third line.

Treatment selection

Gaballa selects treatment for R/R FL on the basis of several patient-related and disease-specific factors, such as patient age, comorbidities, and POD24 status. To choose among the many third-line options, Gaballa discusses all the options with the patients, covering adverse events, route of administration, and monitoring requirements. For example, he noted that copanlisib is administered intravenously, whereas the other PI3K inhibitors that are FDA approved for R/R FL in the third line are oral. Umbralisib has a better safety profile than that of earlier PI3K inhibitors, and the EZH2 inhibitor tazemetostat is very well tolerated and does not require a lot of monitoring.

At this time, molecular testing is not necessary to determine optimal treatment—even for use of tazemetostat. “If [tazemetostat is used for a] later line of therapy and you think there [are] no good

Watch the full video at [CancerNetwork.com](https://www.CancerNetwork.com).

Sameh Gaballa, MD
Moffitt Cancer Center

Kristie L. Kahl
Editorial Director, CancerNetwork®

Learn more about treatment options for relapsed/refractory follicular lymphoma and perspectives shared by faculty panelist Sameh Gaballa, MD.

alternatives, you don't have to do the testing," Gaballa said, alluding to the approval of tazemetostat to treat patients with and without an *EZH2* mutation. He noted that molecular testing to identify the *EZH2* mutation could add value if a clinician wanted to use tazemetostat as an earlier line of treatment.²

Conclusions

Looking ahead, Gaballa stated that the biggest unmet need for FL beyond the second-line setting involves POD24 patients, who have a lower survival rate than other R/R FL patients. "It [will] be great if we have better tools to risk stratify these patients and identify [them] early on," he said. He also noted the potential benefit of moving some of the approved third-line therapies (eg, tazemetostat) and regimens to earlier lines of therapy or combining them with other agents. ■

"Beyond first line, there is not a 1-standard-of-care regimen. Rituximab plus lenalidomide combination is now commonly used in the second line," Gaballa said. For third line, there are now several options, including PI3K inhibitors (eg, idelalisib, copanlisib, duvelisib, umbralisib), an EZH2 inhibitor (tazemetostat), and chimeric antigen receptor T-cell therapy, which was just recently FDA approved for third line.

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Management of Genitourinary Malignancies

Around the Practice is a monthly urologic virtual live event featuring case reviews from multidisciplinary experts, presented by *Urology Times*[®] in partnership with the Large Urology Group Practice Association. On April 21, 2021, a panel convened to discuss cases involving high-risk renal cell carcinoma

(RCC) and metastatic castrate-resistant prostate cancer. What follows is an edited portion of the panel's conversation regarding the RCC case. The panelists for this case included moderator Raoul S. Concepcion, MD, FACS; Vahan Kassabian, MD; Paul J. Kim, MD; and Abhishek Tripathi, MD.

High-risk renal cell carcinoma

CASE 1

- A 51-year-old man presented with left flank pain and groin hematuria.
- Past medical history indicates diabetes mellitus type 2, hypertension, hypercholesterolemia, hypogonadism, and depression.
- Past surgical history indicates right inguinal hernia repair.
- Allergies: aspirin, iodine contrast dye, walnuts, and cats.
- Medications: glyburide, a statin drug, lisinopril, actos, clonidine patch (Catapres-TTS), propoxyphene napsylate, and acetaminophen
- Review of systems: noncontributory
- Social history: married; significant occupational exposure from a coal plant; 1 cigar per month; 2 beers per week
- Family history: father, esophageal cancer
- Physical exam: no cutaneous lesions, no abdominal masses
- Laboratory values: complete blood count, basic metabolic panel, and liver function tests are normal, with the exception of slightly elevated alkaline phosphatase
- CT image reveals large enhancing left renal mass of 11 cm without lymphadenopathy or evidence of metastatic disease
- Chest x-ray and bone scans show no evidence of metastatic disease

CONCEPCION: This patient is a 51-year-old man who presents with left flank pain and gross hematuria. His medical history is significant for type 2 diabetes, hypertension, elevated cholesterol, hypogonadism, and depression. He's had

a right inguinal herniorrhaphy. He has allergies to aspirin, iodine contrast, walnuts, and cats. He's taking a number of medications, including glyburide, statins, and lisinopril. His review of systems is noncontributory. He is married, has

significant occupational exposure, and has a significant family history of esophageal cancer in his father. On exam, he has no abdominal masses and doesn't exhibit any cutaneous lesions. For lab evaluations, his complete blood count, basic metabolic panel, and liver function test are all normal. His alkaline phosphatase is slightly elevated. On CAT scan imaging, he has a large enhancing left renal mass of about 11 cm, no lymphadenopathy, and no evidence of metastatic disease. There is no evidence of metastases on his chest x-ray or bone scan.

After shared decision-making, the patient opted for a left robotically assisted radical nephrectomy. The final pathology showed mixed clear and granular cell type. The tumor itself was 10 by 7 cm. It was Fuhrman [nuclear] grade 3, with invasion into the renal vein, but negative margin at the renal vein resection site. He also had extension of the tumor into the perirenal fat and renal sinus adipose tissue, but Gerota fascia was not involved and it is intact. He has a pathologic T3N0M0 lesion. Dr Tripathi, tell us a little bit about how you would manage this patient, especially in light of some of the existing therapies that are now approved for the high-risk patient.

TRIPATHI: High-risk RCC has been an area of active research for the past decade, if not longer, with several trials aimed at investigating different adjuvant therapies. These trials resulted in the approval of sunitinib [Sutent] in the adjuvant setting for high-risk RCC, which this patient meets the criteria for. However, this happens to be one of those situations where even though there is an FDA approval, there is not widespread consensus on whether we should be offering or strongly recommending these therapies for patients with high-risk disease.

The reason for that is the discordance between the results of the AS-SURE [NCT00326898] and S-TRAC [NCT00375674] trials, and the lack of an overall survival benefit to date and

high rate of grade 3 adverse events.

Considering these factors, our practice is to try to enroll patients in a clinical trial if possible, and if a clinical trial is not available, then we have a balanced discussion with the patient regarding the available literature. A majority of the time, patients end up declining adjuvant sunitinib after understanding the limitations of current evidence. Interestingly, even though sunitinib is approved in the US, its approval raised quite a debate. The European Medical Agency did not approve the use of sunitinib considering all elements of the data together. Consistent with these, the National Comprehensive Cancer Network has a category 2B recommendation on using sunitinib.

So this is one of those rare circumstances where there is a positive trial, but it did not necessarily change the practice for the majority of patients. Taking those things into account, I usually discuss the data and the adverse event profile and I don't strongly recommend it, but it is an option for patients in the adjuvant setting.

CONCEPCION: Interesting. So we have an agent that's FDA approved but NCCN gives it a 2B recommendation. Dr Kassabian, is that what's happening with patients in your region also? Are you talking to them about the role of adjuvant therapy? Are you recommending that they see the medical oncology [department]? What's been your practice pattern?

KASSABIAN: I have found that every single patient I sent to medical oncology colleagues for discussion and therapy with sunitinib have all declined for the reasons already explained. It was a category 2B recommendation, it had a lot of grade 3 toxicity, and it was for at least 9 months and there were a lot of dose interruptions and dose reductions. Basically, the consensus was that every patient I referred declined to have therapy.

Now, just a couple of points for this particular patient. I don't do robotics but I think this patient would have been

a great candidate for open surgery given the size of the mass. The other point I want to make is that, at least in the metastatic setting of RCC, unimodality therapy is being replaced by multimodality therapy, especially immunotherapy. So I see in the future that perhaps single-agent therapy would not be efficacious in the high-risk patient following nephrectomy such as this, but I think multimodality therapy may be more efficacious and probably widely accepted.

CONCEPCION: Dr Kim, is there any role for radiation? Are there any data for radiation in a high-risk patient in the adjuvant setting?

KIM: There are not many good-quality data in terms of randomized trials. I think one of the few [trials whose results were] ever published was from a couple of decades ago...a study from Copenhagen with a low number of patients.¹ They gave about 50 Gy for what they perceived to be high-risk pathologic features that would increase the risk of local recurrence, and they just didn't find much of a benefit in terms of overall survival.

One of the challenges is that once you remove the kidney it gets filled up with bowel. The bowel is one of the most sensitive organs to radiation and to try to deliver a therapeutic dose is difficult. I think that has contributed to some of what we're seeing in the data where there's not much of a clinical benefit.

CONCEPCION: At 6 months, the patient undergoes CT of the abdomen and pelvis, which shows subcentimeter nodules in the lower lung fields. Dedicated CT shows 6 nodules in the right lung and 4 nodules in the left lung, with the largest nodule being 7 mm. There is no change at follow-up at 12, 24, and 36 months. At 48 months, however, a chest CT shows a bilateral noncalcified pulmonary nodule, which has increased in size from 10 to 16 mm.

PET-CT was done, which showed no significant uptake in pulmonary nodules

bilaterally. However, there is a mild uptake noted at the left lung base, which measured 2.6 on early and 2.6 on delayed. Dr Kassabian, what do you think about the increase in this nodule from 10 to 16 mm?

KASSABIAN: I think it's significant. We're always concerned that these are metastatic sites even though they're small. They are clearly growing. Given his pathology, and the fact that he had this huge mass at such a young age, he has a high chance of recurrence and obviously now he has something that's visible. I would think that starting off with a biopsy or resection to prove or disprove that he has metastatic disease before initiating therapy is perfectly reasonable.

CONCEPCION: This patient was referred to the interventional radiology [department] and had a CT-guided core biopsy of the left upper lobe nodule, which was negative. He also had a left thorascopic wedge resection, left lower lobe wedge resection, and bronchoscopy. Pathology on both lesions shows metastatic RCC, mixed clear cell and granular type. Pleura and margins are negative. So now we have a patient with documented pulmonary metastatic disease that has been resected. Dr Tripathi, what are your thoughts at this point?

TRIPATHI: At the time of diagnosis, this patient had high-risk, locally advanced disease. But after the resection, he had a relatively indolent course for about 4 years, after which he started developing growth in the pulmonary nodule. So based on the IMDC [International Metastatic RCC Database Consortium] criteria, I think he belongs in the favorable-risk category with oligometastatic disease and was treated appropriately with metastasis-directed therapy.

We can think about it in a couple of ways. This is a patient with favorable-risk disease who has shown indolent biology over the past 4 years with only recent change in growth dynamics. He has been rendered NED [no evidence of disease]

after metastasis-directed surgery. I think one option would be to follow the patient closely. We have had longitudinal data on the subset of patients who have low-volume disease and undergo metastasectomy. A significant proportion of these patients can be followed post surgery and delay the need for and adverse events associated with systemic therapy. The post-metastasectomy pazopanib [Votrient] data presented in 2019 that showed us that postmetastasectomy pazopanib in patients who were rendered potentially NED didn't improve disease-free survival, and there was a trend toward worse overall survival in patients assigned to the experimental arm.²

Secondly, we have a lot of retrospective and corroborative data published recently indicating that a significant subset of favorable-risk patients with low-volume metastatic disease can delay the need for systemic therapy. As our therapies are getting more and more effective, patients are on these therapies for a much longer duration, and the cumulative toxicity, both financial and physical, could [be difficult for them to bear]. So we have to be mindful about the decision to start systemic therapy in these patients. That being said, I think if there was a patient in whom there was still residual measurable disease and the patient was strongly interested in starting systemic therapy, I would start that patient off on the combination regimen of a VEGF TKI [tyrosine kinase inhibitor] and immunotherapy, which have shown improved overall survival compared to single-agent TKI therapy.

The regimen of choice is probably dependent upon the comfort of the treating physician in terms of management of adverse events. They all have an overall survival benefit over sunitinib. This includes axitinib [Inlyta] and pembrolizumab [Keytruda], lenvatinib [Lenvima] and pembrolizumab, and cabozantinib [Cabometyx] and nivolumab [Opdivo]. All 3 regimens are reasonable to consider as initial systemic therapy.

CONCEPCION: So basically you're saying if the patient had measurable disease that more than likely you would proceed with a doublet of an oral TKI and an immunotherapy. But in this particular case, given the fact that we don't really have any other evidence of metastatic disease that's measurable, then observation is also an option, correct?

TRIPATHI: Absolutely, and the rationale for that is to avoid adverse events for as long as we can.

CONCEPCION: Is there a role for monotherapy immunotherapy in this particular patient?

TRIPATHI: We have data on that. The KEYNOTE-427 trial [NCT02853344] investigated pembrolizumab monotherapy in patients with favorable-, intermediate-, and poor-risk disease and had a response rate of around 35%. Although some patients had a durable response, that's not the approved indication at this point, but it is a very rational question to understand which patients need intensification with both agents and who could get by with just monotherapy.

I think biomarkers would play a role potentially. There are some data that suggest that favorable-risk patients are driven by VEGF signaling in tumors. And these tumors are sensitive to and more likely to respond to a tyrosine kinase inhibitor. Although a subset of patients with favorable-risk disease do respond to immunotherapy, I would not consider monotherapy with a PD-1 inhibitor to be standard of care. I would consider it only as part of a clinical trial in this situation, considering the available randomized data and the FDA label.

CONCEPCION: Let's just say the patient also had a concomitant positive bone scan. As we know, bone metastases are not all that common in RCC, but it does obviously occur. Dr Kim, what about bone metastases

in the setting of RCC? How do those patients generally respond to radiotherapy?

KIM: RCC as a histology is considered to be one of the more radio-resistant types. You would need a pretty high biological

effective dose to deliver an ablative therapy. Fortunately, the technology has matured where we are able to do that, and now it's supported by data from studies such as the SABR-COMET trial [NCT01446744], which shows that in patients with limited

oligometastases you can improve clinical outcomes by delivering ablative therapy in a case like this, up to 5 metastases. So, that is being done more and more these days ever since these data were published.

Metastatic castration-resistant prostate cancer

CASE 2

- A 65-year-old man was referred from his primary care physician with recently elevated prostate-specific antigen (4.4 ng/dL) and abnormal digital rectal exam.
- Past medical history indicates hypertension, hyperthyroidism, lumbar stenosis, and vitiligo.
- Past surgical history a knee arthroscopy.
- Medications: levothyroxine, propranolol (Inderal)
- Review of systems: noncontributory
- Social history: High school basketball coach, no history of tobacco or alcohol use
- Family history: positive for prostate cancer, paternal uncle and older brother diagnoses in their 50s
- Digital rectal exam: about 45 g with 15-mm nodule to right base
- Physical exam: no cutaneous lesions, no abdominal masses
- Transrectal ultrasound-guided biopsy: 12 of 12 positive cores Gleason Grade Group 5 (4 + 5)
- CT of the abdomen/pelvis: fatty liver and hiatal hernia, mild bladder wall thickening
- Bone scan: increased uptake in multiple ribs, right T8 vertebral body, left posterior acetabular region, right proximal femur.

CONCEPCION: In this case, we have a 65-year-old African American man referred from primary care with a recent elevation of his prostate-specific antigen [PSA] level of 4.4 ng/dL and an abnormal digital rectal exam. His past medical history includes hypertension, hypothyroidism, lumbar stenosis, and vitiligo. He's had some knee arthroscopy, and he's on a thyroid replacement drug and a β -blocker. He is not a smoker and does not consume excessive amounts of alcohol. He does have a family history of prostate cancer in his paternal uncle and older brother, both diagnosed in their 50s. On digital rectal exam, his prostate was felt to be about 45 gms with a 15-mm nodule to the right base. He underwent transrectal ultrasound-guided biopsy of the

prostate and had 12 of 12 positive cores for Gleason Grade Group 5 (4 + 5). CT of the abdomen and pelvis found no evidence of metastatic disease.

Bone scan showed increased uptake in multiple ribs, right T8 vertebral body, left posterior acetabular region, and right proximal femur. So this is a patient [who] essentially is now presenting with newly diagnosed, very high-risk metastatic castration-sensitive prostate cancer. Dr Kim, what's going to be the role of managing his primary tumor?

KIM: I think that radiotherapy to the primary site has 2 roles. One, if the patient was symptomatic, then you can give a palliative course of radiation. But interestingly, as part of the STAMPEDE trial

[NCT00268476], they did look at patients with low-volume disease; I think in that trial it was fewer than 4 bone metastases. They gave a pretty therapeutic dose to the prostate in 36- and 6-Gy fractions. They found that patients had improved clinical outcomes, as an alternative to docetaxel [Taxotere], so there are good data to support radiation to the primary site for limited metastatic disease. In this case, since there are more than 4 bone metastases, it would be a stretch to apply that data, but there are good grounds to do so in a case with oligometastases.

CONCEPCION: Dr Kassabian, in your practice, how are you currently deploying genomic testing? What is your preference in somebody like this? Are you doing both germline and somatic?

KASSABIAN: For patients who present with metastatic hormone-sensitive prostate cancer, which unfortunately we're seeing more of because of the PSA debacle in 2012, I start off with germline testing, especially if they have a family history; but per the National Comprehensive Cancer Network guidelines, the fact that they're presenting with metastatic disease indicates that they clearly are candidates for germline testing. If the germline testing is positive, I stop there; I no longer need to go to somatic testing. If the germline testing is negative, I will proceed at some point in time in their journey of prostate cancer with somatic testing.

I may do it now if I have enough tissue, but as you know, it only affects treatment once they fail either abiraterone [Zytiga]

or enzalutamide [Xtandi] along with androgen deprivation therapy [ADT]. It's further down the road that we can prescribe one of the PARP inhibitors. So for that reason, I wait to see. When I get enough tissue—for example, if they have a channel transurethral resection of the prostate because they went into retention—I'll do it then, or if I have a significant amount of adenopathy that's easy to biopsy. As you know, bone biopsies are difficult and can be painful. I'm in favor of treating the primary with radiation therapy, especially if they have a big, bulky prostate. The bigger and bulkier the prostate, the more chance they're going to have bladder outlet obstruction and local progression, so I think it helps alleviate some of that.

I don't necessarily start the radiation right away; I'll give him several months of ADT and then consider it. But in patients who present with a benign-feeling prostate, I may have second thoughts about initiating radiation to the prostate.

CONCEPCION: Dr Tripathi, from the medical oncology standpoint, how do you deploy genomic testing in these patients with newly diagnosed disease who are very high risk and present with metastatic castration-sensitive disease?

TRIPATHI: Our approach has been to do both germline and somatic testing. This is important because these tests provide complementary pieces of information. Germline testing is mostly limited to a smaller panel of genes [that] have significant implications for family in terms of cancer screening and can identify therapeutic options down the road as well. Somatic testing panels are much larger and are able to capture a larger subset of these genes. They may still open up a treatment option such as a PARP inhibitor for these patients. For instance, the list of genes that is listed in the approval for PARP inhibitors is quite extensive and not all of them may be captured in germline testing.

So, I usually do both, and I help the

patient understand why we need both. In terms of sequencing, I think everybody should get germline at the minimum, and then somatic testing can be done later. The challenge is that sometimes, [further] down the line, there's not enough tissue available or a biopsy may not be feasible. If they have bone-only metastases, as previously said, these can be quite painful to biopsy. So in those situations, our options are usually limited to either going back to the original prostate specimen or doing a blood-based cell-free DNA assay, which also has quite concordant results. But I do make sure that all of our patients get both tests at some point during the course of their treatment history.

CONCEPCION: The patient's germline testing was negative, so he did not have any mutations in homologous recombination or mismatch repair. Somatic testing showed a mutation in SPEN; it looks like it was a nonsense mutation with loss of function. Tumor mutation burden was low, and he was MSI stable. To summarize, we've got a fairly healthy 65-year-old African American man with strong family history of prostate cancer, Gleason Grade Group 5 (4 + 5), germline negative, no pathogenic somatic mutation, who presents with metastatic castration-sensitive disease. Dr Kassabian, what is your treatment preference for this patient?

KASSABIAN: The patient has high-volume, metastatic hormone-sensitive or castration-sensitive prostate cancer. Your options are ADT as the foundation, but I think adding [docetaxel], or abiraterone, or enzalutamide, or apalutamide [Erleada] are all reasonable options. I think it depends.... [If] you want to be one and done and then follow these patients, which is the case with chemotherapy or for patients that are chemotherapy averse, I would consider the oral therapies. A lot of studies have shown a significant advantage of adding any of these therapies, especially in these high-volume patients.

CONCEPCION: Dr Tripathi, what are your thoughts from a medical oncology perspective?

TRIPATHI: I would ask the patient not which treatment they would like but which treatment they would prefer as first-line therapy. This is because we know that patients are going to need all of these therapies in different sequences. We know that androgen receptor [AR] inhibitors are cross-resistant based on the phase 2 crossover trial data. Based on the results, if a patient received abiraterone or enzalutamide as initial therapy, we would recommend against using another AR-targeted agent as next line of therapy because of cross-resistance and the lower response rates.

I would discuss with the patient that there are hormone-based therapies—abiraterone, enzalutamide, apalutamide—and [that] there are chemotherapy options. If the patient chooses a hormone-based therapy, then chemotherapy will most likely be his second option going forward. If he chooses chemotherapy now, his options would be open to both hormonal therapy or the novel taxane cabazitaxel.

I try to get patients to understand that it's not a matter of picking and choosing one treatment; it's more a matter of sequencing. There are other aspects to the discussion, such as toxicities. How old is the patient? What is his performance status? How symptomatic is he? I also discuss financial toxicity. Docetaxel is a facility-administered drug and patients usually do not have a lot of financial liability for that, but some of these oral agents can be a little expensive. All of these elements have to be considered when forming a decision. This patient has high-volume disease by CHAARTED criteria; he would have been eligible for inclusion in most of those studies in the hormone-sensitive setting, and all of them would have shown an improved overall survival with therapy intensification with one of these agents.

One thing I would like to bring up that I'm asked frequently is: Can we do both of them? For example, chemotherapy followed by switching to abiraterone and enzalutamide. I don't think that we have the data to support adding both a novel hormonal agent and a chemotherapy agent. Subgroup analysis from the ENZAMET data showed that [among] the patients who received docetaxel on that trial, the addition of enzalutamide did not seem to have an incremental benefit. Treatment intensification beyond doublets at this point is not supported by data just yet.

CONCEPCION: We haven't really talked too much about cabazitaxel. It's currently approved for patients who have failed or did not tolerate prior docetaxel therapy. But there was a recent study that found that using cabazitaxel in patients with aggressive high-grade disease seems to have some advantages. Dr Tripathi, do you have any experience with using cabazitaxel very early on? In a patient like this, obviously it would be off label, but if the patient was not a candidate for docetaxel for whatever reason, have you ever used cabazitaxel in that setting with these very aggressive Gleason 4 + 5 cancers?

TRIPATHI: I would say not in the up-front setting, considering the comparison trial between cabazitaxel and docetaxel showed similar outcomes. Using cabazitaxel before progression on docetaxel would be off-label use, and we haven't used that in the up-front [setting] yet for these patients. Further, patients who are not docetaxel candidates might not be candidates for cabazitaxel either, so I think there are some shared patient characteristics that may play a role there.

For some patients with very low PSA, high volume of disease, and an androgen-indifferent phenotype, we have considered early chemotherapy. Again, I would probably give docetaxel as first-line therapy in line with the indication. If the patient is intolerant of docetaxel

or progresses, I'd switch them to cabazitaxel immediately.

CONCEPCION: I think the key point here is that in patients who present with metastatic castration-sensitive disease, it is no longer acceptable to put them on ADT alone and that the data support that the addition of a second agent, whether it be a taxane or an AR-targeting agent, delays the time to castration-resistant prostate cancer and improves survival.

Continuing with this case, the patient was given ADT and was started on denosumab [Xgeva] to reduce skeletal-related events. He was also given abiraterone acetate, vitamin D, and calcium. His PSA nadir was 0.1 ng/dL. At year 1, CT scan showed no evidence of metastatic disease; bone scan showed marked improvement.

But then in year 2, he started to have a progressive rise in his PSA to 5.1. He reported back pain and left hip pain, [had an] ECOG status of 1, and progression was seen on bone scan with new lesions to the right manubrium sternum, left T6 vertebra, right posterior seventh rib, and the left acetabular region, which obviously is now symptomatic based upon his clinical presentation.

He was moved from abiraterone and was given docetaxel. He had some peripheral neuropathy and mucositis on a rash following cycle 1. They changed his dosing from 75 mg/m² to 30 mg/m² with split dosing. So again, he presented with metastatic castration-sensitive, ADT abiraterone progressed with new bony lesions, received docetaxel and had some mild symptoms, had a reduction in his dose, year 1, post taxane, PSA stable, bone scan, no further progression.

At year 2, the patient reported worsening pain to his left hip and back again. He was reimaged and received treatment with radium 223. By year 3, post taxane, he has progression of new lesions and now some pelvic lymphadenopathy, and his PSA is 16.2. Dr Kassabian, what are his options at this point?

KASSABIAN: I would have treated him a little bit differently. When he became castrate resistant, I would have offered him immunotherapy in the form of sipuleucel-T [Provenge] and then given him chemotherapy after some time. The reason I say that is because this patient was African American and his PSA was in the single digits when it became castrate resistant, and that's the ideal patient to receive immunotherapy. I don't disagree with the treatment that he received—chemo is absolutely efficacious—but I would have reserved it for a little bit further down the line after giving him immunotherapy.

We have a lot of treatment options in patients with advanced prostate cancer, and I like to offer all these therapies at some point. Right now, I don't think he's an ideal candidate for immunotherapy. I think at this point, I would offer him cabazitaxel.

CONCEPCION: Although cabazitaxel is not currently approved as up-front therapy, it is approved for patients who have failed or not tolerated docetaxel. Dr Tripathi, please update us a little bit on some of the data that have come out regarding cabazitaxel, especially the CARD data, as well as the dosing data as it relates to [adverse] effects with the use of that agent.

TRIPATHI: Cabazitaxel, as we know, was approved initially in the post docetaxel setting. I think at the initial dose of 25 mg/m², we were seeing a lot more hematologic toxicity, which was turning out to be dose limiting in certain instances, and in practice, it was quite frequent to see dose reductions to 20.

Subsequently, we had the noninferiority study of 20 and 25 mg/m² that showed that even with the dose reduction to 20 mg/m², the overall survival was noninferior and there was a lower incidence of adverse events. In practice, I think most of our patients are treated with 20 mg/m² as the starting dose because of that data. In terms of sequencing, there have been interesting data presented

“...the key point here is that in patients who present with metastatic castration-sensitive disease, it is no longer acceptable to put them on [androgen deprivation] alone and that the data support that the addition of a second agent.”

—Raoul S. Concepcion, MD, FACS

over the past year or so. We know a little bit about sequencing between hormonal agents from the randomized crossover trial that abiraterone followed by enzalutamide and enzalutamide followed by abiraterone is perhaps not the best and most ideal strategy.

But questions remained as to what should these patients be treated with and what are the randomized data to guide that discussion? In that setting, CARD trial [NCT02485691] data fill that data gap quite nicely. It was a randomized study, and patients who had received prior AR-targeted inhibitors and had progression within 12 months of it were randomized to receive either cabazitaxel or a second hormonal agent that they had not received previously. The trial showed improved outcomes with the patients who were randomized to the cabazitaxel arm.

In practice, with most of these AR inhibitors, we get 1 good shot at it because your best chance of response is with the first agent used. In the majority of the patients, the responses are usually not as durable when the second AR-targeted agent is used sequentially. That's where I think cabazitaxel comes in for patients who are refractory to prior docetaxel and AR-inhibitor therapy as a more effective therapy compared with another AR-targeted agent.

CONCEPCION: Great. Dr Kim, tell us what is going to be forthcoming from a radiologic, nuclear medicine perspective for this type

of patient. Specifically, I'm thinking about radioligand therapy.

KIM: That's an exciting new modality that is going to be arriving shortly. The first step would be to get prostate-specific membrane antigen [PSMA] diagnostics and see if there are other areas that we don't know about and to what extent bony and visceral disease and soft tissue disease exist. And then an armed agent like a PSMA therapeutic agent would be able to deliver radiation to both these sites of disease.

So now the patient trial just closed; apparently, they met their end points, [but we] don't know much beyond that though. [I'm] looking forward to their data. Even along that pathway, there are more agents coming; there are also now alpha emitters being developed, and that's also exciting.

CONCEPCION: So in this particular patient, Dr Kim, he's symptomatic in his left hip, and he has progression. Do you have much experience relative to the delivery for palliation of external beam radiotherapy in a patient who has already received radium?

KIM: I think overall, it seems to be well tolerated. Certainly, it's encouraging that this patient got through all 6 cycles; that tells us it wasn't stopped due to hematologic toxicity. If you can give it focally to areas that are symptomatic, I think patients find that they get a clinical benefit

out of that. A lot of it has to do with the volume you're trying to treat.

If it's focal, it should be very well tolerated without much impact on their hematological parameters. We can give doses as few as a single fraction or 2 fractions, so you can adjust according to what you think the concern is.

CONCEPCION: Perfect. That's great. Dr Kassabian, in this particular patient, cabazitaxel is an option, a clinical trial is an option. What are your thoughts regarding repeating testing to determine what other lines of therapy might be appropriate for this particular patient?

KASSABIAN: I think somatic testing should be revisited. As you know, these tumors can mutate, and so what may have been negative in somatic testing previously you may now find something that is worthwhile and treatable. How do you go about that somatic testing? You can go back to archival tissue or you can go after a new lesion, although as discussed earlier, bone lesions can be painful to biopsy.

Another option is a liquid biopsy, which can pick up some of these somatic changes, circulating tumor cells, if you think they're abundant enough—and I think in this case, they would be. I think a liquid biopsy test may also be worthwhile especially if their archival tissue is insufficient or too old or there aren't any good new lesions to go after in biopsy. ■

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HER2-Positive Breast Cancer: Special Challenges and Expert Insight

Recent developments in HER2-targeted therapy present new challenges for physicians treating patients with metastatic HER2-positive (HER2+) breast cancer, including how to treat patients with brain metastases, how to properly sequence therapies and make sequencing decisions, and how to identify and manage interstitial lung disease (ILD). Experts discussed these topics in a virtual CancerNetwork[®] *Around the Practice* presentation, “HER2+ Breast Cancer: Special Challenges and Expert Insight,” held April 20, 2021, and moderated by **Adam M. Brufsky, MD, PhD**. Members of the audience also participated in an interactive online platform by submitting responses to polling questions that were subsequently discussed by the panelists.

Screening Asymptomatic Patients for Brain Metastases

When polled about how often they screen asymptomatic patients with metastatic HER2+ breast cancer for brain metastases, 60% of audience respondents answered “sometimes” (Figure 1). In the follow-up question, “How often do you treat prophylactically for brain metastases in asymptomatic patients with HER2+ breast cancer?” 50% of respondents answered “never,” 25% answered “rarely,” and 25% answered “sometimes” (Figure 2).

The panelists then discussed approaches to management of a 37-year-old woman with a 5-cm lump in her right breast (Table). Immunohistochemistry (IHC) showed HER2+

breast cancer. The patient obtained a pathologic complete response to 6 cycles of neoadjuvant chemotherapy (docetaxel, carboplatin, trastuzumab, and pertuzumab), lumpectomy, and radiation, followed by maintenance therapy with trastuzumab and pertuzumab. After 32 months, the patient returned to the clinic with fatigue and persistent cough; a CT showed 3 nodules in the left upper lobe of the lung. IHC of the lung biopsy revealed HER2+ metastases, and the patient was treated with docetaxel, trastuzumab, and pertuzumab (THP) chemotherapy and given bisphosphonates every 3 months. After 24 months, a routine CT showed 4 new liver metastases.

The panelists and the poll respondents were evenly divided about whether to screen this patient for brain metastases (Figure 3). The National Comprehensive Cancer Network (NCCN) guidelines recommend brain MRI with contrast for patients with recurrent or stage IV disease who have symptoms suggestive of central nervous system (CNS) metastases, and **Neil M. Iyengar, MD**, said that he does not routinely screen asymptomatic patients because of the lack of evidence to support a corresponding survival benefit.¹

The NCCN guidelines state that clinical trials offer the best management for patients with cancer and encourage participation when possible.¹ **Sara A. Hurvitz, MD**, recommended referring the patient for enrollment in the HER2CLIMB-02 trial (NCT03975647), a

randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of tucatinib plus trastuzumab emtansine (T-DM1) in patients with unresectable locally advanced or metastatic HER2+ breast cancer.² The study uses baseline brain MRI for all participants.²

V. K. Gadi, MD, PhD, said that he is increasingly inclined to screen asymptomatic patients because of the increased availability of trials for patients with CNS metastases. **Hurvitz** added that patient preference also influences her screening decisions.

Prophylactic Treatment of CNS Metastases

Metastases within the CNS are common among patients with HER2+ breast cancer, occurring in 25% to 50% of patients with advanced disease.³

Data from NEfERT-T (NCT00915018), a 5-year, randomized, controlled, open-label, multinational, multicenter study of 479 women with previously untreated recurrent and/or metastatic HER2+ breast cancer, suggest that HER2-targeted agents with CNS activity (such as neratinib) may reduce development of CNS metastases. The trial found that neratinib plus paclitaxel led to significantly fewer ($P = .004$) incidences of CNS recurrence compared with trastuzumab plus paclitaxel in patients with previously untreated, metastatic, HER2+ breast cancer (16.3% vs 31.2%; HR 0.45; 95% CI, 0.26-0.78).⁴

According to **Gadi**, the best opportunity for CNS prophylaxis is likely in the nonmetastatic setting. “In the metastatic setting, I think the cat’s out of the bag,” he said. “I don’t know how much, at this point, a brain met [metastasis] changes overall outcomes for patients.”

Sequencing of HER2-Targeted Therapies

Of audience poll respondents, 57% said they would choose T-DM1 for the case patient if they did not know whether she had brain metastases (Figure 4). **Gadi**

Table. Case Study: Woman With HER2+ Breast Cancer

Characteristics	Description
Age, sex	37 years, female
IHC biopsy of 5-cm lump in right breast	HER2+ breast cancer
Frontline treatment	<ul style="list-style-type: none"> • Neoadjuvant TCHP (6 cycles) • Lumpectomy • Radiation • Obtained pCR; given maintenance therapy with trastuzumab and pertuzumab
Status at 32 months post frontline treatment	<ul style="list-style-type: none"> • Patient complained of fatigue and persistent cough.
Chest CT results	<ul style="list-style-type: none"> • 3 nodules in the left upper lobe, 2-3 cm each
IHC of lung biopsy	<ul style="list-style-type: none"> • HER2+ MBC
Second-line treatment	<ul style="list-style-type: none"> • THP (8 cycles) • Bisphosphonates every 3 months
Status at 24 months post second-line treatment	<ul style="list-style-type: none"> • CT detects 4 new liver metastases: three 1-2 cm and one ~3 cm

HER2+, HER2-positive; IHC, immunohistochemistry; MBC, metastatic breast cancer; pCR, pathologic complete response; TCHP, docetaxel, carboplatin, trastuzumab, and pertuzumab; THP, docetaxel, trastuzumab, and pertuzumab.

and **Hurvitz** agreed, saying current data supports this choice in a second-line setting.

If a brain MRI revealed that the case patient had two 1 cm in diameter lesions, all audience poll respondents said they would choose a regimen of tucatinib, trastuzumab, and capecitabine. The panelists agreed that tucatinib-based therapy is preferable in this scenario based on data from HER2CLIMB (NCT02614794), an international, randomized, double-blind trial comparing tucatinib plus trastuzumab and capecitabine with placebo plus trastuzumab and capecitabine in patients with HER2+ metastatic brain cancer ([MBC]; N=612).⁵ The study showed

that the risk of death in the overall trial population was 34% lower with addition of tucatinib to trastuzumab and capecitabine than with placebo (HR, 0.66; 95% CI, 0.50-0.88; $P = .005$).⁶ Among patients with brain metastases, the estimated progression-free survival at 1 year was 24.9% (95% CI, 16.5-34.3) and 0% in the tucatinib and placebo groups, respectively.⁶

“I have been fairly impressed by the combination of the systemic and CNS activity of the tucatinib-based regimen, so this is the kind of setting where I would now change treatment to tucatinib,” **Iyengar** said.

However, **Gadi** pointed out that while

Figure 1. How often do you screen asymptomatic patients with metastatic HER2+ breast cancer for brain metastases?^a

HER2+, HER2-positive.
^aPoll results: Screening for brain metastases in asymptomatic patients with HER2+ breast cancer.

Figure 2. How often do you treat prophylactically for brain metastases in asymptomatic patients with HER2+ breast cancer?^a

HER2+, HER2-positive.
^aPoll results: Treatment prophylaxis for brain metastases in asymptomatic patients with HER2+ breast cancer.

Figure 3. Would you screen this patient for brain metastases?^{a,b}

^aPoll results: Necessity of brain metastases screening in case study patient.
^bPatient is a 37-year-old woman with HER2-positive metastatic breast cancer who was treated with docetaxel, trastuzumab, and pertuzumab for 2 years.

a tucatinib-based regimen may be optimal, patient preferences and insurance coverage are important considerations.

“If a patient says, ‘Doc, I’m not ready to take 17 pills a day and...I can’t get insurance coverage,’ [then] I think it’s important for us to talk about a simple 1-drug regimen, like T-DM1, following [stereotactic radiosurgery],” he said.

All audience poll respondents preferred T-DM1 in the second-line setting for approximately 70% of their patients. Two years after the THP treatment, the case study patient received a diagnosis of liver metastases, which were asymptomatic and accompanied by normal liver function tests. She was prescribed T-DM1 and did not receive a brain MRI.

In this situation, **Iyengar** said he would obtain another biopsy to confirm HER2 status and give a tucatinib-based regimen. “My practice has been largely to use [a] tucatinib-based regimen in the third-line setting, partly because of the systemic activity of that regimen but also partly because we know from the trastuzumab deruxtecan data that it is quite an active drug, even in late lines of therapy,” he said.

The tucatinib-based regimen and trastuzumab deruxtecan are both “reasonable options,” for this patient, **Hurvitz**

said, adding that efficacy rates for trastuzumab deruxtecan are “phenomenal,” as observed in the DESTINY-Breast01 trial (NCT03248492). This phase 2, open-label, single-arm, 2-part, multicenter study of 184 patients showed a confirmed response rate of 60.9% to trastuzumab deruxtecan in patients with HER2+, unresectable and/or MBC who were previously treated with T-DM1 and received a median of 6 prior lines of therapy (n = 112; 95% CI, 53.4-68.0).⁷

However, 13.6% of patients in the study (n = 25) experienced trastuzumab deruxtecan-related ILD, a group of diseases (including interstitial pneumonitis) characterized by lung fibrosis and inflammation that causes breathing difficulties; 4 of these patients died.^{7,8}

Data from the HER2CLIMB trial indicate that tucatinib is relatively safe, **Hurvitz** said.⁶ The most common adverse events observed in patients treated with tucatinib (n = 404) were diarrhea (any grade, 80.9%; grade ≥3, 12.9%), palmar-plantar erythrodysesthesia syndrome (any grade, 63.4%; grade ≥3, 13.1%), nausea (any grade, 58.4%; grade ≥3, 3.7%), fatigue (any grade, 45%; grade ≥3, 4.7%), and vomiting (any grade 35.9%; grade ≥3, 3%).⁶ Less than 6% of patients discontinued treatment with

tucatinib because of adverse events.⁶

Ultimately, the panelists agreed that the patient would need to be involved in the treatment decision-making process and informed about the risks and benefits associated with each agent.

Interstitial Lung Disease

When asked whether they screen patients with HER2+ breast cancer for signs of pneumonitis, 50% of audience respondents said they screen only symptomatic patients, 25% said they screen all patients, and 25% said they screen only patients on immunotherapy (**Figure 5**).

The underlying mechanism of ILD is poorly understood, but the cytotoxic component of trastuzumab may be causing damage when it binds to HER2 receptors in lung tissue, **Hurvitz** noted. “[ILD] doesn’t seem to universally respond to steroids, so an immune-based underlying etiology is not entirely clear,” she said.

Audience poll respondents were evenly split on whether dyspnea (50%) or cough (50%) would be the first trigger to initiate a work-up for ILD (**Figure 6**). In a follow-up question about the typical initial response to grade 2 ILD in patients with HER2+ breast cancer, 50% responded “treatment discon-

Figure 4. Which of the following treatments would you choose next for this patient if you did not know whether she had brain metastases?^a

^aPoll results: Treatment options for case study patient if brain metastases status is unknown. T-DM1, trastuzumab emtansine; THP, docetaxel, trastuzumab, and pertuzumab.

Figure 5. Do you screen your patients with HER2+ breast cancer for signs or symptoms of pneumonitis?^a

^aPoll results: Screening for pneumonitis in patients with HER2+ breast cancer. HER2+, HER2-positive.

Figure 6. Which of the following would be your first trigger to work up a patient with HER2+ breast cancer for ILD?^a

^aPoll results: Screening patients with HER2+ breast cancer for ILD. HER2+, HER2-positive; ILD, interstitial lung disease.

tinuation and steroids;" the remaining respondents were divided between "dose reduction and steroids" and "treatment hold and steroids."

In the case patient, a CT performed 12 months after starting T-DM1 showed progression in the liver. She started on trastuzumab deruxtecan and had a response in the liver after 3 months, but a CT of the chest, abdomen, and pelvis showed an asymptomatic inflammatory pattern in the right lower lobe. The panelists generally agreed with erring on the side of caution regarding further treatment.

Iyengar said that he monitors patients very closely and discontinues the treatment immediately if a patient with mild symptoms shows any sign of worsening. "If it truly is ILD related to the drug, it can progress rapidly," he said.

Hurvitz said that she stops therapy with grade 1 ILD and does not consider resuming therapy until imaging shows resolution.

Brufsky emphasized the importance of proactive management of patients with any sign of ILD. "I think that you've got to be very, very careful," he said.

For patients with lung metastases, **Hurvitz** and **Iyengar** said that they would consider trastuzumab deruxtecan

because data analysis from multiple studies did not find evidence that pulmonary metastases is a risk factor for ILD.⁹

Iyengar added that caution should be exercised in patients with lymphangitic carcinomatosis but agreed that "you really want to try to get a response in the lungs, and using an active agent in this setting may be very helpful."

Closing Remarks

At the conclusion of the discussion, **Iyengar** noted that the field of HER2+ breast cancer is a rapidly evolving space, with multiple clinical trials of therapies and combinations in different disease settings.

Hurvitz said she would like to see more data about managing leptomeningeal metastases, which remains an unmet need.

Gadi predicted that the conversation about treatment of metastatic HER2+ breast cancer could be very different just 18 months from now. "I'm just really happy for our patients to have [so many] options available to them," he said. "I don't care so much about sequencing. At the end of the day, being able to get these drugs to those folks who need them when they need them...that's probably the most important thing." ■

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CLINICAL TRIALS IN PROGRESS

COMMIT STUDY

TITLE: NRG-GI004/SWOG-S1610: Colorectal Cancer Metastatic dMMR/MSI-H Immunotherapy (COMMIT) Study: A Randomized Phase 3 Study of mFOLFOX6/Bevacizumab/Atezolizumab Combination vs Single Agent Atezolizumab in the First-Line Treatment of Patients With Deficient DNA Mismatch Repair (dMMR)/Microsatellite Instability–High (MSI-H) Metastatic Colorectal Cancer (NCT02997228).

BACKGROUND: In metastatic colorectal cancer that is dMMR/MSI-H, the superiority of inhibition of the PD-1 pathway over chemotherapy with either anti-VEGFR or anti-EGFR antibodies has been demonstrated in a phase 3 trial.¹ However, more patients had progressive disease as the best response in the anti-PD-1 monotherapy arm (29.4% vs 12.3%), with mean progression-free survival (PFS) of 13.7 months. Preclinical models have demonstrated synergistic interactions among folinic acid, fluorouracil, and oxaliplatin (FOLFOX); anti-VEGF; and anti-PD-1.

The primary objective of this study is to determine the efficacy of the combination of mFOLFOX6/bevacizumab (Avastin) plus atezolizumab (Tecentrig) as compared with single-agent atezolizumab, based on PFS. Secondary objectives include overall survival, objective response rate, duration of response, duration of stable disease, rate of PFS, and disease control rate (complete and partial responses and stable disease) at 12 months.

SELECTED INCLUSION CRITERIA:

Eligible patients must be 18 years or older with metastatic adenocarcinoma of the colon or rectum, without previous therapy for metastatic colorectal cancer; have an ECOG performance status of 0, 1, or 2; and have measurable metastatic disease and adequate organ function. Additionally, they must have their tumor determined to be dMMR by CLIA-certified immunohistochemical (IHC) assay with a panel of all 4 IHC markers, including MLH1, MSH2,

PMS2, and MSH6; or, alternatively, MSI-H status diagnosed by polymerase chain reaction–based assessment of microsatellite alterations (either Bethesda markers or Pentaplex panel) or by next-generation sequencing. Those with prior treatment with anti-PD-1 or anti-PD-L1 therapeutic antibody or pathway-targeting agents are excluded.

PATIENT ACCRUAL INFORMATION

- Reopen date: January 29, 2021
- Accrual goal: 211 patients
- Percent accrued: 28%

STUDY SITES: NRG Oncology, SWOG, ECOG-ACRIN Cancer Research Group, and The Alliance for Clinical Trials in Oncology.

Reference

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SCHEMA FOR NRG-GI004/SWOG-S1610

Patients with mCRC that is dMMR by IHC and/or MSI high by PCR or NGS who have no prior systemic treatment for metastatic disease (N = 221)

Atezolizumab
(single agent)

1:1 RANDOMIZATION

mFOLFOX6/bevacizumab
+ atezolizumab
(Combination)

dMMR, mismatch repair deficiency; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; N, accrual goal; NGS, next-generation sequencing; PCR, polymerase chain reaction; R, randomization.

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CONTINUING MEDICAL EDUCATION (CME)

Targeting TAp63 in Breast Cancer

FACULTY

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

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LEARNING OBJECTIVES

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

- Describe the physiologic function of TAp63 in breast cancer
- Explain the rationale for targeting TAp63 as a mechanism for treating breast cancer

RELEASE DATE: June 1, 2021

EXPIRATION DATE: June 1, 2022

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ACTIVITY

p63 is a member of the p53 tumor suppressor family of transcription factors.^{1,2} The TP63 gene encodes for multiple isoforms including TAp63, a full-length isoform that contains a p53-like transactivation (TA) domain, and ΔNp63, an N-terminal truncated isoform. Both isoforms are involved in oncogenesis, but they exert distinct and often antagonistic functions.^{1,2} ΔNp63 is an oncogenic driver, whereas TAp63 acts primarily as a tumor suppressor in different cancers including breast cancer.

TAp63 is either undetectable or expressed at very low levels in different types of tumor tissue, including invasive and metastatic lesions of mammary carcinoma.² Gain-of-function studies in cancer cell lines demonstrated that TAp63 overexpression induces cell-cycle arrest and cell death.³ The TP63 gene is rarely mutated in cancer; however, in squamous cell carcinoma TP63 mutations are located in the TA domain, suggesting that TAp63 might be involved in tumor suppression.⁴ In triple-negative breast cancer tumor samples, TAp63 expression was associated with androgen receptor, BRCA1/2 wild-type status, and phosphatase and tensin homolog (PTEN) positivity.⁵ Furthermore, patients with TAp63 expression had lower rates of disease recurrence and improved overall survival. Mice lacking copies of the TAp63 gene (ie, TAp63^{+/-} and TAp63^{-/-}) developed highly metastatic mammary adenocarcinoma that spread to the lung and brain.⁶ Compared with the wild-type, TAp63^{+/-} and TAp63^{-/-} genotypes were also associated with a significantly shorter life span. Similarly, in TAp63-deficient mammary epithelial cells, pathways promoting transition of mammary cancer cells to tumor-initiating cells were activated.⁷

TAp63 also had a direct effect on the transcriptional regulation of Dicer, an endonuclease that processes microRNA (miRNA) precursors into functional RNA molecules.⁶ In TAp63-deficient cells, miRNA processing was defective

and miR-130b expression was downregulated. Low levels of miR-130b correlated with increased invasion in wild-type cells, suggesting its direct involvement in metastasis. Mutant p53 was also shown to downregulate Dicer expression, both through mechanisms independent of TAp63 and through direct inhibition of TAp63 transcriptional activity, suggesting that mutant p53 enhances tumor metastasis, in part, via inhibiting TAp63 activity.⁸ In another recent study, TAp63 was seen to modulate the expression of oncogenic long non-coding RNAs, two of which are correlated with cancer progression.⁹

“I think the most exciting possibility in activating TAp63 as a cancer therapy is the idea that it may function as a specific metastasis suppressor.

We have lots of ways to kill tumor cells. We have lots of ways to induce growth arrest in tumor cells.

We don’t have very many specific ways to prevent metastasis, particularly in breast cancer.”

Collectively, these preclinical data indicate that TAp63 downregulation or its functional inhibition by mutant p53 can increase the metastatic potential of cancer cells. In chemo-resistant ovarian cancer cells, inducing the activity of TAp63 through treatment with its direct downstream target, miR-130b, decreased migration/invasion and tumor formation.¹⁰ When mice with ovarian xenograft tumors were injected with miR-130b in

liposomes, tumor burden rates as low as those observed in mice treated with chemotherapy were seen. In addition, 20% of the mice treated with the combination of chemotherapy and miR-130b were tumor-free at the time of analysis. Systemic injections of miR-130b in a clinically tested, tumor-targeted nanocomplex plus chemotherapy improved survival in 60% of mice with tumor xenografts, with a complete remission rate of 40%.¹⁰ Using similar strategies for targeting the miR-130b/TAp63 axis is considered a potential treatment pathway in p53-altered breast cancer.

Leif W. Ellisen, MD, PhD, reviews recent advances in understanding the oncogenic mechanism of TAp63 in breast cancer and the potential role of targeting TAp63 in the treatment of breast cancer.

Q: What is the physiologic function of TAp63 in healthy individuals?

ELLISEN: TAp63 is an interesting molecule because it's the product of the TP63 gene that encodes 2 different isoforms: (1) ΔNp63, which is shown to be a tumor driver in many circumstances, and (2) TAp63, which is in many ways a tumor suppressor.^{2,11} In healthy individuals, ΔNp63 is important for development of skin, breast, and prostate tissue. In contrast, TAp63 is not so important in normal development, but it has a very selective role in protecting the ovaries from genotoxic damage.^{12,13}

Q: What is the oncogenic mechanism of TAp63 in breast cancer?

ELLISEN: One way to think about TAp63 mechanisms is that TAp63, in many ways, resembles p53. In fact, it's a cousin protein to p53, which is of course a very important tumor suppressor. When it was discovered about 20 years ago, TAp63 was thought to function like p53 and, indeed, some of their functions overlap. TAp63 can inhibit survival pathways and induce cell death under some circumstances.² But in many ways, the most exciting role of TAp63, as a tumor suppressor, is its ability to suppress

cancer metastasis, which has been shown in several animal models.^{6,7,9,14}

Q: What is the rationale for targeting TAp63 in breast cancer versus other cancers?

ELLISEN: It turns out that p63 and TAp63 has a very selective role in certain epithelial tissues, including the breast.^{5,7,14,15} It has been demonstrated that TAp63 is quite significantly expressed in many breast cancers. In some circumstances, TAp63 can also interact with mutant p53 in breast cancer, and in animal models, it can inhibit metastasis of breast cancer.^{2,6} Therefore, the idea is that if we could activate, reactivate, and induce TAp63 in the setting of certain breast cancers, we might be able to invoke all these interesting and important tumor-suppressor and metastasis-suppressor effects.

Q: Which strategies are currently being explored for the development of agents targeting TAp63 for the treatment of breast cancer?

ELLISEN: The idea that we can manipulate TAp63 levels for cancer therapy is a very exciting one. It turns out that there are many different strategies to do this. Several of them are in the preclinical space, but it's possible that some of the cancer therapies whose mechanisms we don't fully understand partly function through the activation of TAp63. For example, retinoic acid is used to treat certain cancers. It has been shown that it might function, in part, by activating TAp63, and this is a strategy that has been tried in preclinical models.¹⁶ Furthermore, we know that mutant p53 inactivates TAp63,² and many clinical trials are now in development and ongoing to reactivate or inhibit mutant p53, which, again, would

be a way to activate the TAp63 normally inhibited by mutant p53.

The other general approach is not to target TAp63 itself, but rather to target its downstream pathways. TAp63 activates a number of miRNAs, and we now have ways to deliver miRNAs in clinical trials, such as nano-complexes.^{10,17-19} Delivering these miRNAs, we hope, might have similar effects to TAp63, because these miRNAs are induced by p63. Furthermore, there are other ways that we could target some of the downstream pathways of TAp63, including things like the aurora kinase pathway or BCL2 pathway. Targeting these pathways is a way to target the effects of TAp63.

Q: What are the key clinical trials, particularly any late-phase trials, evaluating investigational agents targeting TAp63 and its pathway?

ELLISEN: It's a very good question. Most of the work that focuses specifically on TAp63 is in the preclinical space or in the early clinical-trial space. But, I would say there are two exciting areas. The first one is the ability to deliver miRNAs induced by TAp63. We would call them tumor-suppressor miRNAs, and there are various ways to deliver these through specialized complexes. As I mentioned, the use of nano-complexes is one way that's currently being studied in clinical trials in a variety of cancers.^{18,19} Similarly, I mentioned that mutant p53 can inhibit TAp63, so in clinical trials we have small molecules that could reconfigure or inhibit mutant p53 as a way to activate TAp63. Those are also in early clinical trials.^{20,21} In later clinical trials are more of these downstream pathway inhibitors, such as aurora kinase inhibitors and BCL2-family inhibitors, which indirectly work

on the downstream pathways regulated by TAp63.

Q: What are some of the major adverse events that have been associated with TAp63?

ELLISEN: One of the challenges in the field is that, like p53, TAp63 has a whole bunch of downstream effects. We would call it pleiotropic, and those tumor-suppressor effects, if activated in normal cells, could lead to a variety of cell toxicities and side effects for patients. Therefore, we have to be careful about how we activate p63, and we have to evaluate, both preclinically and clinically, what the best strategies are. Because, certainly with any potent tumor-suppressor pathway, we run the risk of lack of specificity. Either the delivery of the activator of TAp63 or the way TAp63 is activated might lead to a host of adverse effects related to the tumor-suppressor mechanism that gets activated in normal cells.

Q: How do you anticipate that agents targeting TAp63 will impact the treatment landscape for patients with breast cancer?

ELLISEN: Well, I think the most exciting possibility in activating TAp63 as a cancer therapy is the idea that it may function as a specific metastasis suppressor. We have lots of ways to kill tumor cells. We have lots of ways to induce growth arrest in tumor cells. We don't have very many specific ways to prevent metastasis, particularly in breast cancer. Animal models have suggested that TAp63 is really important, specifically in suppressing the metastatic ability of cancer cells.^{2,6} So, to me, the most exciting possibility is a TAp63-directed therapy that could be combined with standard therapies. For

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example, the primary tumor would be treated with the standard therapy, and the companion TAp63-directed therapy would block the metastatic pathways at the same time.

Q: What other cancers would you anticipate agents targeting TAp63 may be investigated in as potential therapies?

ELLISEN: There are a number of other cancers in which TAp63 may play a significant role. In squamous cancers of the head, neck, and lung, for example, the other p63 form called $\Delta Np63$ is an oncogenic driver;² and the idea that we might oppose that oncogenic effect through activating TAp63 is an exciting possibility. Furthermore, in some preclinical studies and animal studies, TAp63 has been shown to play a role in ovarian cancers and lymphomas, where it also appears to function as a tumor-suppressor.^{10,22,23} So, in theory, there could be a broad group of cancers where activation of TAp63 might have an important role.

Q: Is there anything you would like to add specifically regarding targeting TAp63 in breast cancer or in any other cancer that we haven't touched on?

ELLISEN: Yes. I think that from a context point of view, one of the most useful ways to think about TAp63 is that it's like p53. We think of all the different pathways that p53 regulates to suppress tumors. TAp63 regulates some overlapping pathways, but also different ones. So, just like we have so much more to learn about p53, the same is true for p63. Because it's a very pleiotropic factor, and appears to have potent effects in cancer, we have much to learn about what exactly its critical roles are. What are the specific cancer contexts? How might we use it in breast cancer, and how can we most effectively manipulate the TAp63 axis in the setting of cancer therapy?

One thing I would like to further emphasize is that an important piece of data from human cancer suggest-

ing the relevance of TAp63 is that p53 is the most important tumor suppressor we have. We know that for sure in human cancer. We know that mutant p53 is highly expressed in many cancers, but it has been a big mystery what mutant p53 does, even though we know that mutant p53 is very important. One of the strongest pieces of evidence that TAp63 is important is that it seems to be specifically targeted by mutant p53 in human cancer, where it is bound and inhibited by mutant p53. Numerous studies have shown that part of the important role of p53, and mutant p53, in human cancer is its ability to inactivate TAp63.² So, if you think about the whole world of research on p63, much of it is supported by the fact that p63 has this very intimate role in terms of regulation by p53, specifically mutant p53. In many ways, mutant p53 is one of, if not the most important molecules in all of human cancer, and given that one of its functions is to inhibit TAp63, this really speaks to why TAp63 is so important and what we might gain by targeting and activating TAp63. ■

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Let's make referral simple. Learn more about our comprehensive oncology program by calling us at **317.944.5576** or visiting **rileychildrens.org/oncology**.

Riley Children's Health
Indiana University Health

A National Leader in Pediatric Oncology

Riley Children's Health offers the highest level of pediatric oncology care, treating more than 80% of children with cancer in Indiana and providing excellent patient outcomes, from infants to young adults. With an 85% five-year cancer survival rate and long-term survivorship program, patients have access to state-of-the-art survivorship care, including adolescent medicine, fertility, cardiology/cardiac disease prevention care, exercise and wellness programming connections, mental health evaluations, connections for follow-up across the state, innovative research and upcoming genomics testing.

Pediatric Oncology Program Highlights:

- Full floor of the hospital dedicated to pediatric cancer care
- Each year, more than 300 new oncology patients, over 700 new hematology patients and more than 13,000 outpatient visits
- Indiana's largest and most skilled rehabilitation team
- The only dedicated pediatric neuroradiology team and the only pediatric neuroradiology fellowship in the state
- Indiana's only hospital offering antibody therapy for neuroblastoma

One of Only Five CureWorks Research Hospitals.

Through an exclusive partnership with CureWorks—a unique collaboration among five elite academic children's hospitals that includes Riley Hospital for Children—our stem cell transplant and immunotherapy physicians are able to offer greater access to novel clinical trial options in CAR-T cell therapy science to children with cancer. Member hospitals are supported in launching and participating in a network of exclusive clinical trials for children with the most difficult-to-treat cancers. This collaboration allows for streamlining immunotherapy production, clinical trial enrollment and the trial coordination process. In addition to expanding access to the latest treatments, the collaboration allows Riley patients to get this more advanced care closer to home.

Affiliated with the Indiana University Simon Cancer Center—Indiana's only NCI-designated Comprehensive Cancer Center.

Learn more, visit rileychildrens.org/oncology

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