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PRACTICAL, PEER-REVIEWED PERSPECTIVES

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EARLY-CAREER ONCOLOGY: ORIGINAL RESEARCH

Association of Financial Conflicts of Interest With Academic Productivity Among Junior Faculty in Hematology and Oncology

INTERVIEW

Leveraging Surgical Oncology to Treat Gastrointestinal Cancers

MICHAEL CHOTI, MD, MBA, FACS

2021 American Society of Hematology: Program Highlights

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The 2021 American Society of Hematology Annual Meeting & Exposition (ASH 2021) took place in December in Atlanta, Georgia, and included an in-person event as well as a virtual platform. Presenters and attendees from the United States as well as many international locations were able to participate. Health and safety protocols due to COVID-19 were in place and followed carefully to try to prevent transmission for the in-person attendees. Thankfully, the virtual platform allowed many more attendees from around the world to view and participate in the meeting.

Throughout the meeting, a number of awards and lectureships based upon the awardees' work were presented, including:

- Wallace H. Coulter Award for Lifetime Achievement in Hematology to Harvey F. Lodish, PhD, professor of biology and biomedical engineering at Whitehead Institute for Biomedical Research and Massachusetts Institute of Technology, for his key contributions and studies of the structure and biogenesis of red blood cells;
- Ernest Beutler Basic Science Award to Margaret A. Shipp, MD, director of the Dana-Farber/Harvard Cancer Center Lymphoma Research Program, for her work on the genetic basis of PD-1–mediated immune evasion in Hodgkin lymphoma and primary mediastinal B-cell lymphoma; and
- Ernest Beutler Translational/Clinical Award to Stephen M. Ansell, MD, PhD, chair of the Mayo Clinic Lymphoma Group, for his work in understanding the tumor microenvironment in lymphomas, including PD-1 blockade. Many more awards and lectureships outlining key findings in hematology were included at ASH 2021.

There were many sessions, round tables, and educational sessions on areas of high interest such as COVID-19 and the viral effects on patients with hematologic or thrombotic conditions, including some patients' decreased ability to mount an immune response to COVID-19 vaccines. A focus on diversity, equity, and inclusion included informative sessions on barriers to clinical trial design and enrollment, availability of transplantation to minority patients, race and science, and lessons from a global pandemic.

The scientific and poster sessions were wide-ranging in the topics presented. The hybrid of in-person and virtual meetings in some ways was beneficial to the presenters in the ability to reach a much wider audience. The plenary session included an introducer for each abstract to discuss the background of the abstract topic. Topics of abstracts in the plenary session included:

- SARS-CoV-2 and the pathologic mechanism of prothrombotic events caused by the virus;
- Studies of the molecular landscape of *TP53*-mutated leukemic transformation in myeloproliferative neoplasms;
- Primary analysis of the ZUMA-7 study (NCT03391466): a phase 3 randomized trial of axicabtagene ciloleucel (axi-cel) versus standard-of-care therapy in patients with relapsed/refractory large B-cell lymphoma;
- Efficacy and safety of fitusiran, an siRNA therapeutic, in a multicenter phase 3 study in individuals with hemophilia A or B, with inhibitors;
- Decreased risk of Alzheimer disease in patients with clonal hematopoiesis of indeterminate potential; and
- Profiling of circulating tumor DNA for noninvasive disease detection, risk stratification, and minimal residual disease monitoring in patients with central nervous system lymphoma.

I hope over the next few years the world becomes a safer place and we can get back to more normal educational and scientific sessions for the American Society of Hematology as well as other hematology and oncology meetings. ■

WHEN HER2+ MBC PROGRESSES

PURSUE UNPRECEDENTED SURVIVAL

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine[1]

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.

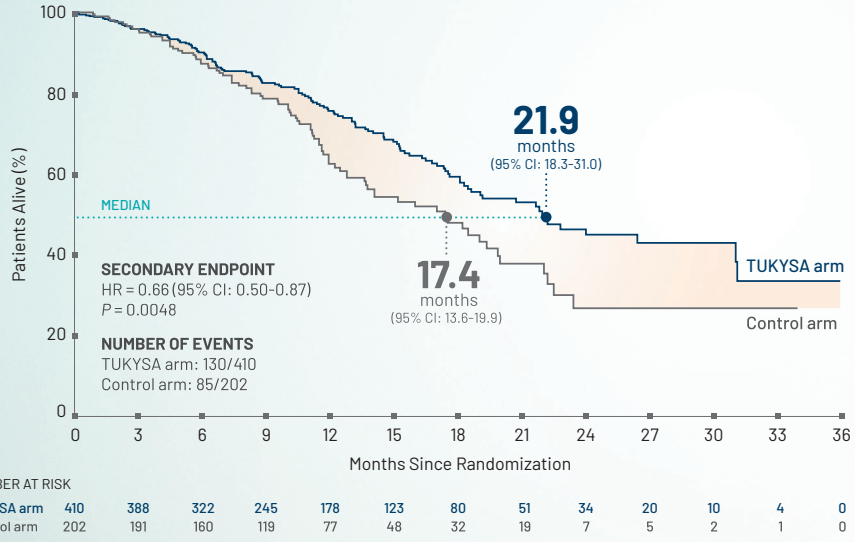
Please see full Important Safety Information on the following pages.

TUKYSA® tucatinib
50 mg | 150 mg tablets

RAISING THE STANDARD FOR **SURVIVAL**

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*[1]



NUMBER AT RISK

TUKYSA arm	410	388	322	245	178	123	80	51	34	20	10	4	0
Control arm	202	191	160	119	77	48	32	19	7	5	2	1	0

4.5 MONTH IMPROVEMENT IN MEDIAN OS

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash[1]

Important Safety Information

Warnings and Precautions

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

  If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients.

  Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

Adverse Reactions

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

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

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

TUKYSAhcp.com

In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

PRIMARY ENDPOINT*

PFS

46% reduction in the risk of disease progression or death[1]

- 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-free[2]

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 ≥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 (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. TUKYSA [Prescribing Information]. Bothell, WA: Seagen Inc. April 2020.
2. 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.

Seagen

TUKYSA® tucatinib
50 mg | 150 mg tablets

TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA® (tucatinib) tablets, for oral use

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

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

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

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

Dosage Modifications for Adverse Reactions

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

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

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

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

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

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

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

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

Clinical Trials Experience

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

HER2-Positive Metastatic Breast Cancer *(HER2CLIMB)*

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

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

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

Effects of TUKYSA on Other Drugs

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

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

Females and Males of Reproductive Potential

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

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

Contraception:

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

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

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

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

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

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

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

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2L=second line; DLBCL=diffuse large B-cell lymphoma; PFS=progression-free survival; R/R=relapsed/refractory.

References: 1. Zahid U, Akbar F, Amaraneni A, et al. A review of autologous stem cell transplantation in lymphoma. *Curr Hematol Malig Rep*. 2017;12(3):217-226. doi:10.1007/s11899-017-0382-1 **2.** Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333(23):1540-1545. doi:10.1056/NEJM199512073332305 **3.** Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505. doi:10.1182/asheducation-2011.1.498

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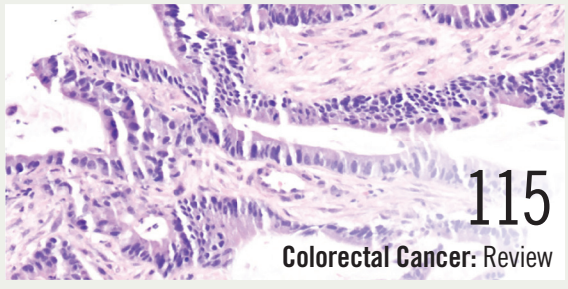

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Examining Aspects of Early-Career Oncology

In this issue of *ONCOLOGY®*, contributors focus on elements of an oncologist's early career that correlate with overall success.

In original research first presented at the 2021 American Society of Clinical Oncology Annual Meeting, Suneel D. Kamath, MD, of Cleveland Clinic Taussig Cancer Institute in Ohio, and colleagues examined financial conflicts of interest (COIs) and relationships with industry partners as they relate to success of junior faculty in top hematology and oncology academic centers (*see pages 84-91*). Findings included that the number of self-reported COIs were directly tied to the sum of payments from industry and that there was a nonsignificant relationship between years since fellowship and the number of COIs. Despite these data, the investigators were unable to determine the causality of the association. "The direction of this relationship—specifically, whether payments drive success or whether industry representatives identify promising and productive junior faculty and then provide greater financial support to them—could not be distinguished. As there are many factors that drive early career success, no causal association in our analyses could be established."

In a Peer Perspective on the topic, *ONCOLOGY®* editorial advisory board member Nora Janjan, MD, MPSA, MBA, discussed COIs as a responsibility that is shared across stakeholders, including both individuals and entities involved in research (*see page 90*). "Potential COI issues are managed and monitored through redundancies that exist within and outside of academic institutions," she wrote. "Involvement of junior faculty in conducting industry-funded clinical trials is crucial to maintaining the pipeline of academic oncologists to investigate future therapeutic advancements."

In a contribution from the editors at *Medical Economics®*, Heidi Moawad, MD, wrote about the importance of mentorships for both young and established physicians. She suggests establishing the expectations of the mentorship and the frequency and duration of meetings, as well as ensuring each participant has the bandwidth for the meetings (*see page 127*).

As always, keep up with our latest issues of the journal for more on this and other breaking topics. ■

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MEET OUR EXPERT

Michael Choti, MD, MBA, FACS is a surgical oncologist of the hepatobiliary tract and the pancreas; division chief of surgery at Banner MD Anderson Cancer Center at Banner Gateway Medical Center in Gilbert, Arizona, and co-chair of the *7th Annual* School of Gastrointestinal Oncology® Conference hosted by Physicians' Education Resource, LLC (PER®).

Leveraging Surgical Oncology to Treat Gastrointestinal Cancers

"The pendulum is moving fast towards giving chemotherapy prior to surgery, and the research is going on to continue that trend."

Surgical oncology is one part of the larger multidisciplinary team dedicated to bettering outcomes for patients with cancer. Standard of care integrative approaches incorporate chemotherapy and other systemic treatments after surgical resection of tumors. Now, that standard is evolving and other treatment modalities, such as chemotherapy or radiation, are being used prior to surgery with antitumor results evaluated after overall therapy.

In an interview with *ONCOLOGY*®, **Michael Choti, MD, MBA, FACS,** discussed how he has seen the surgical landscape change throughout his career. He spoke about the use of circulating tumor DNA (ctDNA) and molecular genotype testing to help improve management of gastrointestinal (GI) cancers.

Choti explained how his institution was one of the first to implement chemotherapy prior to surgery, and how other institutions are beginning to recognize this advancement. He discussed the need for genotyping, improved results through multidisciplinary care, and how ctDNA can treat GI cancers.

Q: Can you begin by discussing how surgery is evolving, aside from advancements in technique?

A: What's exciting is this area of integration, the timing of surgery, [and use of] molecular genetics [to indicate when] surgery has benefit rather than just rushing into surgery. We're using innovative areas to give preoperative chemotherapy, and in some cases [we] molecularly study the nuances of the cancer to know which patients may benefit more from surgery or not, or which patients get chemotherapy prior to surgery versus surgery up front. The most exciting area, besides technical robotic and other techniques, is related to understanding the biology of cancer and knowing when surgery is [appropriate]. So that's an area [to focus on].

A couple of other areas [where] there's work going on now is in ctDNA. We're looking at the ongoing studies where after the surgery, we can measure residual [disease] in the bloodstream when we think we "got it all out." We can then measure whether there may be residual cancer DNA in the bloodstream, and that can dictate whether there's residual cancer and whether to [give chemotherapy] after [surgery]. This may not be a surgical question, but it's very important to the surgical oncologist in understanding the completeness of the surgery and so forth.

On the imaging side, more sophisticated imaging that can either detect cancer sooner or earlier, in which case patients can undergo surgery or [the imaging], can help guide surgery. I pivot away from the pure technical question as

to how we stitch and how we sew and how we take out a cancer. Yes, there are some innovations—as I mentioned, in robotics and so forth—but I would say the most exciting area is regarding these other aspects.

Q: Are there any specific cancers where surgery has changed for use in conjunction with other modalities?

A: I would say the concept [began] 2 decades ago and started with rectal cancer where the standard 20 years ago was to remove the cancer and give chemo-radiation therapy after that. Now, most [patients] except [those with] very early-stage rectal cancer is treated with chemotherapy, and/or sometimes radiation therapy first. The innovative thing now in rectal cancers is to give [chemotherapy] prior to radiation therapy. Rather than giving someone chemo-radiation first and then the surgery and then [chemotherapy] after the surgery, we're giving more or all the chemotherapy prior to surgery, maybe with radiation, and then surgery later. The preoperative [area] has been there a long time but [continuously giving more chemotherapy,] not just chemoradiation, and giving more of it up front is what's innovative in the rectal cancer space.

In other areas such as pancreatic cancer if it's an operable pancreatic cancer, many around the country are still doing surgery first. [Banner Health] was one of the first centers [to do this] and now the NCCN [National Comprehensive Cancer Network] guidelines and others are finally recognizing that [patients should receive] preoperative chemotherapy for all pancreatic adenocarcinomas should get chemotherapy prior to surgery, not so much radiation.

The other area is stomach cancer or gastric cancer. The pendulum is moving fast towards giving chemotherapy prior to surgery, and the research is going on to continue that trend. The surgical management of cancer is giving more and more systemic chemotherapy prior to surgery rather than the standard [of care] which is take [the cancer] out and then give it after. I mentioned rectal cancer, pancreas, stomach, and now the areas of study are to continue that expansion to liver cancer, biliary cancer, cholangiocarcinoma, where now there is research going on [regarding which] patients we should be giving chemotherapy to prior to surgery. The standard now for cholangiocarcinoma, or bile duct [cancer, is] if it's operable, to do surgery first, just as it was with stomach cancer or pancreatic cancer. There are ongoing studies to see if it will become the standard now to consider chemotherapy [prior to surgery for] GI cancers such as bile duct cancers and so forth.

Q: Has the coordination between surgeons and other oncology professionals evolved? Or does it need improvement?

A: We call it the multidisciplinary care, and that means historically cancer care was linearly managed. You see a surgeon [after you have received a] diagnosis by a gastroenterologist who refers to surgery, then an oncologist, and then referred for [chemotherapy] after rather than when you have the diagnosis at the beginning. In early-stage cancer [such as] stomach cancer, you may do surgery first or [patients] may never need chemotherapy. Quality of the imaging [and] of the molecular testing [needed to be] a priority before you have this unified plan among the whole team about which weapons or which arrows in your quiver to use to optimize the cancer care of that patient. Up front, that's a so-called multidisciplinary care.

Candidly, it's a challenging way in cancer care in America because it's all fragmented. That's why there's a big push toward integrated cancer care, [including] tumor boards and multidisciplinary conferences. We're building MDCs, multidisciplinary clinics, where not just the care is coordinated but there's 1 visit for the patient, who shows up and sees everybody at the same time. We're fortunate to [offer the] integrated cancer center; we can deliver that level of care that our competitors sometimes can't.

Q: What do surgeons need to know about the genotype of tumors they're operating on?

A: Oncologists need to have an understanding [that] molecular genetics are not necessarily only in the realm of the medical oncologist; as new targeted therapies are being developed based on the molecular signature of the tumor. They're drug related, and we don't have too many models of which molecular signature may change or dictate the nature of the operation itself. There are some selected cases where that may be the case. For example, if it's a hereditary form of colon cancer that has a molecular signature, it may change the extent or nature of the operation, or it may change the prognosis after surgery based on a certain molecular signature. There may be cases in which a patient has a unique molecular signature, and we may not need to do surgery [because] chemotherapy is so effective. It's rare at least in solid malignancies, but there are some examples of that.

We may want to change the sequencing of surgery versus [chemotherapy] based on the molecular signature. I do think it's valuable and [it's important to] put emphasis on that for anyone caring for patients with cancer. [Clinicians] need to understand the value of the of the molecular analysis of the tumor and how exciting this is as a paradigm shift. [This is] particularly true in the in the realm of immunotherapy. It's still a minority of patients who may be candidates for immunotherapy, but there's a lot of

research going on into how we can expand immunotherapy drugs in patients who don't necessarily have an immunogenic form of cancer. [With] ctDNA, which is molecular genetics of not just the tumor or biopsy but of the shed cancer in the bloodstream, you can potentially profile the genetics of a cancer by sequencing in the bloodstream.

It's like a liquid biopsy from the blood. From a surgical standpoint, what's particularly exciting is the ability after surgery to take the tumor, measure the molecular genetics in the tumor, and then develop a personalized molecular test for that patient to measure in their blood for minimal residual cancer after surgery, which can then dictate whether to take [chemotherapy]. The ctDNA aspect is going to be increasingly useful across the board. It will expand not just for [chemotherapy], but it will guide the response to therapy, the management of therapy, and whether to give further treatment after surgery.

Q: How close are we to using ctDNA to diagnose or guide treatment for GI cancers?

A: There are already some aspects where it's currently being used selectively and insurance is paying, but it's limited. There are a variety of domains. One is to be able to achieve the value of the molecular genetics of the tumor. You can use ctDNA to determine the full genomic profile of a patient with cancer. The other way is the response to therapy. If somebody has advanced cancer and they're getting chemotherapy, we start [chemotherapy] and we give [chemotherapy] for a month or 2 and see if the spots shrink on scans. A month or 2 later, in theory, you can give 1 dose and see the next day or a week later whether the burden of mutation goes down. You can then nimbly adjust and determine if that therapy is working. You don't have to be pummeling somebody with an ineffective form of chemotherapy again; [you can use] response to therapy to determine more quickly in real time the efficacy of therapy.

Even now, there are some examples of resistance clones where a patient [has tumor shrinkage initially but it] starts to grow with chemotherapy because there's a mutation emerging. You must switch the chemotherapy. Those are things that now some medical oncologists are using ctDNA for advanced cancer. The key is to get the word out because the research needs to be done to validate it. The second is to have insurance and [consider] it as part of a standard of practice so that we can then use it. ■

Association of Financial Conflicts of Interest With Academic Productivity Among Junior Faculty in Hematology and Oncology

Suneel D. Kamath, MD[1]; Angela J. Fought, MS[2]; Melissa M. Shaw, MD[3]; and Andrew A. Davis, MD[4]

ABSTRACT

INTRODUCTION: Financial conflicts of interest (COIs) represent a common and complex issue in hematology and oncology. However, little is known about the timing of when COIs begin to develop during a career trajectory. We evaluated self-reported COIs for junior faculty members at top cancer centers to determine how these financial relationships correlated with measures of academic career productivity.

METHODS: We analyzed data from 230 assistant professors at 10 academic cancer centers. Financial COIs were identified from the CMS Open Payments (Sunshine Act dollars) database. Self-reported COIs were obtained from American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) disclosures, and from disclosures in recent publications. Number of publications and h-index (defined as the largest number of publications [h] such that h publications each have at least h citations) were used as measures of academic productivity. Scatter plots and Spearman correlation coefficients were used to assess the relationship between COIs or Sunshine Act dollars with number of publications and h-index. Linear regression modeling was used to analyze the relationships between COIs or Sunshine Act dollars with number of publications and h-index, adjusting for years of experience since completing fellowship (YSF).

RESULTS: A total of 46% of junior faculty had at least 1 COI. Number of COIs reported to ASCO/ASH was positively correlated with total Sunshine Act dollars (Spearman correlation, 0.53; $P < .01$). The number of COIs and the number of Sunshine Act dollars increased with years in practice (Spearman correlation, 0.38 and 0.25, respectively; $P < .01$ for both). COIs and Sunshine Act dollars correlated with h-index (Spearman correlation, 0.41 and 0.37, respectively; both $P < .01$). After adjusting for YSF, linear regression demonstrated that log-transformed h-index and number of publications were associated with Sunshine Act dollars (both $P < .01$) and COIs (ASCO/ASH) (both $P = .01$).

CONCLUSIONS: Financial COIs increased with number of YSF. Measures of academic productivity were positively correlated with COIs (ASCO/ASH) and Sunshine Act dollars. These data suggest that the cultivation of industry relationships is associated with the early academic productivity of junior faculty.

PERSPECTIVE

Nora Janjan, MD, MPSA, MBA, provides perspective on page 90

Introduction

Financial conflicts of interest (COIs) are increasingly important in oncology due to their potential influence on policy makers, scientific investigators, and clinicians. In the drug regulatory space, a significant percentage of expert speakers advising the FDA Oncologic Drugs Advisory Committee on new drug approvals receive payments from the pharmaceutical companies that are producing the drugs under consideration.[1] An analysis of industry relationships among authors of the National Comprehensive Cancer Network guidelines showed that 86% had at least 1 COI and 47% received research payments, including for funding of clinical trials, with a mean value of $236,066.[2] These data reinforce how common research payments in oncology are, as well as the need to carefully examine their potential influence on research and clinical practice. Additionally, inconsistent disclosure guidelines for COIs across journals and professional societies make transparency regarding COIs extremely challenging.[3-5]

While the potential negative effects of financial COIs on research and clinical practice have been well described, industry relationships may be important for academic career success. With success rates for applications to governmental funding mechanisms at or below 20%, industry represents an increasing source of funding for researchers in oncology and a potential driver of career success.[6-8] For example, a study of 435 senior academic physicians published in high-impact factor journals demonstrated a positive association between receiving industry funding and increased publication rate.[9] However, the timing of when these industry relationships begin to develop remains largely unknown.

As such, we conducted a cross-sectional study of junior faculty in hematology and oncology at major academic cancer centers to evaluate patterns of COIs with the number of years of experience since completing fellowship (YSF) and to determine if increasing COIs and industry funding correlate with greater academic success.

Materials and Methods

Study Population

All faculty with assistant professor positions or titles of similar rank from the top 10 US cancer centers, based on the 2018 *U.S. News & World Report* hospital rankings, were included in the study. Faculty members who had only a PhD (ie, no MD) were excluded. Assistant professors were identified by review of the cancer centers' academic and/or clinical websites. Baseline characteristics including gender, number of degrees (MD alone vs MD + additional graduate/doctoral degree), board certifications, and YSF in categories (2004-2012; 2013-2014; 2015-2016; 2017-2018) were collected from each faculty member's webpage and analyzed using descriptive statistics. Data were collected from February 2019 to May 2019. Measures of academic success, including number of publications, h-index (defined as the largest number of publications [h] such that h publications each have at least h citations), and National Institutes of Health (NIH) funding, were collected. Number of publications and h-index were collected from the Scopus website.*

NIH funding was collected from the NIH RePORT tool and recorded as both the presence or absence of NIH funding and the dollar amount. All data were collected up to December 31, 2018.

Measures of potential financial COIs including Sunshine Act data (the sum of dollars received from industry payments from 2013-2017 were used, based on available data as of May 2018) and disclosed relationships from recent publications and professional society databases were collected. Further, the subset of payments demarcated as research related was also examined. The CMS Open Payment database was accessed to collect the total number of dollars received and number of transactions with industry for each junior faculty member. CMS Open Payment dollars will be referred to as Sunshine Act dollars. If no Sunshine Act dollars were reported, we indicated these values as 0 for the individual.

Professional society disclosures were collected from the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) websites. If no COIs were identified on these websites, other hematologic or oncologic professional society databases (eg, the American Association for Cancer Research) were used.

Statistical Analysis

Descriptive statistics of institution and faculty characteristics were included. Scatter plots and Spearman correlation coefficients were used to assess the relationship among COIs reported to ASCO/ASH, the highest number of COIs reported in recent publications, Sunshine Act dollars (US), YSF categories (listed in increasing amount of experience: 2017-2018, 2015-2016, 2013-2014, 2004-2012), h-index, and total number of publications. We also evaluated the Spearman correlation between the number of research-specific COIs and Sunshine Act dollars. We visually assessed the relationships among the outcome, h-index, and the number of COIs (ASCO/ASH) and Sunshine Act dollars, using scatter plots stratified by the YSF categories.

*https://www.scopus.com/freelookup/form/author.uri?zone=TopNavBar&origin=NO%20ORIGIN%20DEFINED

TABLE. **Number of Faculty From Each Included Academic Institution and Junior Faculty Characteristics**

Characteristic	N (%)
Institution	
Cleveland Clinic Taussig Cancer Institute	13 (6)
Dana-Farber/Brigham and Women's Cancer Center	38 (17)
H. Lee Moffitt Cancer Center of the University of South Florida	25 (11)
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University	25 (11)
The University of Texas MD Anderson Cancer Center	32 (14)
Mayo Clinic Cancer Center	10 (4)
Memorial Sloan Kettering Cancer Center	37 (16)
Seattle Cancer Alliance/University of Washington Medical Center	25 (11)
University of California San Francisco Helen Diller Family Comprehensive Cancer Center	6 (3)
University of Pennsylvania Abramson Cancer Center	19 (8)
Sex	
Female	103 (45)
Male	127 (55)
Board certification	
Single	149 (65)
Double	81 (35)
Degrees	
MD only	140 (61)
Dual degree	90 (39)
Year of fellowship completion (groups listed by increasing amount of experience)	
2017-2018	40 (17)
2015-2016	49 (21)
2013-2014	67 (29)
2004-2012	74 (32)
Any NIH funding, 2013-2017	
No	195 (85)
Yes	35 (15)

We also performed 2 linear regression models with log-transformed h-index as the outcome. The first included YSF categories and total number of COIs (ASCO/ASH), and their interaction as covariates. The second model included Sunshine Act dollars, YSF categories, and their interaction. Next, we repeated these models with log-transformed total number of publications as the outcome. All analyses were performed using SAS 9.4. A significance level of $P < .05$ was used for the Spearman correlations and linear regression models.

Results

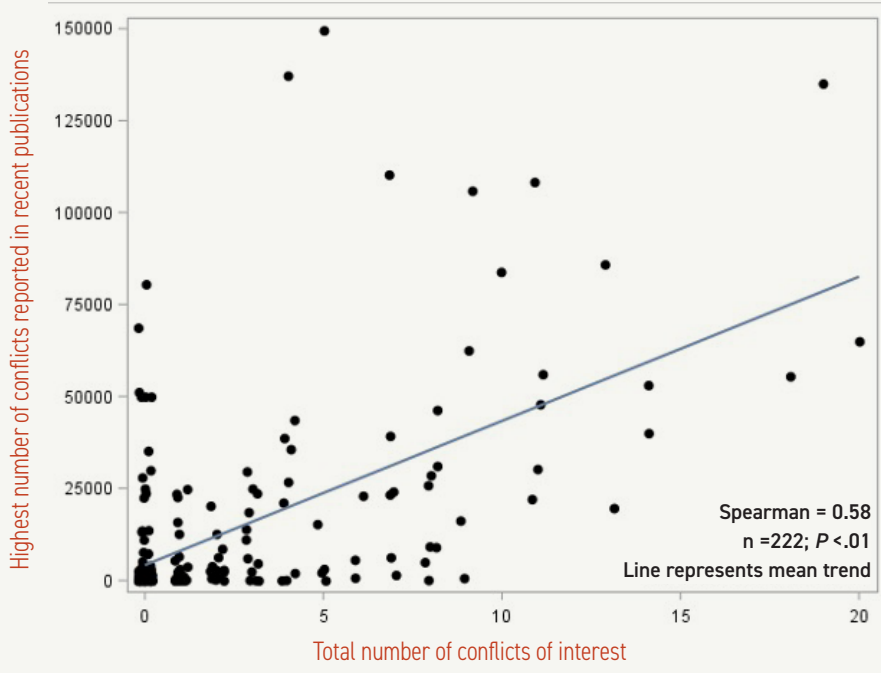
We identified 230 junior faculty members from the 10 cancer centers included in our analysis (Cleveland Clinic Taussig Cancer Institute, Dana-Farber/Brigham and Women's Cancer Center, H. Lee Moffitt Cancer Center of the University of South Florida, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Mayo Clinic Cancer Center, The University of Texas MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Seattle Cancer Alliance/University of Washington Medical Center, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, and University of Pennsylvania Abramson Cancer Center). The cohort consisted of 55% males and 45% females. The majority of physicians were single-boarded in either medical oncology or hematology (n = 149; 65%). Thirty-nine percent of faculty members had an advanced degree in addition to an MD or an MD equivalent. Fifteen percent of junior faculty had received NIH funding at the time of our analysis. These data and other physician characteristics are summarized in the **Table**.

For reported COIs to ASCO or ASH, 46% (103 of 224; 6 missing values) of the junior faculty had at least 1 COI. The median number of COIs was 0 (range, 0-25) and the median number of Sunshine Act dollars received was $1338 (range, $0-$823,399). Note that $823,399 was significantly higher than the next highest value, $149,558. Since $823,399 was an influential outlier, it was excluded from the linear regression models with Sunshine Act dollars as a predictor.

In the overall population, there was a moderate positive correlation between COIs disclosed to ASCO/ASH and the highest number of COIs from recent peer-reviewed publications (Spearman correlation coefficient, 0.58; $P < .01$). Both had medians of 0 and similar ranges, but the 75th percentile was higher for COIs from ASCO/ASH as compared with the highest number of COIs reported in recent publications: 3 vs 1, respectively. While the measures of COI were not statistically different overall, the goal was to capture as many COIs as possible, and we therefore used COIs from ASCO/ASH primarily, referring to this as COIs moving forward. Reported COIs were positively correlated with the number of Sunshine Act dollars received from industry (Spearman correlation, 0.53; $P < .01$; **Figure 1**). Similarly, we found a positive association between the number of research-specific COIs and Sunshine Act dollars (Spearman correlation, 0.42; $P < .01$).

To illustrate the relationship between YSF and development of COIs, we divided the sample into 4 categories based on timeframe since

FIGURE 1. **Correlation Between Total Sunshine Act Dollars and Total Number of Reported Conflicts of Interest**



Scatter plot showing the Spearman correlation coefficient between total Sunshine Act dollars earned and total number of conflicts of interest reported to the American Society of Clinical Oncology and/or the American Society of Hematology for the included junior faculty. The blue line indicates the mean trend line. Since the maximum value, $823,399, decreases the visual display of the relationship, it was excluded from the plot but not the Spearman correlation.

completing fellowship, in increasing order of experience: 2017-2018 (n = 40; 17%); 2015-2016 (n = 49; 21%); 2013-2014 (n = 67; 29%); and 2004-2012 (n = 74; 32%). The total number of COIs and Sunshine Act dollars obtained from industry increased as YSF increased (**Figures 2A and 2B**). For new junior faculty who completed fellowship in 2017 or 2018, the median number of COIs was 0 (range, 0-3) and the median number of Sunshine Act dollars was $173 (range, $0-$23,547). Only 2 individuals of the 40 in this group (5%) received more than $10,000 in Sunshine Act dollars. In contrast, 35 of 74 faculty (47%) who completed fellowship between 2004 and 2012 received more than $10,000 in Sunshine Act funds and 7 of the 74 in this group (9%) received more than $100,000 (**Figure 3**).

COIs and dollars obtained from industry correlated with h-index (Spearman correlation coefficient, 0.41 and 0.37, respectively; both P <.01). Multivariate analysis demonstrated that in addition to a positive association between YSF and the outcome log-transformed h-index (P <.01), there was an independent positive relationship with Sunshine Act dollars (P <.01). Similarly, there was a positive relationship between log-transformed h-index and COIs (P = .01), adjusting for YSF (P <.01). Figure 2 visually displays the relationship between the log-transformed h-index outcome with COIs (2A) or industry dollars (2B), stratified by YSF.

Total number of publications was also related to COIs and dollars obtained from industry (Spearman correlation coefficient, 0.45 and 0.44, respectively; both P <.01). No clear differences existed between junior faculty with or without NIH funding regarding the impact of COI on outcome measures. In each of the 2 multivariate linear regression models (with log-transformed number of publications as the outcome), COIs (P = .01) and industry dollars (P <.01) were significant, adjusted for YSF (P <.01 for both models).

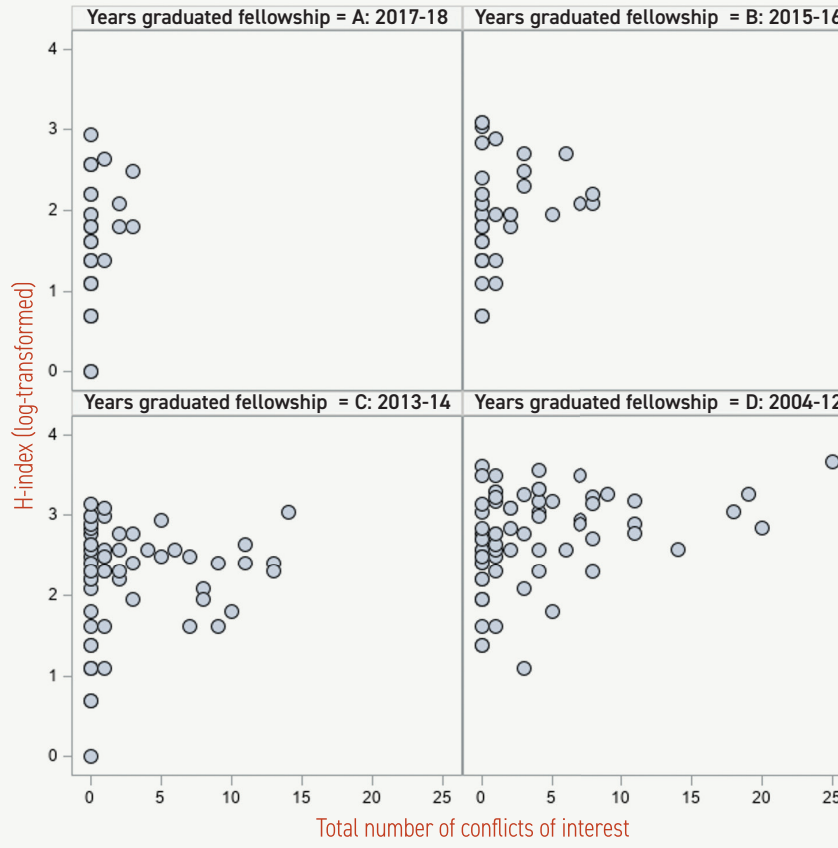
Discussion

Financial COIs and relationships with industry were common among junior faculty in hematology and oncology at top academic centers. Our study findings confirmed our primary hypothesis that financial relationships with industry were correlated with traditional markers of early career success, independent of YSF. The direction of this relationship—specifically, whether payments drive success, or whether industry representatives identify promising and

productive junior faculty and then provide greater financial support to them—could not be distinguished. As there are many factors that drive early career success, no causal association in our analyses could be established.

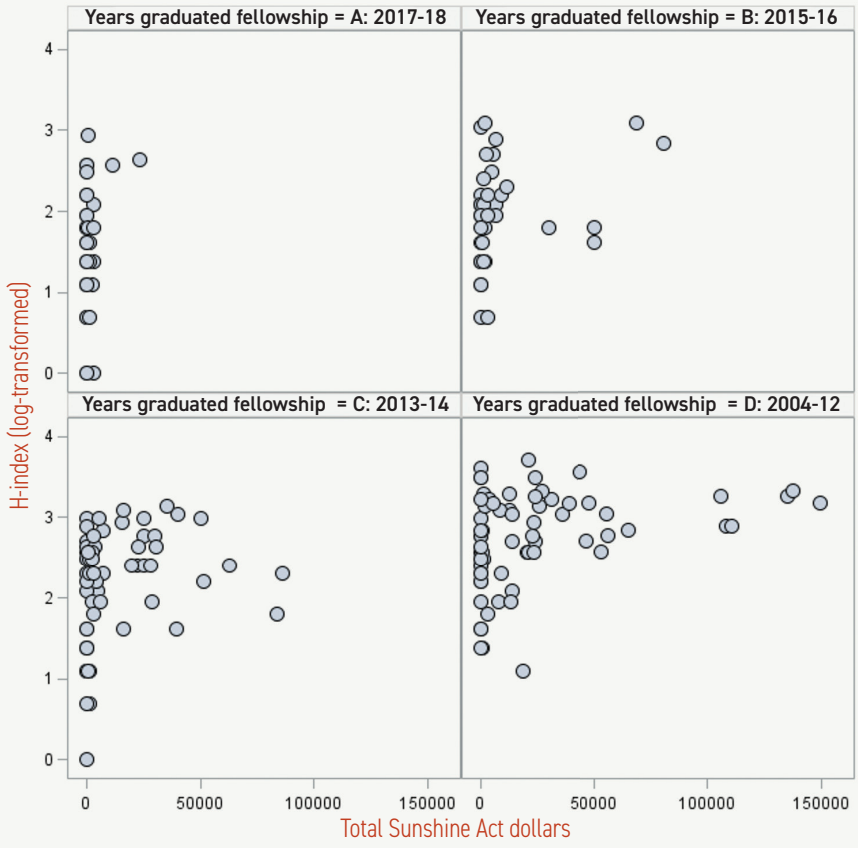
Our study demonstrated several other key findings with important implications. First, the number of self-reported COIs was directly correlated with Sunshine Act dollars; this serves as a surrogate for industry relationships. These measures were independent markers of academic success in multivariate analysis. Second, while the interaction between COIs and YSF was not significant, there appeared to be a relationship, as shown in Figure 2A. Interestingly, both individuals with and without NIH funding received payments from industry and reported potential COIs. Third, financial COIs accumulated over time in terms of Sunshine Act dollars received from industry and number of reported COIs. Fourth, interactions with industry were highly variable across individuals. While the median number of reported COIs was low at 0, the range of 0 to 20 was broad. Similarly, the median number of Sunshine Act dollars was relatively low at $1366, but there was a broad range of $0 to $149,558, with an outlier of $823,399. Further, while there was relatively good correlation between COIs reported to ASCO/ASH and in recent publications, there was variability among individuals. This may exist because ASCO and ASH COI reporting guidelines encourage faculty to disclose all potential COIs more broadly, while journal disclosure guidelines may be less clear and not standardized. These data, combined with results of prior studies, emphasize the critical need for standardized guidelines for reporting of COIs across publications and professional societies.[10,11]

FIGURE 2A. **Relationships Between H-Index and Number of Conflicts of Interest Stratified by Years Since Completing Fellowship**



Across all disciplines, and in oncology in particular, traditional funding sources from the government are fiercely competitive, with NIH grant success rates at or below 20%.[8] Even for some of the elite cancer centers in the United States, NIH grants had been given to only 15% of junior faculty members included in the study. Given the scarcity of academic resources, coupled with pressure to produce scientific output to be eligible for promotion, many hematology and oncology faculty rely on interactions with pharmaceutical and/or biotechnology companies to help fund clinical trials or correlative studies. In fact, from 2006 to 2014, NIH-funded clinical trials decreased by 24%, while industry-funded trials increased by 43%.[6] As a result, industry has become the dominant source for biomedical research funding in the United States.[12] Furthermore, many therapeutic trials led by the National Cancer Institute include funding from pharmaceutical companies. For physicians, the mechanisms for obtaining this funding are less formalized compared with traditional grant applications, but they are likely to be facilitated by greater overall interaction with the private sector. Junior faculty may use this "non–grant-based"

FIGURE 2B. **Relationships Between H-Index and Sunshine Act Dollars Stratified by Years Since Completing Fellowship**



Scatter plots displaying the relationship between total number of conflicts of interest reported to the American Society of Clinical Oncology and/or the American Society of Hematology and log-transformed h-index (2A) and between total number of Sunshine Act dollars and h-index (2B), stratified into 4 groups based on year of completing fellowship. Since the maximum Sunshine Act value, $823,399, decreases the display of the visual relationship, it was excluded from the 2B plot.

funding mechanism to help advance their careers as physician-scientists or clinical investigators. However, the exact mechanisms and potential causations for how this may occur were not explicitly tested in our analyses.

Limitations and Strengths

This study is the first to specifically evaluate the relationship between early-career interactions with industry and how these may correlate with career success for junior faculty in academic hematology and oncology. There are several limitations to our work. First, measures of academic success tend to increase over time. Therefore, while COIs correlated with academic success in our results, increasing experience and time remained a confounding factor and thus no causal relationship between COIs and academic success could be established. Given the cross-sectional nature of the analysis, the ability to characterize promotion to associate professor or departure to other career trajectories (eg, private practice) could not be addressed, as these decisions depend on multiple factors. Second, Sunshine Act dollars are not a direct reflection of research funding (because many payments are for travel or speaking engagements) and may only serve as an indicator of industry interactions. In addition, these dollars may not fully reflect payments received from biotechnology firms, medical device companies, and businesses outside of the United States. Recent data have also reported significant discordance between self-reported and industry-related COIs, which indicates some degree of inaccuracy in these measures. In addition, guidelines associated with reporting of COIs to ASCO and ASH have changed over time, and there are some differences between how each society reports COIs.[5] However, we attempted to limit this reporting bias by obtaining the COI information from multiple sources, including professional society websites and recent publications. Third, other sources of funding, including institutional grants or foundation grants, were

PERSPECTIVE BY

Nora Janjan, MD, MPSA, MBA

Academic Promotion and Oncology Drug Development: Role, Responsibilities, and Integrity

Conflicts of interest ultimately focus on roles, responsibility, and integrity. Drug development, especially in oncology, is a complicated process that involves many individuals and entities. Each makes a specific contribution to the process and provides redundant oversight. This redundancy is intended to minimize bias and risk while evaluating benefit to the patient. At any stage of their career, those responsible for the lives of patients must have unquestionable credibility and integrity.

Every sector of medicine has a role in the process of evaluating a drug, both before and after regulatory approval. Pharmaceutical companies develop molecules, navigate regulatory pathways, fund clinical trials, manufacture the drug, and ultimately distribute the medication to pharmacies. Academic oncology centers conduct clinical trials to confirm the safety and efficacy of a drug, both before and after FDA approval. Health economics and outcomes research (HEOR) is increasingly being performed by health care policy institutes within academia and independent entities. Clinical research is scrutinized through peer review by institutional review boards (IRB), program committees of organized medicine, and medical journals before publication.

Conflicts of interest (COI) for every physician and entity come down to integrity. Research integrity, as defined by the National Institutes of Health (NIH), involves honesty, accuracy, efficiency, and objectivity.[1] Integrity also requires transparency, especially regarding financial and other personally beneficial relationships.[2] Beyond investigators, the NIH also has strict COI rules for reviewers of NIH applications and contract proposals.[3]

The concerns regarding COI generally focus on the pharmaceutical firm and the faculty member. Faculty, in an American Society of Clinical Oncology audit of its journal authors, were found to be thorough in disclosing research and consulting relationships.[4] Within an academic construct, the institution's legal and IRB approvals must first be obtained before a clinical trial can only be conducted. The academic institution is ultimately responsible for approving, monitoring, and managing the clinical trial and faculty COI disclosures.

The authors in this study emphasize that clinical research would be highly restricted if it were only funded by the NIH given its limited scope of research and budget. Within this survey, only 15% of these junior faculty had NIH funding.[5] Approximately one-third of all clinical trials registered on ClinicalTrials.gov are industry sponsored.

With long-standing experience in the conduct of clinical trials, academic oncology centers provide specific benefit to patients. Patients often seek care at academic institutions to participate in clinical trials and receive cutting-edge therapy. Before FDA approval, faculty physicians within an academic institution gain experience with an agent, and closely monitor and treat adverse events. Outside of academic centers, few oncology practice centers have a sufficient health care infrastructure that could safely conduct (especially early phase) clinical trials for pharmaceuticals prior to FDA approval.

Through the conduct of these clinical trials, junior academic oncology faculty gain specialized expertise that can direct their research careers. Practice-influencing results from these clinical trials, after peer review, are presented within plenary sessions or as keynote presentations within high-profile annual specialty society meetings to inform oncologists of the outcomes. Publication of the clinical trial results in high-impact factor journals subsequently are included in regulatory filings and influence clinical practice guidelines that broadly expand patient access to the therapeutic.

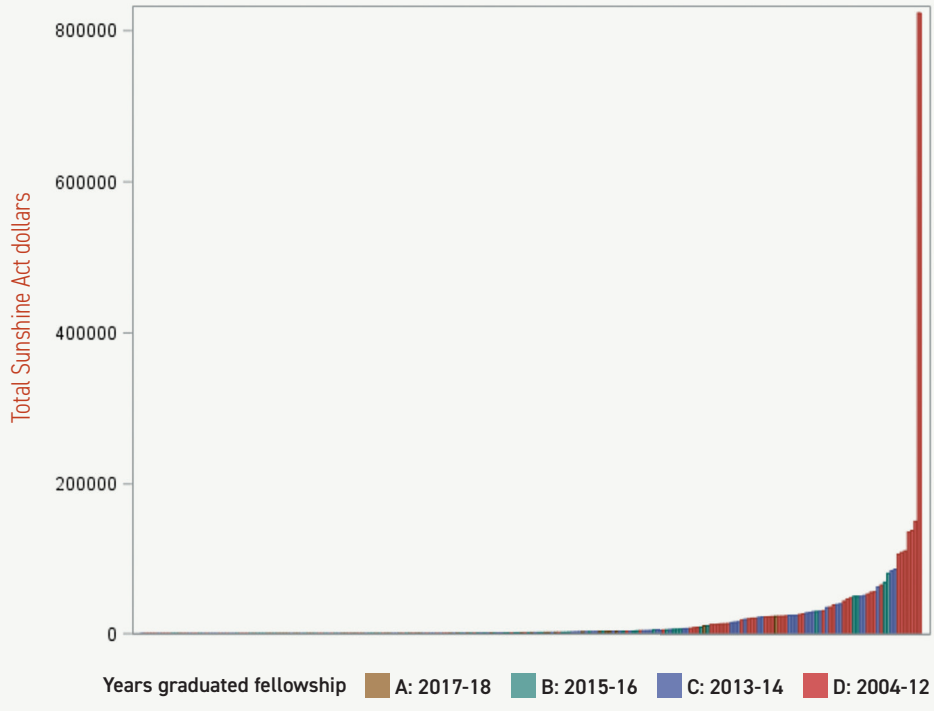
The encouraging finding from this study is that a high percentage of junior faculty are given opportunities to conduct significant clinical trials that allow career advancement, which supports a future pipeline of academic oncologists. Although the number of women enrolling in medical school now exceeds men, the number of women among medical oncology academic faculty is only 37.1%.[6,7] In this study, women accounted for 45% of the 230 young academics from the top 10 cancer centers who were involved with industry-sponsored studies, suggesting recognition of the continued need for mentorship.

Given limited NIH funding opportunities, many junior faculty members launch successful academic careers by conducting industry-funded clinical trials. Potential COI issues are managed and monitored through redundancies that exist within and outside of academic institutions. Contrary to COI concerns, involvement of junior faculty in conducting industry-funded clinical trials is crucial to maintaining the pipeline of academic oncologists to investigate future therapeutic advancements.

Janjan is a senior fellow in health care policy at the Goodman Institute of Dallas, Texas, which is headed by economist John Goodman, PhD, the father of health savings accounts. She is also the chief medical officer of STATinMED Research, a for-profit company that conducts HEOR for various entities including pharmaceutical firms.

For references visit cancernetwork.com/Janjan_2.22

FIGURE 3. **Sunshine Act Dollars Received By Faculty Categorized By Years Since Completing Fellowship**



Plot showing the number of faculty (n = 230) who received Sunshine Act dollars, categorized by years since completing fellowship. The 4 groups are denoted by 4 different colors.

not captured in our data, and these funding sources may also contribute to junior faculty career success.

Conclusions

The aim of our analysis was to evaluate the prevalence and associations of COIs over time in junior faculty in hematology and oncology in a representative sample of academic medical centers. We found that COIs and industry payments accumulated over time after faculty members completed fellowship training. Furthermore, interactions with industry correlated with measures of academic success (ie, h-index and number of publications). These data suggest that early academic success may be linked to funding, either obtained from industry or traditional government-based grant sources, but whether industry payments alone drive career success could not be established. In addition, there is an ongoing need to harmonize the reporting of COIs across meeting and publication platforms. ■

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CONTRIBUTIONS: AAD and SDK designed the study. AAD, MMS, and SDK generated the data. AAD, AJF, and SDK analyzed the data. SDK and AAD wrote the first draft of the manuscript. All authors approved the manuscript.

For references visit cancernetwork.com/Kamath_2.22

BAVENCIO® avelumab Injection 20 mg/mL

First-line maintenance treatment of urothelial carcinoma

BAVENCIO® (avelumab) is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

Based on overall survival (OS) data

The FIRST and ONLY immunotherapy approved in the first-line maintenance setting

NCCN CATEGORY 1 & PREFERRED

National Comprehensive Cancer Network® (NCCN®) Recommendation

Avelumab (BAVENCIO) maintenance is the only NCCN **CATEGORY 1** and **PREFERRED** immunotherapy option for both cisplatin-eligible and -ineligible patients with locally advanced or metastatic UC that has not progressed on first-line platinum-containing chemotherapy.[1]

Category 1=Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Preferred intervention=Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

IMPORTANT SAFETY INFORMATION (continues on following pages)

BAVENCIO can cause **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

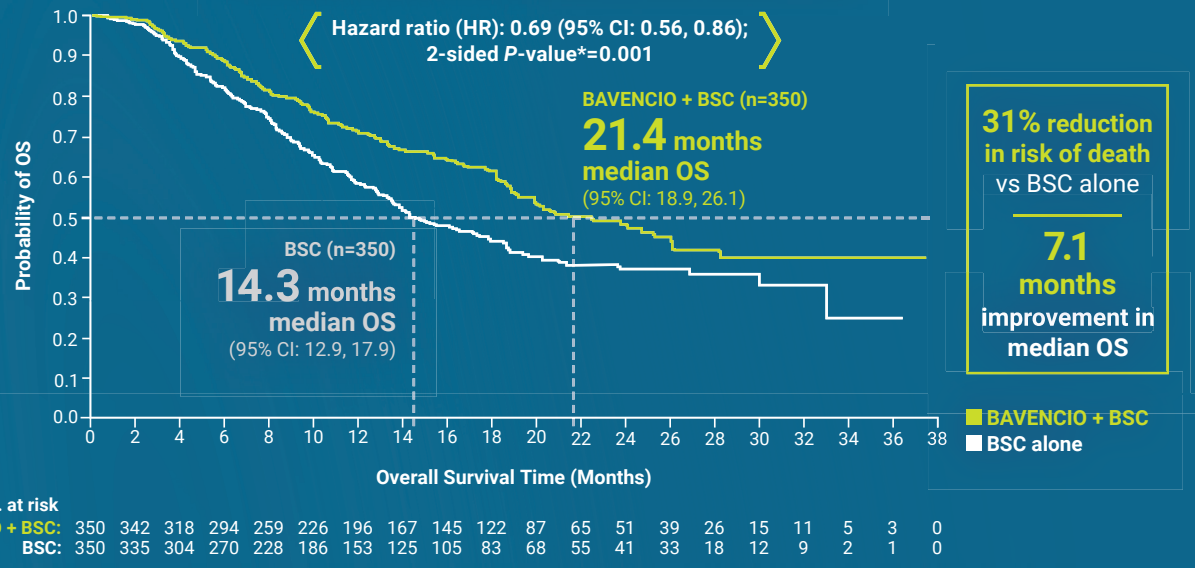
BAVENCIO can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

JAVELIN Bladder 100 Trial—a Phase 3, randomized, open-label, multicenter study in patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=700)[2]

BAVENCIO® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone

All randomized patients (major efficacy outcome measure)



No. at risk																			
BAVENCIO + BSC:	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC:	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

- OS was measured post-randomization (after chemotherapy)

- OS in patients with PD-L1-positive tumors† (major efficacy outcome measure). BAVENCIO + BSC showed statistically significant improvement in OS vs BSC alone in patients with PD-L1-positive tumors (n=358, 51%); HR: 0.56; (95% CI: 0.40, 0.79; 2-sided *P*-value <0.001)
- OS in patients with PD-L1-negative tumors† (exploratory analysis). In patients with PD-L1-negative tumors (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18)

Most common adverse reactions in the JAVELIN Bladder 100 Trial

The most common adverse reactions (≥20%) in patients receiving BAVENCIO + BSC vs BSC alone were:

- Fatigue (35% vs 13%)
- Musculoskeletal pain (24% vs 15%)
- Urinary tract infection (20% vs 11%)
- Rash (20% vs 2.3%)

For information on warnings and precautions, see Important Safety Information starting on the previous page.

Study design: The JAVELIN Bladder 100 Trial was a Phase 3, 1:1 randomized, open-label, multicenter study of BAVENCIO as a first-line maintenance treatment in 700 patients with unresectable, locally advanced or metastatic UC who did not progress on 4 to 6 cycles of platinum-containing chemotherapy (gemcitabine + cisplatin and/or gemcitabine + carboplatin), and an ECOG PS of 0 or 1.[2] Patients with autoimmune diseases or medical conditions requiring systemic immunosuppression were excluded. Patients were randomized to BAVENCIO 10 mg/kg intravenous infusion every 2 weeks + best supportive care (BSC) (n=350) or BSC alone‡ (n=350) until disease progression or unacceptable toxicity. Treatment was initiated within 4 to 10 weeks after chemotherapy. OS was the major efficacy outcome measure in all randomized patients and patients with PD-L1-positive tumors.§

**P*-value based on stratified log-rank.

† Using the VENTANA PD-L1 (SP263) assay, PD-L1-positive status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively. If none of these criteria were met, PD-L1 status was considered negative.[2]

‡ BSC was administered as deemed appropriate by the treating physician, and could include treatment with antibiotics, nutritional support, and other patient management approaches with palliative intent (excludes systemic antitumor therapy).[2]

§ PD-L1 expression was assessed in tumor samples using the VENTANA PD-L1 (SP263) assay.[2]

BICR=blinded independent central review; CI=confidence interval;
ECOG PS=Eastern Cooperative Oncology Group (ECOG) Performance Status;
PD-1=programmed death-1 receptor; PD-L1=programmed death ligand-1.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.

IMPORTANT SAFETY INFORMATION (continued)

BAVENCIO® (avelumab) can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

BAVENCIO can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

BAVENCIO can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

BAVENCIO can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

BAVENCIO can result in **other immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

A **fatal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving BAVENCIO + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

The **most common adverse reactions** (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 13%), musculoskeletal pain (24% vs 15%), urinary tract infection (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving BAVENCIO, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Selected laboratory abnormalities (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

Please see Brief Summary of Prescribing Information on following pages.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 3, 2021. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content or its use or application and disclaims any responsibility for its use or application in any way. **2.** Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383(13):1218-1230.

May 2021 US-AVE-00615 V.2.1

BAVENCIO® (avelumab) injection, for intravenous use **Rx only**
BRIEF SUMMARY: Please see package insert for Full Prescribing Information

INDICATION AND USAGE

First-Line Maintenance Treatment of Urothelial Carcinoma
BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions: BAVENCIO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue BAVENCIO depending on severity. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis: BAVENCIO can cause immune-mediated pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (21/21) patients with pneumonitis. Pneumonitis resolved in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colitis: BAVENCIO can cause immune-mediated colitis. The primary component of the immune-mediated colitis consisted of diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.5% (26/1738) of patients receiving BAVENCIO, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Colitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.5% of patients. Systemic corticosteroids were required in all (26/26) patients with colitis. Colitis resolved in 69% (18/26) of the patients. Of the 8 patients in whom BAVENCIO was withheld for colitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, 40% had recurrence of colitis.

Hepatotoxicity and Immune-Mediated Hepatitis: *BAVENCIO as a single agent*: BAVENCIO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.9% (16/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Hepatitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.2% of patients. Systemic corticosteroids were required in all (16/16) patients with hepatitis. Hepatitis resolved in 56% (9/16) of the patients. Of the 3 patients in whom BAVENCIO was withheld for hepatitis, 3 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies: *Adrenal Insufficiency*: BAVENCIO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving BAVENCIO, including Grade 3 (0.1%), and Grade 2 (0.3%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency. Adrenal insufficiency did not resolve in any patient (0/8). Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO. ***Hypophysitis:*** BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients receiving BAVENCIO which was a Grade 2 (0.1%) adverse reactions. Hypopituitarism did not lead to withholding of BAVENCIO in this patient. Systemic corticosteroids were not required in this patient. ***Thyroid Disorders:*** BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity. ***Thyroiditis*** occurred in 0.2% (4/1738) of patients receiving BAVENCIO, including Grade 2 (0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation or withholding of BAVENCIO in any patients. No patients with thyroiditis required systemic corticosteroids. Thyroiditis did not resolve in any patients (0/4). ***Hyperthyroidism*** occurred in 0.4% (7/1738) of patients receiving BAVENCIO, including Grade 2 (0.3%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of BAVENCIO in any patients and led to withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hyperthyroidism resolved in 86% (6/7) of the patients. Of the 2 patients in whom BAVENCIO was withheld for hyperthyroidism, 2 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hyperthyroidism. ***Hypothyroidism*** occurred in 5% (90/1738) of patients receiving BAVENCIO, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.5% of patients. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism. Hypothyroidism resolved in 4% (4/90) of the patients. Of the 8 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated BAVENCIO. ***Type I Diabetes Mellitus, which can present with Diabetic Ketoacidosis:*** Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO depending on severity. Immune-mediated Type I diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including Grade 3 (0.1%) adverse reactions. Type I diabetes mellitus led to permanent discontinuation of BAVENCIO in these two patients. Type I diabetes mellitus did not lead to withholding of BAVENCIO in any patient. Systemic corticosteroids were not required in any patient with Type I diabetes mellitus. Type I diabetes mellitus resolved in no patient and all patients required ongoing insulin treatment.

Immune-Mediated Nephritis with Renal Dysfunction: BAVENCIO can cause immune-mediated nephritis. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients receiving BAVENCIO, which was a Grade 2 (0.1%) adverse reactions. Nephritis with renal dysfunction led to permanent discontinuation of BAVENCIO in this patient. Nephritis did not lead to withholding of BAVENCIO in any patient. Systemic corticosteroids were required in this patient. Nephritis with renal dysfunction did not resolve in this patient.

Immune-Mediated Dermatologic Adverse Reactions: BAVENCIO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue BAVENCIO depending on severity. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients receiving BAVENCIO, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of BAVENCIO in 0.3% of patients and withholding of BAVENCIO in 0.4% of patients. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions. One patient required the addition of tacrolimus to high-dose corticosteroids. Dermatologic adverse reactions resolved in 41% (37/90) of the patients. Of the 7 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 3 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. *Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis. *Gastrointestinal:* Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis. *Nervous System:* Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy. *Ocular:* Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss. *Musculoskeletal and Connective Tissue:* Myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatic. *Endocrine:* Hypoparathyroidism. *Other (Hematologic/Immune):* Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

Infusion-Related Reactions: BAVENCIO can cause severe or life-threatening infusion-related reactions. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% of patients treated with BAVENCIO including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Ninety-three percent of patients received premedication with antihistamine and acetaminophen. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids. Fourteen percent of patients had infusion-related reactions that occurred after the BAVENCIO infusion was completed.

Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least one month after the last dose of BAVENCIO.

ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeneic HSCT

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks as a single agent in 1738 patients enrolled in the JAVELIN Merkel 200 and JAVELIN Solid Tumor trials and to BAVENCIO 10 mg/kg intravenously every 2 weeks in combination with axitinib 5 mg orally twice daily in 489 patients enrolled in the JAVELIN Renal 100 and JAVELIN Renal 101 trials. In the BAVENCIO monotherapy population, 24% of patients were exposed for ≥ 6 months and 7% were exposed for ≥ 12 months. The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology.

Locally Advanced or Metastatic Urothelial Carcinoma
First-Line Maintenance Treatment of Urothelial Carcinoma
The safety of BAVENCIO was evaluated in the JAVELIN Bladder 100 trial where patients received BAVENCIO 10 mg/kg every 2 weeks plus best supportive care (BSC) (N=344) or BSC alone (N=345). Patients with autoimmune diseases or conditions requiring systemic immunosuppression were excluded. In the BAVENCIO plus BSC arm, 47% were exposed to BAVENCIO for > 6 months and 28% were exposed for > 1 year. The median age of patients treated with BAVENCIO plus BSC was 69 years (range: 37 to 90), 63% of patients were 65 years or older, 76% were male, 67% were White, and the ECOG performance score was 0 (61%) or 1 (39%). A fatal adverse reaction (sepsis) occurred in one (0.3%) patient receiving BAVENCIO plus BSC. Serious adverse reactions occurred in 28% of patients receiving BAVENCIO plus BSC. Serious adverse reactions in ≥ 1% of patients included urinary tract infection (including kidney infection, pyelonephritis, and urosepsis) (6.1%), pain (including abdominal, back, bone, flank, extremity, and pelvic pain) (3.2%), acute kidney injury (1.7%), hematuria (1.5%), sepsis (1.2%), and infusion-related reaction (1.2%). Permanent discontinuation due to an adverse reaction of BAVENCIO plus BSC occurred in 12% of patients.

Adverse reactions resulting in permanent discontinuation of BAVENCIO in > 1% of patients were myocardial infarction (including acute myocardial infarction and troponin T increased) (1.5%) and infusion-related reaction (1.2%). Dose interruptions due to an adverse reaction, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in 41% of patients receiving BAVENCIO plus BSC. Adverse reactions leading to interruption of BAVENCIO in > 2% of patients were urinary tract infection (including pyelonephritis) (4.7%) and blood creatinine increased (including acute kidney injury, renal impairment, and renal failure) (3.8%). The most common adverse reactions (≥ 20%) in patients receiving BAVENCIO plus BSC were fatigue, musculoskeletal pain, urinary tract infection, and rash. Thirty-one (9%) patients treated with BAVENCIO plus BSC received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction. Table 5 summarizes adverse reactions that occurred in ≥ 10% of patients treated with BAVENCIO plus BSC.

Table 5: Adverse Reactions (≥ 10%) of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

Adverse Reactions	BAVENCIO plus BSC (N=344)		BSC (N=345)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
General Disorders and Administration Site Conditions				
Fatigue[a]	35	1.7	13	1.7
Pyrexia	15	0.3	3.5	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[b]	24	1.2	15	2.6
Arthralgia	16	0.6	6	0
Skin and Subcutaneous Tissue Disorders				
Rash[c]	20	1.2	2.3	0
Pruritus	17	0.3	1.7	0
Infections and Infestations				
Urinary tract infection[d]	20	6	11	3.8
Gastrointestinal Disorders				
Diarrhea	17	0.6	4.9	0.3
Constipation	16	0.6	9.0	0
Nausea	16	0.3	6	0.6
Vomiting	13	1.2	3.5	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough[e]	14	0.3	4.6	0
Metabolism and Nutrition Disorders				
Decreased appetite	14	0.3	7	0.6
Endocrine disorders				
Hypothyroidism	12	0.3	0.6	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	10	0.9	0	0

[a]Fatigue is a composite term that includes fatigue, asthenia and malaise.
[b]Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.
[c]Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash pruritic, drug eruption and lichen planus.
[d]Urinary tract infection is a composite term that includes urinary tract infection, urosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Escherichia urinary tract infection.
[e]Cough is a composite term that includes cough and productive cough.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO plus BSC.

Table 6: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

Laboratory Abnormality	BAVENCIO plus BSC*		BSC*	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 3-4 %
Chemistry				
Blood triglycerides increased	34	2.1	28	1.2
Alkaline phosphatase increased	30	2.9	20	2.3
Blood sodium decreased	28	6	20	2.6
Lipase increased	25	8	16	6
Aspartate aminotransferase (AST) increased	24	1.7	12	0.9
Blood potassium increased	24	3.8	16	0.9
Alanine aminotransferase (ALT) increased	24	2.6	12	0.6
Blood cholesterol increased	22	1.2	16	0.3
Serum amylase increased	21	5	12	1.8
CPK increased	19	2.4	12	0
Phosphate decreased	19	3.2	15	1.2
Hematology				
Hemoglobin decreased	28	4.4	18	3.2
White blood cell decreased	20	0.6	10	0
Platelet count decreased	18	0.6	12	0.3

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO plus BSC group (range: 339 to 344 patients) and BSC group (range: 329 to 341 patients).

Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to avelumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Of the 344 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks plus BSC, 325 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 62 (19.1%) tested positive in the JAVELIN Bladder 100 trial. Patients who tested positive for treatment-emergent ADA had decreased systemic BAVENCIO exposure. In exploratory analyses, the effect of ADA on the efficacy or safety could not be determined due to insufficient numbers of patients in the ADA-positive subgroup and confounding variables.

USE IN SPECIFIC POPULATIONS

Pregnancy, Risk Summary: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient 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:*** Animal reproduction studies have not been conducted with BAVENCIO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering BAVENCIO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to BAVENCIO may increase the risk of developing immune-related disorders or altering the normal immune response.

Lactation, Risk Summary: There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

Females and Males of Reproductive Potential, Contraception: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

Pediatric Use: Safety and effectiveness of BAVENCIO have not been established in pediatric patients.

Geriatric Use

Locally Advanced or Metastatic Urothelial Carcinoma: Of the 344 patients randomized to BAVENCIO 10 mg/kg plus BSC in the JAVELIN Bladder 100 trial, 63% were 65 years or older and 24% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

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

Immune-Mediated Adverse Reactions: Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus.
- Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of skin rash, itchy skin, rash with tiny spots and bumps, reddening of skin, blisters or peeling.

Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Complications of Allogeneic HSCT: Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications

Embryo-Fetal Toxicity: Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use effective contraception during and for at least one month after the last dose of BAVENCIO.

Lactation: Advise nursing mothers not to breastfeed while taking BAVENCIO and for at least one month after the final dose.

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Follicular Lymphoma: a Focus on Current and Emerging Therapies

Kirk E. Cahill, MD[1]; and Sonali M. Smith, MD[1]

Abstract

Follicular lymphoma (FL) is the most common indolent lymphoma and is characterized by a relapsing and remitting course. In addition to significant biologic heterogeneity, the clinical trajectory for patients is variable, with some being observed for many years, and others having aggressive disease requiring multiple treatment courses. Unfortunately, FL remains incurable, and continues to cause early mortality. Improved understanding of the genetic and immune biology of FL has led to several FDA-approved therapies in the relapsed and refractory setting, including PI3K inhibitors; immunomodulatory agents; the EZH2 inhibitor, tazemetostat; and anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, axicabtagene ciloleucel. This review outlines the current approach to the diagnosis and treatment of FL with a focus on emerging investigational therapies, including targeted protein inhibitors, antibody-drug conjugates, monoclonal antibodies, bispecific antibodies, and novel combination strategies.

KEY WORDS: follicular lymphoma; treatment; novel therapies

PERSPECTIVE

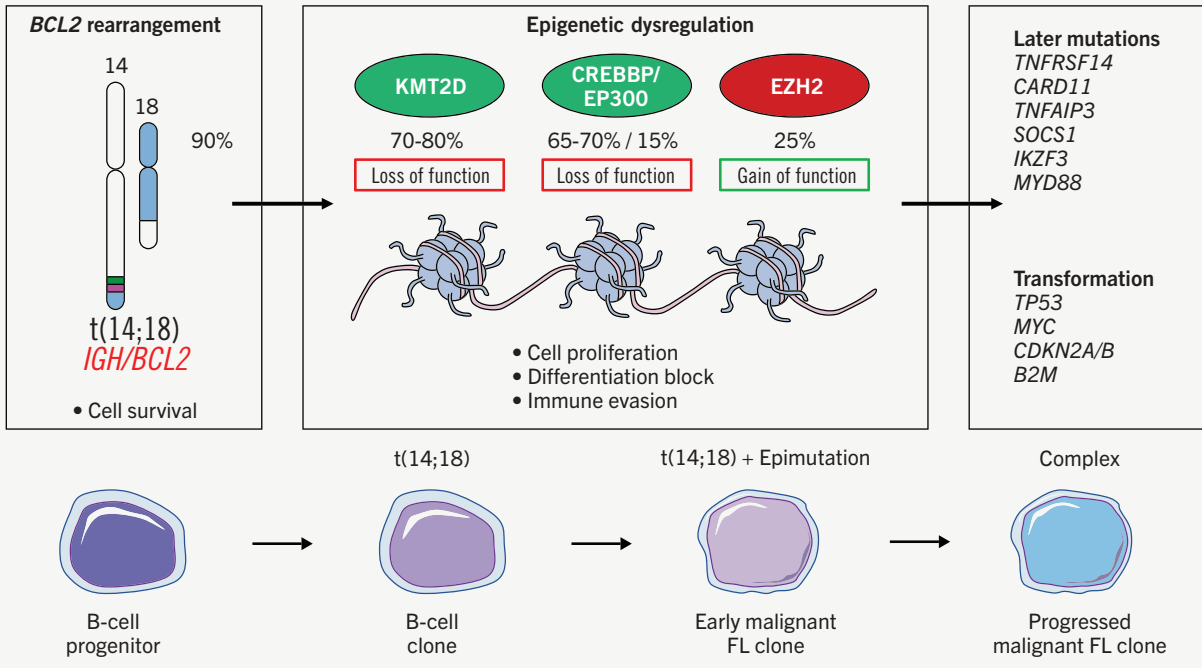
Jonathan R. Day, MD, PharmD; and Brian K. Link, MD, provide perspective on page 100

Introduction

Follicular lymphoma (FL) is an incurable B-cell lymphoid neoplasm with significant biological and clinical heterogeneity. As the most common indolent lymphoma and second most common non-Hodgkin lymphoma (NHL), it has a relapsing and remitting course with risk of transformation to aggressive disease.[1,2] Most patients present with advanced disease and will eventually require treatment for symptomatic disease. Given the range of clinical behaviors, the decision of *when* to treat is equally important as *how* to treat, noting that therapeutic goals include meaningful remission, symptom palliation, and prolongation of life.

While the majority of patients have survival approximating 2 decades, a subset of patients have aggressive disease with poor outcomes.[3] Unfortunately, baseline identification of these patients remains challenging. Approximately 20% of patients with FL have progressive disease within 2 years of initial chemoimmunotherapy and a 5-year overall survival (OS) of 50%.[4] Cumulative toxicity from repeated exposure to palliative cytotoxic chemotherapy also contributes to morbidity and mortality. While anti–CD20-based chemoimmunotherapy remains an important standard of care, more rational and biologically driven agents are either approved or in development. In this review, we examine the current approach to the diagnosis and treatment of FL with a focus on targeted therapy and other novel agents.

FIGURE 1. **Genomic Hallmarks of FL**



BCL2 rearrangement with t(14;18) and mutations in epigenetic regulators are key molecular features in FL. *BCL2* rearrangement is necessary, but not sufficient for lymphomagenesis. Founder mutations in FL often involve chromatin modifying proteins such as histone methyltransferases and acetyltransferases. Abnormal DNA methylation programming cooperates with somatic mutations to drive lymphomagenesis, while the acquisition of additional mutations contribute to disease progression and the risk of transformation to diffuse large B-cell lymphoma.

FL, follicular lymphoma.

Current Standards for Diagnosis

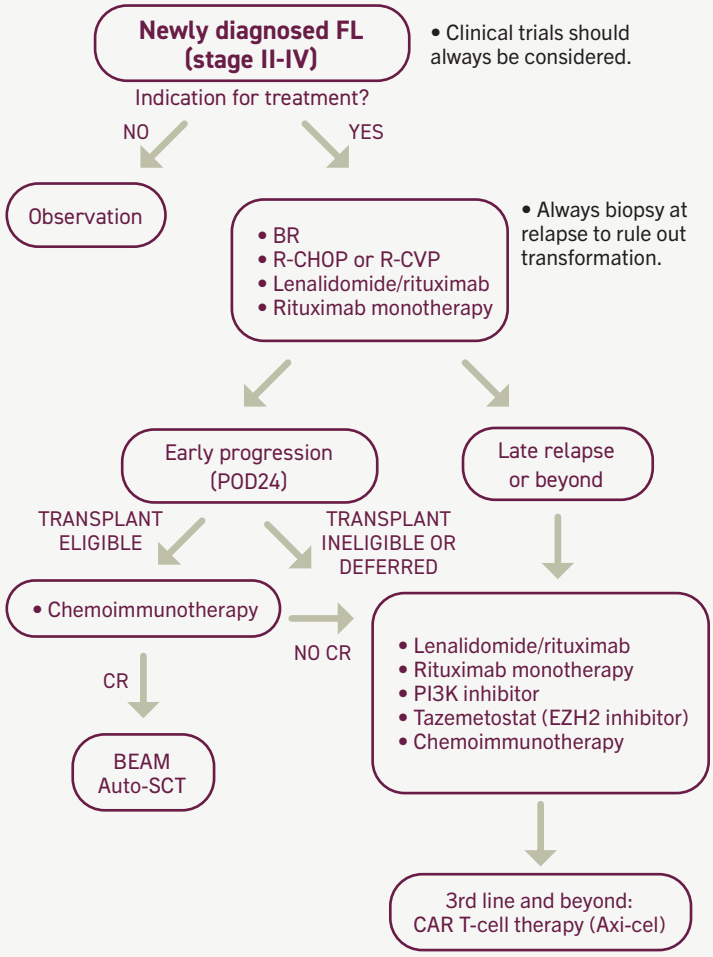
A diagnosis of FL requires histologic examination of a lymph node biopsy for assessment of nodal architecture and grading.[5] FL is characterized by neoplastic germinal center B-cells growing in densely packed follicles with distortion of the normal nodal architecture. Grading depends on the number of centroblasts/high-power field. Grade 1-3a are considered indolent, whereas 3b is more aggressive and clinically approached as diffuse large B-cell lymphoma (DLBCL).[6] The classic immunophenotype includes the B-cell antigens CD19, CD20, and CD79a; lymphoid progenitor marker, CD10; and nuclear proteins, BCL-2 and BCL-6. Unlike mantle cell lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma, it is negative for CD5.

Molecular Testing

Cytogenetically, FL is characterized by the translocation *t(14;18)*, which occurs in up to 90% of cases, as a result of aberrant V(D)J recombination. This results in BCL-2 protein overexpression and increased cell survival (**Figure 1**).[7] As a hallmark of FL, it is necessary, but alone insufficient, for lymphomagenesis.[8-10] An important recent finding is early mutations in genes coding for chromatin modifying proteins.[11-13] These 'epimutations' are a second hallmark of FL and include: *KMT2D* (~70-80%), *CREBBP* (~65-70%), *EZH2* (~25%), and *EP300* (~14%).[12,14] These transcriptionally repressive mutations result in increased germinal center proliferation, differentiation block, and immune evasion.[15-17] Along with the *BCL2* translocation, these mutations are early events occurring in a common progenitor cell.

Through divergent clonal evolution, other mutations are subsequently acquired including mutations in genes involved in immune modulation (*TNFRSF14*); JAK-STAT signaling (*STAT6*, *SOCS1*); and B-cell receptor–NF-kB signaling (*CARD11*, *TNFAIP3*, *MYD88*).[12] While conventional karyotyping and fluorescent in situ hybridization (FISH) for

FIGURE 2. **A Proposed Treatment Approach for Advanced-Stage FL**



Unless there is an indication for treatment based on GELF or NCCN criteria, patients may be observed. When treatment is indicated, clinical trials should always be considered. Standard therapy includes chemoimmunotherapy with BR, which is the most common, and has improved PFS with less toxicity compared to R-CHOP. Lenalidomide with rituximab is an excellent first-line or second-line option, but this combination requires longer treatment duration than R-CHOP or BR. Rituximab monotherapy is also effective in the frontline and relapsed/refractory setting, especially with low disease burden. Patients with early relapse within 24 months (POD24) are a high-risk subset. Salvage chemoimmunotherapy includes bendamustine or CHOP with an anti-CD20 agent, followed by auto-SCT. Targeted agents such as PI3K inhibitors and tazemetostat may also be used. The optimal sequence of subsequent-line agents is unknown, and there are multiple options that can be used prior to CAR T-cell therapy, which is approved after 2 or more lines of therapy.

auto-SCT, autologous stem cell transplant; BEAM, BCNU (carmustine), etoposide, cytarabine, and melphalan; BR, bendamustine and rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete remission; FL, follicular lymphoma; R-CHOP, rituximab with CHOP.

t(14;18) are part of the standard evaluation for FL, genomic sequencing is limited to testing for the *EZH2* mutation when tazemetostat is being considered.[18] Nonetheless, next-generation sequencing has revealed the diverse mutational landscape of FL and provides insight into disease pathogenesis, as well as opportunities for more precise therapeutic strategies.

Stratification for Treatment Selection

The treatment of FL must consider individual parameters and balance the risk of cumulative toxicity versus remission and palliation of symptoms. The conventional approach to FL is clinical observation until there is an indication to treat, typically based on criteria of the Groupe d'Etude des Lymphomes Folliculaires (GELF) or National Comprehensive Cancer Network (NCCN).[19,20] There are several prognostic indices in FL including the Follicular Lymphoma International Prognostic Index (FLIPI), FLIPI-2, and m7-FLIPI, but none dictate the timing or type of treatment at an individual patient level.[14,21,22]

The m7-FLIPI and gene expression profiling panels include genomic features, but have varied performance and are not validated for clinical practice.[23] Staging with positron emission tomography (PET) imaging helps to identify the extent of disease and preferred sites for biopsy when histologic transformation to DLBCL is suspected, as this occurs in up to 15% of patients.[3] The assumption here is that higher uptake values correspond with more rapid cell turnover and aggressive histology. This is somewhat controversial, and PET alone does not appear to predict histologic transformation.[24] Nonetheless, PET imaging does result in disease upstaging in approximately 10% to 60% of cases, which often has treatment implications.[25,26]

Therapy Selection

First-line Treatment

For patients with stage I-II disease, there are several options including observation, rituximab (Rituxan), chemoimmunotherapy, or radiation, with the majority of patients having similar excellent long-term survival regardless of initial approach.[27] Approximately 70% of patients have advanced disease (stage III or IV) at diagnosis.[3,28] Asymptomatic patients with low disease burden

PERSPECTIVE BY

Jonathan R. Day, MD, PharmD;[1] and Brian K. Link, MD[1]

Perspectives on Follicular Lymphoma Treatment From New and Experienced Clinicians: New, Old, & Old Is New.

The accompanying article is an excellent overview of a field perceived to be evolving quickly, but how quick is that evolution in reality?

Perspective of Experienced Clinician (BKL)

Providing peer review and perspective on the accompanying article, which nicely summarizes the biology and management of follicular lymphoma (FL), was a pleasure. The joy was derived from the high quality of the writing and from sharing this assignment with a senior internal medicine resident recently dedicated to the study of a field I have pondered for more than 30 years. The fresh perspective on many of the topics sparked an interesting dialogue on new vs old and rapid vs indolent.

Perspective of a New Clinician (JRD)

The accompanying article highlights many reasons for new clinicians to be excited about entering the field of hematology and oncology. New clinicians see a landscape with abundant options for patients and can be optimistic for improvements in FL treatment. These new options move beyond standard anti-CD20 antibodies plus cytotoxic chemotherapeutics to new and varied mechanisms of action and novel therapeutics. A fascinating, multifaceted array of options and mechanisms is depicted in the article's Figure 3, highlighting targeted inhibition of biologic pathways and complex approaches to harnessing the immune system.

Although new options are arriving in the clinic at a rapid pace, the story of improving therapy for FL is, summarily, persistence.

Targeting Pathways

Efforts to find selective molecular pathway targets to subdue aberrant cellular activity in cancer has long been a goal in cancer pharmacology. One pathway that regulates multiple hallmarks of malignancy is the mTOR–AKT–PI3K pathway. Efforts focused on mTOR inhibition in lymphoma date back to the early 2000s, but clinical trial results were less robust than hoped for.[1-6] Therefore, efforts shifted elsewhere in the pathway. For example, Bruton tyrosine kinase (BTK) is activated by PI3K, and BTK inhibition has achieved great results in chronic lymphocytic leukemia (CLL). Its role in FL, however, remains to be established—although it also remains under investigation.[7-11]

The persistent efforts to interrupt this pathway seem to be finally paying off. As noted in the accompanying article, 4 of 7 new agents recently approved for FL are PI3K inhibitors. Other mechanistic approaches like BCL-2 inhibitors failed to have the initially expected impact, and perhaps more persistence is needed to understand how BCL-2 inhibition should be utilized.[12]

Harnessing the Immune System

Novel methods to fight cancer, including harnessing the immune system, are exciting, but this concept is hardly new. Some of the newest treatments can trace their beginnings to more than 30 years ago. Initial efforts to manipulate the immune system were less elegant than they are today, utilizing systemic interferon and interleukin.[13-16] The 1984 Nobel Prize was awarded for technology used to create monoclonal antibodies; this opened a Pandora's box that was widely expected to quickly revolutionize the treatment of lymphoma. Early breakthroughs with anti-CD20 monoclonal antibodies provided to have meaningful benefit for patients before the century turned, but efforts at targeting other antigens (those that come to mind were against CD19, CD22, and CD80) were not immediately fruitful.[17,18] Immunoconjugates with biotoxins and radioisotopes were variably active but did not meaningfully change the treatment landscape. Even the vision of bispecific antibodies to retarget autologous T cells was clear from preclinical models in the early 1990s, but challenges with protein chemistry stunted clinical development.[19]

Other immune-mediated strategies, such as tumor vaccines, were first trialed in the 1990s.[20] Large phase 3 trials in the 2000s had conflicting results, which led to an ongoing pause in momentum for vaccination strategies.[21-23] Immunomodulation with lenalidomide (Revlimid) was undergoing testing in hematologic malignancies by 2002, and it gained approval for multiple myeloma and myelodysplastic syndrome by 2006, but its utility in FL wasn't fully realized until recent combinations with antibodies targeting CD20 and perhaps CD19.[24,25]

Early efforts to capitalize on recent exciting

techniques for immunologic checkpoint inhibition have been underwhelming in FL, but as highlighted in the featured article, ongoing studies with antibody combinations may unlock the hoped-for potential.[26,27] These examples illustrate the blurred lines between new and old. Other new therapies for FL, such as chimeric antigen receptor T cells, are inspiring examples of the efficiency seen from combining the newest technologies with the newest biology. Nonetheless, persistence and an open mind to reevaluation of previously "failed" ideas will no doubt result in more immunotherapy options in the future. In contrast with a relatively spartan treatment landscape a generation ago, we are now looking at a plethora of emerging therapies to treat patients. The next generational challenge will be establishing sequences and combinations optimal for long-term management of this disease, which so far remains incurable. A significant challenge for clinical researchers is how to measure improvement. The use of overall survival (OS) as a primary end point is challenging in FL due to the infrequency of early deaths. Patients with early progression of disease after immunochemotherapy has been identified as a population with unmet need; however, this group is heterogenous and relatively small. How to best individualize these therapies for patients will be a challenge. Perhaps a reevaluation of end points is in order. OS and even progression-free survival do not measure the complete impact of FL on patients. How do we incorporate acute and chronic toxicities, quality of life, and cost factors? Should we target cure as goal and if so, how do we define cure in FL?

The persistence of previous generations of researchers with biological discoveries has resulted in more therapeutic options to work with. The next generation will undoubtedly persist in redefining loftier measures of success for patients and incorporating new options to achieve those measures.

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may be actively monitored. When treatment is indicated for patients with low tumor-burden advanced disease, rituximab monotherapy is often used, given the high overall response rate (ORR; complete remission [CR] plus partial remission [PR]) of 71%, low toxicity, and long median time to treatment failure of approximately 4 years, which delays the need for cytotoxic therapy.[29]

When selecting initial treatment for patients with high tumor burden and symptomatic advanced FL, there are several considerations regarding the chemotherapy backbone, the anti-CD20 antibody, the use of maintenance strategies, and whether to opt for a nonchemotherapy regimen (**Figure 2**). Based on the StiL (NCT00991211) and BRIGHT (NCT00877006) trials, bendamustine and rituximab (BR) or rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), are both options with ORR >90%.[30,31]

BR has become a preferred option based on superior progression-free survival (PFS) over R-CHOP (70 vs 31 months, respectively) and it is also not associated with alopecia, anthracycline-associated cardiotoxicity, vinca alkaloid-associated neuropathy, or steroid-associated risks. R-CHOP may be preferred in cases where occult transformation is suspected, or immune suppression associated with bendamustine is to be avoided. In patients treated with R-CHOP or rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP), maintenance therapy with rituximab every 8 weeks for 2 years compared with placebo improves PFS, but not OS, based on the PRIMA study (NCT00140582).[32]

It is unclear whether this extends to patients treated with BR. In the GALLIUM study (NCT01332968), chemoimmunotherapy with obinutuzumab (Gazyva) versus rituximab improved PFS, with no difference in OS, but did result in high grade 3-5 adverse events, including infusion-related events and infections.[33,34] The use of maintenance therapy is controversial, and even more so during the COVID-19 pandemic. Among surveyed physicians who treat indolent lymphomas with a maintenance therapy strategy, 53% hold rituximab maintenance to allow for vaccination.[35] Lenalidomide (Revlimid)with rituximab is an alternative to chemoimmunotherapy with similar response rates, PFS, and OS to chemoimmunotherapy (R-CHOP, BR, or R-CVP).[36] Similar to chemoimmunotherapy, it is a fixed-duration treatment, but with a much longer time frame at 18 months. It remains an option for patients wishing to avoid cytotoxic chemotherapy.

Relapsed/Refractory Treatment

There is no standard treatment or sequence of treatments for relapsed/refractory FL (RR-FL), but the number of options is increasing. Approximately 20% of patients have early relapse and progression of disease within 24 months (POD24), and these patients have poor outcomes.[4] Unfortunately, upfront identification of these patients is not possible, and more effective treatments for these patients are needed. For all patients with RR-FL, a chemoimmunotherapy regimen (BR, R-CHOP, or R-CVP) different from the first-line therapy is an option.

There is limited data on R-CHOP after BR, but second-line BR in patients with indolent NHL with previous rituximab (39%) or CHOP (54%) had an ORR of 82% and PFS of 34 months.[37] Rituximab monotherapy

TABLE 1. **Recent FDA-Approved Therapies for FL**

Drug	Approval year	Mechanism/target	Indication
Idelalisib	July 2014	PI3K-δ inhibitor	Adults with RR-FL after ≥2 lines of systemic therapy
Copanlisib	September 2017	Pan-PI3K inhibitor	Adults with RR-FL after ≥2 lines of systemic therapy
Duvelisib	September 2018	PI3K-δ and γ inhibitor	Adults with RR-FL after ≥2 lines of systemic therapy
Lenalidomide with rituximab	May 2019	Immunomodulatory; cereblon inhibitor	Adults with RR-FL
Tazemetostat	June 2020	EZH2 inhibitor	1. Adults with RR-FL after ≥2 lines of systemic therapy and an *EZH2* mutation 2. Adults with RR-FL, without other treatment options
Umbralisib	February 2021	PI3K-δ and CK1-ε inhibitor	Adults with RR-FL after ≥3 lines of systemic therapy
Axicabtagene ciloleucel	March 2021	Anti-CD19 CAR T-cell therapy	Adults with RR-FL after ≥2 lines of systemic therapy

CAR, chimeric antigen receptor; CK, casein kinase; RR-FL, relapsed/refractory follicular lymphoma.

is also effective for some patients with low tumor burden and previous rituximab-based regimens with an ORR 55% to 64% and PFS of 14 months.[38,39] Obinutuzumab with either bendamustine or CHOP may improve outcomes by overcoming rituximab refractoriness, especially for relapses within 6 to 12 months.[40,41] In transplant-eligible patients with chemosensitive disease to first salvage, consolidative autologous stem cell transplantation (auto-SCT) appears to improve long-term survival based on several retrospective analyses.

Among patients with POD24, auto-SCT has an improved 5-year OS of approximately 77% vs 59% among those without auto-SCT.[42] Similar results were observed for patients undergoing auto-SCT within 1 year of treatment failure, with a 5-year OS of 73% compared with 60% without auto-SCT.[43] It should be noted, however, that the benefit of auto-SCT may simply be due to a favorable response to second-line therapy and randomized studies are needed.

In the era of increased alternative treatments, the use of auto-SCT has been substantially reduced. The use of allogeneic-SCT, a historical option with curative potential in FL, has also declined. While the preferred therapy for high-risk patients with early relapse has yet to be defined, targeted therapy beyond anti-CD20 monoclonal antibodies has been reshaping the treatment landscape of FL since 2014 (**Table 1**), with several new trials focusing on this population, including a US Intergroup Study S1608 (NCT03269669).

Lenalidomide

Lenalidomide is an immunomodulatory drug with direct cytotoxicity to lymphoma cells via inhibition of the E3 ubiquitin ligase, cereblon, as well as indirect antitumor effects mediated through changes in the tumor microenvironment.[44] Lenalidomide with rituximab is an active regimen in rituximab-sensitive relapsed FL, as demonstrated in the AUGMENT trial (NCT01938001) with an ORR of 80% (CR 35%) compared with an ORR of 55% (CR 20%) for rituximab alone.[39] The combination had a 2-year OS and median PFS of 95% and 39.4 months compared with 86% and 13.9 months, respectively, for rituximab alone. The combination had a higher incidence of all grades of infections (63% vs 49%, respectively), neutropenia (58% vs 23%), and cutaneous reactions (32% vs 12%). Of the grade 3 or 4 adverse events, a higher incidence of neutropenia (50% vs 13%) was also observed with the combination. This study led to the regulatory approval of lenalidomide with rituximab in patients with RR-FL.

PI3K Inhibitors

Inhibition of PI3K signaling has been a largely successful approach, with 4 FDA-approved agents in RR-FL.[45] PI3K mediates proximal intracellular B-cell receptor signaling, as well as cell survival signals received from the tumor microenvironment. Idelalisib (δ isoform inhibitor; Zydelig) was the first of these agents to be approved and a major breakthrough in the RR-FL space. The ORR was 57% (CR 6%) with a median duration of response (DOR) of 12.5 months and median PFS of 11 months in very heavily pretreated patients.[46] Unfortunately, significant toxicities, including neutropenia, diarrhea, transaminitis, and pneumonia, limited its development. Copanlisib (pan-isoform inhibitor; Aliqopa); duvelisib (δ and γ isoform inhibitor; Copiktra); and umbralisib (δ isoform and CK1 ε inhibitor; Ukoniq) are also approved for RR-FL with comparable efficacy and improved toxicity profiles.[47-49] They all have an ORR ranging from 42% to 59%, median DOR of 10 to 12 months, and median PFS of 9.5 to 11 months. They

have regulatory approval for patients with multiply relapsed FL, based on activity in the heavily pretreated setting.

Tazemetostat

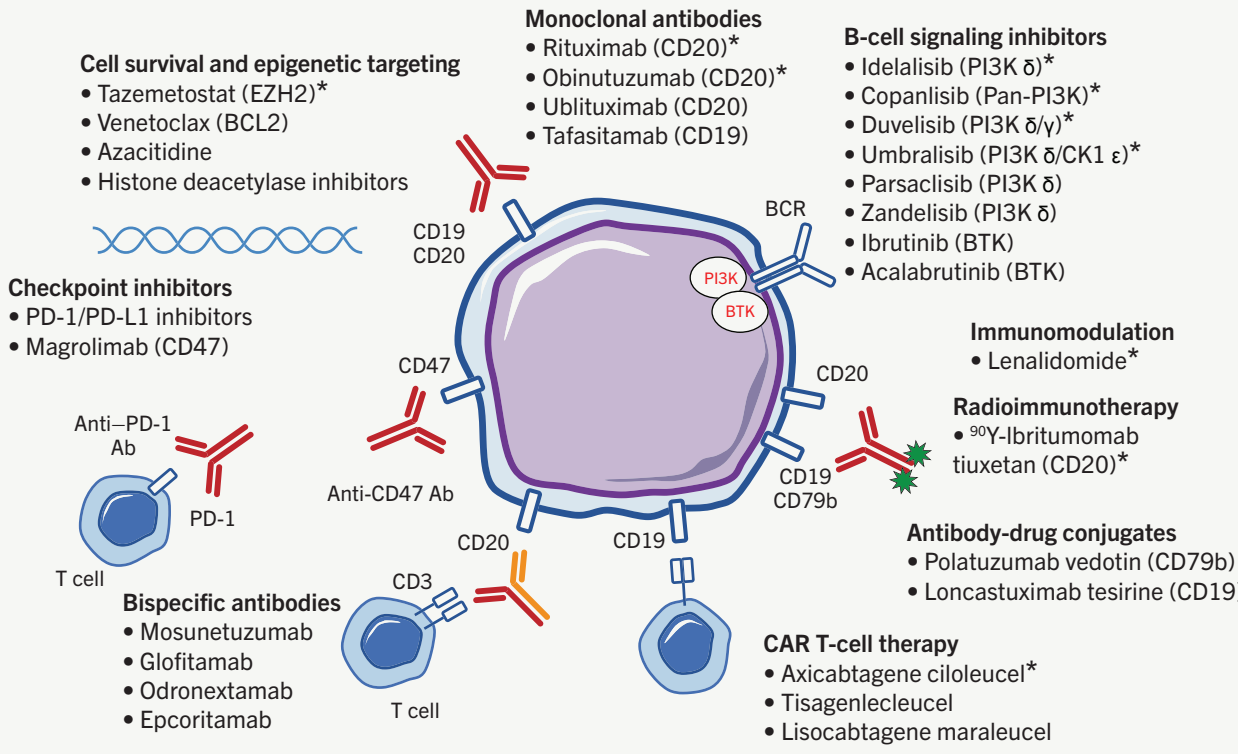
Approximately 25% of patients with FL have a gain of function mutation in the histone methyltransferase protein, EZH2, with consequent increased expression of genes involved in cell proliferation.[12,14,50] Although it contributes to lymphomagenesis, *EZH2* gene mutations are associated with improved PFS.[50] Tazemetostat (Tazverik) is an EZH2 inhibitor that targets this epimutation. It is the first biomarker-directed therapy in FL and has been approved as a third-line option in RR-FL, with an ORR of 69% and CR rate of 13%.[51] With a median follow-up of 22 months, the median PFS was 13.8 months, and median OS was not reached. It also appears to have activity in patients without an *EZH2* gene mutation, with ORR of 35% and similar median PFS and OS. There were few significant treatment-related adverse events, with 3% of patients having grade 3 or 4 myelosuppression and a low discontinuation rate of 8%. Its favorable toxicity profile makes it an attractive oral option.

CAR T-Cell Therapy

While targeted agents have clinical activity in RR-FL, long-term remission is still lacking and most require prolonged treatment courses. CAR T-cell therapy has revolutionized the treatment of aggressive lymphomas like DLBCL, and is also now an option for RR-FL, although follow-up remains short. Axicabtagene ciloleucel (axi-cel; Yescarta) is an anti-CD19 CAR T-cell therapy that received accelerated approval in March 2021 for adult patients with RR-FL (≥ 2 lines of prior therapy) based on the results of the phase 2 study ZUMA-5.[52] In a preliminary report of updated results (median follow-up of 31 months), 86 patients with RR-FL had an ORR of 94% (CR 79%), median DOR and PFS of 38.6 months and 39.6 months, respectively, while OS was not reached.[53] The incidence of cytokine release syndrome (CRS) and neurotoxicity grade ≥ 3 were 6% and 15%, respectively.

The phase 2 ELARA trial (NCT03568461) evaluating tisagenlecleucel (tisa-cel) in patients with RR-FL (≥ 2 lines of prior therapy) had an ORR 86% (CR 69%) without any grade ≥ 3 CRS, and only 3% with grade ≥ 3 neurotoxicity.[54] At a

FIGURE 3. **Approved and Investigational Targeted Agents in FL**



Several FDA-approved targeted therapies(*) exist, as well as many other investigational agents that are changing the treatment landscape of FL. Given the significant genetic heterogeneity and complex interactions with the tumor microenvironment, the cure for FL will likely require a biomarker-based subset-specific approach.

Ab, antibody; BCR, B-cell receptor; BTK, Bruton tyrosine kinase; FL, follicular lymphoma.

TABLE 2. **Select Ongoing Clinical Trials Using Novel Agents or Investigational Combinations of Approved Therapies in FL**

Treatment	Targets	Patients	Phase	Trial number
Venetoclax + Oral AZA (CC-486) + Obinutuzumab	BCL2, epigenetic modulation, CD20	Frontline FL	1/2	NCT04722601
PrE0403: Venetoclax + Obinutuzumab + Bendamustine	BCL2, CD20, DNA damage	Frontline FL	2	NCT03113422
LEVERAGE: Lenalidomide + Venetoclax + Obinutuzumab	Immunomodulation, BCL2, CD20	Frontline FL	1/2	NCT03980171
Acalabrutinib + Obinutuzumab	BTK, CD20	Frontline FL	2	NCT04883437
SWOG S1608 (Randomized): 1: Obinutuzumab + Umbralisib 2. Obinutuzumab + Lenalidomide 3. BO or O-CHOP	CD20, PI3K δ, CK1 ε, immunomodulation, DNA damage	RR-FL (early relapse)	2	NCT03269669
Umbralisib + Ublituximab + Lenalidomide	PI3K δ, CK1 ε, CD20, immuno-modulation	RR-FL	1	NCT04635683
CITADEL-302 (Randomized): 1. Parsaclisib + Rituximab or Obinutuzumab 2. Placebo + Rituximab or Obinutuzumab	PI3K δ	RR-FL	3	NCT04796922
COASTAL (Randomized): 1. Zandelisib + Rituximab 2. BR or R-CHOP	PI3K δ, CD20, DNA damage	RR-FL	3	NCT04745832
Randomized: 1. Tazemetostat + Lenalidomide + Rituximab 2. Placebo + Lenalidomide + Rituximab	EZH2, immunomodulation, CD20	RR-FL	3	NCT04224493
SYMPHONY-2: Tazemetostat + Rituximab	EZH2, CD20	RR-FL	2	NCT04762160
InMIND (Randomized): 1. Tafasitamab + Rituximab + Lenalidomide 2. Placebo + Rituximab + Lenalidomide	CD19, CD20, immunomodulation	RR-FL	3	NCT04680052
LOTIS 6 (Randomized): 1. Loncastuximab tesirine 2. Idelalisib	CD19 ADC, PI3K δ	RR-FL	2	NCT04699461
Loncastuximab tesirine + Venetoclax	CD19 ADC, BCL2	RR-FL	1	NCT05053659
TRASNCEND FL: Lisocabtagene maraleucel	CD19 CAR T cell	RR-FL	2	NCT04245839
VENOM: Venetoclax + Obinutuzumab + Magrolimab	BCL2, CD20, CD47	RR-FL	1	NCT04599634
Magrolimab + Rituximab	CD47, CD20	RR-FL	2	NCT02953509
1. Rituximab + Pembrolizumab 2. Rituximab + Pembrolizumab + Lenalidomide	CD20, PD-1, immunomodulation	RR-FL	2	NCT02446457
Pembrolizumab + Rituximab or Obinutuzumab	PD-1, CD20	RR-FL	2	NCT03401853
Ibrutinib + Nivolumab	BTK, PD-1	RR-FL	1/2	NCT02329847

ADC, antibody-drug conjugate; AZA, azacitidine; BTK, Bruton tyrosine kinase; BO, bendamustine, obinutuzumab; CAR, chimeric antigen receptor; CK, casein kinase; FL, follicular lymphoma; O-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RR-FL, relapsed/refractory follicular lymphoma.

median follow-up of 16.9 months, the median DOR, PFS, and OS were not reached, but 1-year PFS was 67%. The phase 2 TRANSCEND FL trial (NCT04245839) using lisocabtagene maraleucel is ongoing. One of the most crucial challenges is patient selection for CAR T, which remains a costly and aggressive approach. Long-term follow-up and real-world data for CAR T-cell therapy from the commercial setting will be important guides influencing patient selection.

Emerging and Novel Therapies

Beyond the commercially approved targeted therapies in FL, there are multiple emerging agents that target the biology of FL (**Figure 3**). These are reviewed briefly in the following section, which also highlights novel investigational use of these treatments in FL (**Table 2**).

Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) offer an appealing means of antigen-based drug delivery, with several in development. In a phase 2 study in patients with RR-FL, the anti-CD79b ADC, polatuzumab vedotin, (pola; Polivy) was combined with rituximab and resulted in an ORR of 70% (CR 45%) with a 9.4-month DOR.[55] The PFS was 15.3 months with a 2-year OS of 88%. The most common grade 3-4 adverse events were neutropenia (15%) and diarrhea (10%); however, although no grade 3-4 neuropathy was observed, 40% had grade 1-2 neuropathy.

In preliminary reports of early-phase studies evaluating pola combinations in RR-FL, pola with BR did not improve treatment response.[56] Pola with obinutuzumab/lenalidomide had an ORR of 76% (CR of 65%), while pola with obinutuzumab/venetoclax had an ORR of 71% (CR of 57%), and long-term results with updated survival are anticipated.[57,58] In a phase 1 study including 14 patients with RR-FL, the anti-CD19 ADC, loncastuximab tesirine (Zynlonta), had an ORR of 79% (CR of 65%), and cytopenias were the most common adverse effect.[59]

Checkpoint Inhibitors

Although checkpoint blockade monotherapy has low response rates in RR-FL, combinations may be more active. A phase 1/2 trial (NCT02631577) using obinutuzumab, atezolizumab (Tecentriq), and lenalidomide (G-atezo-len) in patients with RR-FL reported an ORR of 78% (CR of 72%), median DOR of 38 months, and 2-year PFS of 65%.[60] Cytopenias were the most common grade ≥ 3 adverse event and occurred in 71% of patients. While the majority of toxicities were manageable, the discontinuation rate of any study drug was 29%.

In a preliminary report of pembrolizumab with rituximab in patients with RR-FL (NCT02446457), the ORR was 80% (CR of 60%), and although safe, the benefit of pembrolizumab (Keytruda) over rituximab monotherapy was unclear, as this trial included patients with rituximab-sensitive disease.[61] In the frontline phase 2 trial (1st FLOR study; NCT03245021), immune priming with nivolumab (Opdivo), followed by rituximab and nivolumab had an ORR of 92% (CR of 54%), with a favorable toxicity profile.[62] Larger studies and a longer follow-up are needed to clarify the role of checkpoint inhibitors as first-line nonchemotherapy options.

Novel Antibodies and Combinations

Antibodies with novel targets are also under investigation in FL. The anti-CD47 antibody, magrolimab (Hu5F9-G4), blocks CD47 on lymphoma cells to enhance macrophage-mediated phagocytosis. In a phase 1 study of patients with RR-NHL, which included 7 patients with RR-FL, magrolimab with rituximab resulted in an ORR of 71% (5/7) and CR rate of 43% (3/7).[63] Although small, these numbers are encouraging, with many patients having rituximab-refractory disease. The phase 2 portion of this study (NCT02953509) is currently recruiting.

Another trial investigating venetoclax (Venclexta) with obinutuzumab and magrolimab (VENOM) in relapsed/refractory indolent lymphomas is recruiting, and the results are eagerly anticipated (NCT04599634). Tafasitamab (Monjuvi) is an anti-CD19 antibody approved in combination with lenalidomide for relapsed/refractory DLBCL, but has low activity as a monotherapy in FL.[64] A phase 3 trial (InMIND) of tafasitamab plus lenalidomide/rituximab versus lenalidomide/rituximab alone in patients with RR-FL or marginal zone lymphoma will determine whether there is a role for tafasitamab in RR-FL (NCT04680052).

Bispecific Antibodies

Bispecific antibodies or bispecific T-cell engagers (BiTes) are novel protein constructs with separate B-cell (CD20) and T-cell targeting (CD3) domains. Mosunetuzumab, glofitamab, odronextamab, and epcoritamab are bispecific antibodies being investigated in early-phase RR-FL trials (**Table 3**), which have shown promising results with ORR ranging from 80% to 100% (CR from 50% to 75%) in heavily pretreated patients.[65-69] Bispecific antibodies provide an off-the-shelf form of T-cell mediated therapy, with the goal of achieving the durable remissions seen with CAR T-cell therapy. Unlike CAR T-cell therapy, they appear to have a lower risk of CRS and neurotoxicity, and favorable responses in patients relapsing after CAR T-cell therapy. The optimal clinical use of bispecific antibodies remains unknown, and trials including novel combinations in FL are ongoing: mosunetuzumab and lenalidomide (NCT04246086); and epcoritamab with lenalidomide/rituximab or BR (NCT04663347).

TABLE 3. **Bispecific Antibodies Under Investigation in FL**

Bispecific Antibody	Mosunetuzumab	Mosunetuzumab + Lenalidomide	Epcoritamab	Glofitamab	Odronextamab
Phase	1/2	1	1/2	1/2	1
Trial	NCT02500407	NCT04246086	NCT03625037	NCT03075696	NCT02290951
Patients (FL)	90 (90)	29 (29)	68 (12)	53 (mono) 19 (+obin)	127 (28)
Median prior therapies (range)	3 (2-10)	1 (1-6)	5 (3-8)	3 (1-12) (mono) 2 (1-5) (+obin)	3 (1-11)
ORR % (CR%)	80 (60)	90 (66)	90 (50)	81 (70) (mono) 100 (74) (+obin)	93 (75)
Median DOR (months)	22.8	NR	NR	NR	8.1
Median PFS (months)	17.9	NR	NR	NR	12.8
Grade ≥3 CRS (%)	2	0	0	4 (mono) 0 (+obin)	6
Grade ≥3 neurotoxicity (%)	0	0	3	0 (mono) 0 (+obin)	4
Median follow-up (months)	18.3	5.4	13.6	4.4 (mono) 5.5 (+obin)	3.9

FL, follicular lymphoma; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; mono, monotherapy; NR, not reported; obin, obinutuzumab; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose.

BCL2 and Epigenetic Targeting

While *BCL2* translocation and epigenetic dysregulation are both frequent features in FL, the efficacy of existing agents has been modest. The BCL2 inhibitor, venetoclax, had low monotherapy activity in FL with an ORR of 38% (CR of 14%),[70] but combination strategies are in development. A preliminary report of the first trial to combine a Bruton tyrosine kinase (BTK) inhibitor, ibrutinib (Imbruvica), with venetoclax in RR-FL showed an ORR of 83% (CR of 33%) with manageable toxicity (NCT02956382).[71] Several frontline trials using venetoclax-based combinations include the following: venetoclax, oral azacitidine (CC-486), and obinutuzumab (NCT04722601); venetoclax, lenalidomide, and obinutuzumab (NCT03980171); and venetoclax, ibrutinib, and obinutuzumab (NCT04450173).

The phase 2 PrECOG 0403 trial with frontline venetoclax, bendamustine, and obinutuzumab (NCT03113422) for patients with high tumor-burden FL (n = 56) showed an ORR of 93% (CR of 73%), 2-year estimated PFS of 86%, and 2-year estimated OS of 94% at a median follow-up of 21 months.[72] Despite the efficacy, the rate of ≥ grade 3 adverse events was high, at 84%, most notably due to tumor lysis, cytopenias, and infections. Unfortunately, this toxicity will preclude its use, but alternative dosing strategies to mitigate adverse effects are being explored. Tazemetostat is also being evaluated in combination with rituximab (NCT04762160), and in combination with lenalidomide and rituximab (NCT04224493).

Conclusions

While chemoimmunotherapy, lenalidomide with rituximab, or rituximab alone are standard first or subsequent line options for advanced FL, the treatment choices for RR-FL have evolved over the last several years. Additional agents for multiply relapsed patients include PI3K inhibitors, tazemetostat, and CAR T-cell therapy. Patient selection for CAR T-cell therapy is evolving, and the optimal sequencing with other therapies remains unknown. There are many emerging investigational products, including ADCs, anti-CD47 monoclonal antibodies, bispecific antibodies, checkpoint-based therapy, and novel combination strategies that are being evaluated. Individualized approaches, trial end points with quality-of-life measures, and information to guide sequencing of available regimens and agents are all desperately needed. These efforts, coupled with ongoing discovery in the biology of FL, are imperative to improving outcomes for patients with FL. ■

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Locoregional Liver–Directed Therapies to Treat Unresectable Colorectal Liver Metastases: A Review

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ABSTRACT

An estimated 70% of patients with colorectal cancer will develop liver metastases during the course of their disease. While the first-line treatment for hepatic metastases is resection, most patients with colorectal liver-only or liver-dominant metastases (CRLM) present with unresectable disease and are not surgical candidates. In the past decade, locoregional liver-directed therapies have demonstrated safety and efficacy in the treatment of patients with unresectable CRLM and chemotherapy-refractory disease. These treatments can be used to attempt conversion to surgical resectability, can control local disease progression, and have the potential to prolong survival. However, they have not yet become the standard of care in many practices. Each treatment has unique risks, and the clinical data are heterogeneous and thus difficult to interpret. In this article, we will review the most recent, high-impact literature on 3 common locoregional therapies used in the treatment of patients with unresectable CRLM: hepatic artery infusion pump chemotherapy, stereotactic body radiation therapy, and selective internal radiation therapy with yttrium-90 embolization. Ultimately, for this patient population, clinical decision-making requires a multidisciplinary discussion which should take into account individual patient characteristics and clinical expertise available at the treatment facility.

KEYWORDS: Colorectal cancer, liver metastases, unresectable, regional therapy, yttrium 90, stereotactic body radiation therapy, hepatic artery infusion pump chemotherapy

Introduction

Colorectal cancer is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths globally, with an incidence that is projected to increase by 60% by the year 2030.[1] For those with colorectal cancer, the liver is the most common site of metastatic disease. Approximately 25% of patients initially present with synchronous liver metastases, while an estimated 70% of patients will develop liver metastases during the course of their disease.[1,2]

The first-line treatment for patients with colorectal liver-only or liver dominant metastases (CRLM) is resection, yet 70% to 80% of patients present with unresectable disease.[2,3] The 5-year survival rate for patients with unresectable CRLM remains poor, at approximately 5%.[4,5] For these patients, the National Comprehensive Cancer Network (NCCN) guidelines recommend systemic chemotherapy with consideration of additional biologic therapies.[6] However, systemic therapies are frequently difficult for patients to tolerate, with approximately 30% of patients discontinuing treatment before completing the full number of cycles.[7,8] Moreover, despite receiving adequate chemotherapy, many patients develop progressive disease.[9]

Over the past decade, locoregional liver-directed therapies have demonstrated safety and efficacy in the treatment of patients with unresectable CRLM with chemotherapy-refractory disease. However,

these therapies have not yet become the standard of care in many practices.[2] Additionally, establishing a consistent and effective management approach is challenging, due to differing practice patterns among institutions as well as a paucity of comparative studies within the literature.[9,10] To address this knowledge gap, this article reviews 3 common locoregional therapies used in the treatment of patients with unresectable CRLM: hepatic artery infusion pump chemotherapy (HAIP), stereotactic body radiation therapy (SBRT), and selective internal radiation therapy with yttrium-90 embolization (Y90). Herein, we will examine recent high-impact literature that reports how these locoregional treatments influence overall survival (OS), progression-free survival (PFS), and conversion to resection, along with their commonly associated adverse events (AEs).

Methods

We performed a comprehensive systematic literature review to identify recent publications discussing the role of HAIP, SBRT, or Y90 in the treatment of unresectable CRLM. We reviewed only literature that focused on a molecularly unselected patient population, which is an important distinction since select tumor mutations in unresectable CRLM may demonstrate durable responses to specific systematic or liver-directed therapies.[11] Specific outcomes of interest included OS; PFS, or local control if PFS data were not reported; conversion to resection; and AEs. AEs were graded using either the Common Toxicity Criteria Adverse Events version 3.0, with specific focus on AEs of grade 3 (serious) or higher, or the Clavien-Dindo classification of surgical complications.[12,13] We included studies published after 2010 and included phase 1, phase 2, and phase 3 trials; systematic reviews; meta-analyses; case-control studies; and prospective or retrospective cohort studies (**Figure**). Consensus guidelines, single-case reports, and meeting abstracts were excluded from this review. A total of 26 papers met inclusion criteria and were analyzed.

Hepatic Artery Infusion Pump Chemotherapy

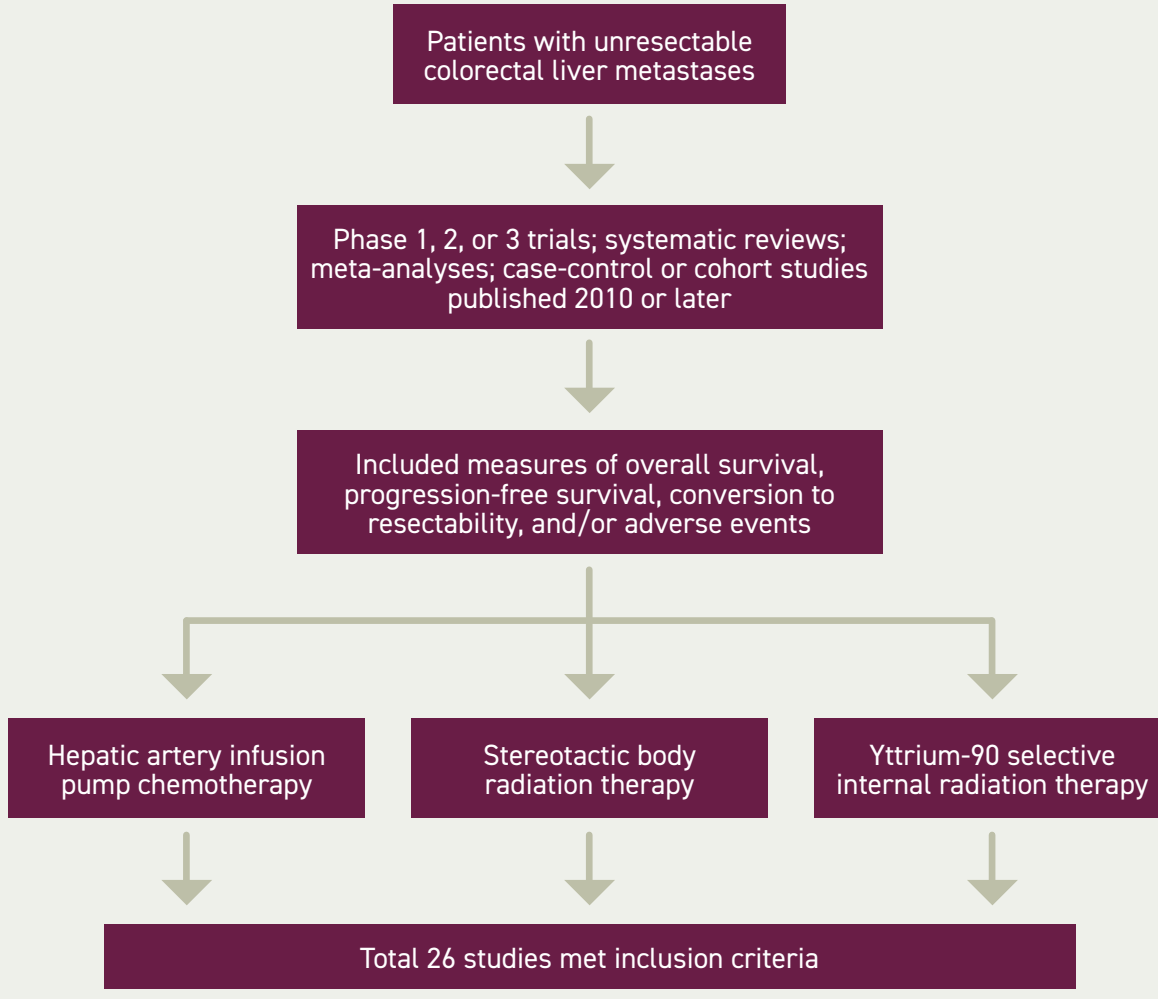
Since its inception in the 1950s, HAIP has been refined as a safe and effective strategy to control disease progression or expand resectability in patients with unresectable CRLM.[14,15] This locoregional therapy capitalizes on the unique blood supply of the liver, as the hepatic artery predominantly supplies liver metastases, while the portal vein perfuses normal hepatocytes. Infusion of chemotherapy directly into the hepatic artery allows selective drug delivery of maximal cytotoxic concentrations to metastatic lesions with relative sparing of the normal liver parenchyma and minimization of systemic AEs. HAIP is typically administered via the gastroduodenal artery by a surgically implanted pump or a percutaneously placed catheter connected to an external pump.[15,16] Furthermore, HAIP allows for high first-pass hepatic extraction and concomitant administration of systemic therapy. The NCCN recommends that HAIP be considered for selected patients with unresectable CRLM; however, it should be implemented only at institutions with surgical and medical oncology expertise in HAIP administration (category 2B recommendation).[6]

We examined 8 peer-reviewed studies focusing on the role of HAIP in the treatment of unresectable CRLM (**Table 1**). This literature review includes 3 prospective phase 2 trials, 2 retrospective multicenter reviews, 2 retrospective single-institution reviews, and 1 meta-analysis. The included studies examined patients who may have received prior chemotherapy but were not previously treated with resection/ablation or HAIP. The publication years ranged from 2015 to 2021 and the number of patients included in each study ranged from 59 to 3000.

The three phase 2 trials examined survival and resection outcomes among patients with unresectable CRLM who received HAIP in addition to systemic chemotherapy.[17-19] Each of these studies, which included 49, 64, and 64 patients respectively, demonstrated relatively similar median OS (25.5-38 months) and PFS (9.3-13 months). More importantly, up to 52% of patients demonstrated conversion to resectability, therefore offering these patients a chance for cure. In the phase 2 study conducted by D'Angelica et al,[17] all patients received HAIP in addition to systemic chemotherapy. However, most patients (65%) were receiving HAIP and chemotherapy as their second- or third-line therapy for unresectable CRLM. Overall, 47% of patients achieved conversion to resection over a median timeframe of 6 months, and conversion was the only factor associated with prolonged OS and PFS in multivariate analyses.

Four retrospective analyses were reviewed, demonstrating promising trends in median OS and conversion to resection when utilizing HAIP for unresectable CRLM. Dhir et al[20] performed a single-institution retrospective case-control study examining 86 patients who received either HAIP plus chemotherapy or chemotherapy alone. OS was statistically longer for patients who received HAIP plus chemotherapy (32.8 months) compared to those who did not receive HAIP (15.3 months; 95% CI, 0.21-0.72). There was no difference in conversion to resection rates between treatment groups. Lim et al[21] performed a multicenter retrospective comparison of 61 patients who either received HAIP plus chemotherapy as first- or second-line treatment

FIGURE. **Schema of Literature Review Process**



for unresectable CRLM vs third- or fourth-line treatment. The authors reported an improvement in median PFS in patients receiving HAIP plus chemotherapy as an earlier treatment - 9 months vs 6 months (95% CI, 0.18-0.66), but the improvement in median OS was not statistically significant. Among all patients, the conversion to resection rate was 16.4%. Two additional retrospective cohort studies including 89 to 154 patients in each study receiving HAIP plus chemotherapy were reviewed.[22,23] Median OS and the rate of conversion to resection was 19.5 months and 7.8%, respectively, in one study, and 20 months and 27%, respectively, in the other.

A recent meta-analysis pooled data from 90 studies that examined 3,000 patients who underwent hepatic artery–directed therapies; it found a median OS for HAIP as first-line treatment of 21.4 months (95% CI, 19.4-23.3) vs 13.2 months (95% CI, 12.2-14.2) as a second-line or later therapy.[24] Overall, the conversion to resection rate was highest among patients receiving HAIP (15%) compared with other hepatic artery therapies such as transcatheter arterial chemoembolization (4%) or radioembolization (2%).

The main drawbacks of HAIP are the requirements for technical expertise, an experienced team of oncologists, and the potential for biliary toxicity, which may necessitate dose adjustment, coadministration with dexamethasone, or stent placement.[14] In the studies examined, the rate of grade

TABLE 1. **Hepatic Artery Infusion Pump Chemotherapy for Treatment of Unresectable CRLM**

Study	Design	Treatment	N	Prior treatments	Median OS, months (95% CI)	Median PFS, months (95% CI)	Conversion to resection/ ablation	Adverse events
D'Angelica et al (2015)[17]	Prospective, phase 2	HAIP + chemotherapy	49	Chemotherapy	33,886 (19.22%)	13 (7-16)	47%	41% grade ≥3
Zacharias et al (2015)[24]	Meta-analysis	HAIP	3000	None or chemotherapy	142,429 (80.78%)	NR	15%	55% grade ≥3
Lévi et al (2016)[18]	Prospective, phase 2	HAIP + chemotherapy	64	Chemotherapy	8287 (19.91%)	9.3 (7.8-10.9)	29.7%	77% grade ≥3
Dhir et al (2017)[20]	Retrospective, single-center	HAIP + chemotherapy vs chemotherapy alone	86	Chemotherapy	33,328 (80.09%)	NR	No group difference	NR
Lim et al (2017)[21]	Retrospective, multicenter	HAIP + chemotherapy: first/second- vs third/fourth-line	61	Chemotherapy	1379 (21.4%)	9 vs 6 (0.2-0.7)	16.4%	16% grade ≥3
Pak et al (2018)[19]	Prospective, phase 2	HAIP + chemotherapy	64	Chemotherapy	5066 (78.6%)	13 (9-16)	52%	≥20% grade ≥3
Boilève et al (2020)[22]	Retrospective, single-center	HAIP + chemotherapy	89	Chemotherapy	24,858 (24.82%)	9 (8-11)	27%	79% grade ≥3
Muaddi et al (2021)[23]	Retrospective, multicenter	HAIP + chemotherapy	154	Chemotherapy	75,298 (75.18%)	3-year PFS, 4.1%*	7.8%	8.4% biliary sclerosis 4.6% Clavien-Dindo ≥3b during hospitalization

CRLM, colorectal liver-only or liver-dominant metastases; HAIP, hepatic artery infusion pump chemotherapy; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; NR, not reported.
*95% CI and/or *P* value not reported

≥3 AEs ranged from 8.4% to 79%, with the most common complications including diarrhea (29%), transaminitis (16%), pump-related complications (14.3%), abdominal pain (12%), biliary sclerosis (8.4%), vomiting (6%), and neutropenia (2%).[17,23] Another possible disadvantage when considering HAIP is that its use may restrict future use of additional locoregional therapies, such as Y90 or transarterial chemoembolization.

In conclusion, in studies of patients who had received prior chemotherapy for unresectable CRLM, the addition of HAIP may improve survival and rates of conversion to resection. However, providers must weigh the potential benefits of HAIP against its risks of toxicity and the need for referral to institutions with HAIP infrastructure and expertise.

Stereotactic Body Radiation Therapy

SBRT aims to precisely deliver large, hypofractionated doses of radiation to target lesions while minimizing its delivery to adjacent normal tissues.[25,26] Through image guidance, this noninvasive locoregional modality induces cell death and coagulation necrosis of the targeted tissue, causing a gradual reduction in tumor size and/or complete replacement by fibrosis.[27,28] Multiple hepatic lesions can be treated simultaneously; however, practitioners must ensure that adequate liver volume is spared from unintended radiation spread.[29] The NCCN states that SBRT is a reasonable treatment option for patients with CRLM who are not candidates for resection, ablation, or participation in a clinical trial.[6]

We analyzed 9 peer-reviewed studies that investigated the clinical outcomes of patients treated with SBRT for unresectable CRLM (**Table 2**). This literature review included 5 retrospective cohort studies, 1 systematic review, and 3 prospective studies. The publication years ranged from 2010 to 2021, and the number of patients examined ranged from 11 to 656 per study. The patient populations across studies varied markedly with respect to previous lines of chemotherapy, prior hepatic interventions, and the presence or absence of extrahepatic metastases. Additionally, we observed substantial variation in the main outcome reported, which included a mixture of median OS, percent survival over time, median PFS, and percent local

TABLE 2. **Stereotactic Body Radiation Therapy for Treatment of Unresectable CRLM**

Study	Design	Treatment	N	Prior treatments	Median OS (±SD#), months (95% CI)	Median PFS, months (95% CI)	Adverse events
van der Pool et al (2010)[37]	Prospective, single-center cohort	SBRT	20	Any	34*	11*	2 cases ≥ grade 3
Kress et al (2012)[30]	Retrospective, single-center cohort	SBRT	11	Any	16.1*	1-year LC: 72%	1 case ≥ grade 3
Scorsetti et al (2015)[36]	Prospective, phase 2	SBRT	42	Any	29.0 ±3.7 (21.8-36.2)	12 ±4.2 (3.8-20.2)	None ≥ grade 3
McPartlin et al (2017)[38]	Prospective, phase 1 and 2	SBRT	60	Any	16.0 (11.9-20.5)	10.8*	1 case ≥ grade 3
Doi et al (2017)[31]	Retrospective, single-center cohort	SBRT	24	Any	45*	NR	Not reported
Petrelli et al (2018)[35]	Systematic review	SBRT	656	Any	31.5*	11.5*	8.7% ≥ grade 3
Vernale-one et al (2019)[32]	Retrospective, single-center cohort	SBRT	38	Any	20.1 (±2.0)	6.6 (±0.9)	None ≥ grade 3
Flamer-ique et al (2020)[33]	Retrospective, single-center cohort	SBRT	22	Any	24*	NR	1 case ≥ grade 3
Py et al (2021)[34]	Retrospective, single-center cohort	SBRT	67	Any	53 (38-66)	1-year LC: 81.9% (70.2%-89.2%) 5-year LC: 13.1% (6.0%-23.0%)	3% ≥ grade 3

CRLM, colorectal liver-only or liver-dominant metastases; LC, local control; OS, overall survival; PFS, progression-free survival; NR, not reported; SBRT, stereotactic body radiation therapy.
*95% CI and/or *P* value not reported.
#Where available.

control. This heterogeneity contributed to the complexity in interpretation of these studies.

We examined 5 retrospective cohort analyses reporting outcomes among patients with unresectable CRLM treated with SBRT; the study populations ranged from 11 to 67 patients.[30-34] Median OS ranged from 16.1 months to 53 months. Only 1 study reported median PFS, which was 6.6 months (SD ±0.93),[32] whereas other studies reported a 1-year local control rate between 73% and 91.9%.[30,34] A final systematic review that pooled data from 18 studies was assessed.[35] Of 656 patients receiving SBRT for unresectable CRLM, Petrelli et al[35] reported a median OS of 31.5 months and a median PFS of 11.5 months. Three prospective single-arm analyses including between 20 and 60 patients in each study who received SBRT were also reviewed.[36-38] In these studies, median OS ranged from 16 months to 34 months and median PFS from 10.8 months to 12 months.

Overall, SBRT is well tolerated as it is a noninvasive modality with short treatment sessions typically lasting less than an hour each.[29] In the studies examined, the rate of grade ≥3 AEs ranged from 3% to 10%, with the most common complications including nausea (5%), gastrointestinal ulcers (5%), thrombocytopenia (2%), and transient transaminitis (2%).[31,33,38] Another possible disadvantage when considering this locoregional therapy is that tumor response can be limited by histologic subtype and prior use of chemotherapy, both of which have been linked to increased rates of local failure.[29]

In conclusion, SBRT may be an attractive option for patients with chemotherapy-refractory, unresectable CRLM in whom more invasive locoregional therapies that require a percutaneous approach are contraindicated. It is also an appealing option for patients who require the treatment of multiple hepatic tumors if an adequate liver volume can be spared from unintentional radiation spread. Unfortunately, due to a paucity of high-impact studies, interpretation of the clinical data is limited. For this reason, further research is warranted regarding the use of SBRT among patients with unresectable CRLM who are unable to receive more invasive liver-directed therapies.

Selective Internal Radiation Therapy With Yttrium 90 Embolization

Treatment with Y90 involves selectively injecting radioactive yttrium-90 microparticles via a catheter into the hepatic artery branch that feeds a tumor.[39,40] These microparticles then become permanently lodged in the tumor vasculature, consequently delivering high-dose beta radiation to the surrounding tissue to induce tumor necrosis.[38-41] The NCCN states that Y90 radioembolization can be considered in select patients with unresectable CRLM who have chemotherapy-resistant or refractory disease and predominant hepatic metastases.[6]

We examined 9 peer-reviewed studies that focused on the role of Y90 radioembolization in the treatment of unresectable CRLM (**Table 3**). This included 1 systematic review, 1 prospective and 3 retrospective cohort studies, 1 prospective case series, and 3 reports that collectively discussed a total of 3 prospective randomized control studies. The papers were published between 2014 and 2019 and included between 52 and 1103 patients in each study.

SIRFLOX, FOXFIRE, and FOXFIRE-Global were all multicenter phase 3 randomized control trials showing that Y90 radioembolization in addition to FOLFOX-based chemotherapy does not improve OS or PFS when compared with chemotherapy alone as first-line treatment for unresectable CRLM.[42,43] A subsequent subgroup analysis of the SIRFLOX and FOXFIRE-Global trials by Gibbs et al[44] showed a 4.9-month increase in median OS ($P = .008$) in only those patients with right-sided primary tumors.[44]

TABLE 3. **Yttrium-90 Selective Internal Radiation Therapy for Treatment of Unresectable CRLM**

Study	Design	Treatment	N	Prior treatments	Median OS, months (95% CI)	Median PFS, months	Adverse events
Saxena et al (2014)[49]	Systematic review	Y90	979 (20 studies)	Chemo ± hepatic intervention	12 (range, 8.3-36.0)	9 (range, 6-16)*	Not reported
Saxena et al (2015)[45]	Retrospective, single-center cohort	Y90	302	Chemo ± hepatic intervention	10.5*	NR	None ≥ grade 3
Hickey et al (2015)[46]	Retrospective, multicenter cohort	Y90	531	Any	10.6 (8.8-12.4)	NR	13% ≥ grade 3
Abbott et al (2015)[47]	Retrospective, single-center cohort	Y90	68	Chemo ± hepatic intervention	11.6*	NR	7.3% ≥ grade 3
Golfieri et al (2015)[48]	Prospective, single-center case series	Y90	52	Chemo ± hepatic intervention	11.0 (8.0-14.0)	NR	6% ≥ grade 3
Van Hazel et al (2016)[43]	Prospective, multicenter RCT	Chemo vs chemo + Y90	530	None	NR	10.2 (chemo) vs 10.7 (chemo + Y90); $P = .4$	74.4% (chemo) vs 85.4% (chemo + Y90) grade ≥ 3; $P = .5$
Wasan et al (2017)[42]	3 multicenter RCTs (combined analysis)	Chemo vs chemo + Y90	1103	None	23.3 (chemo) vs 22.6 (chemo + Y90); $P = .6$	10.3 (chemo) vs 11.0 (chemo + Y90); $P = .1$	Y90 group greater odds of grade ≥ 3
Gibbs et al (2018)[44]	2 multicenter RCTs (combined analysis)	Chemo vs chemo + Y90, stratified by primary tumor side	739	None	RSP: 22.0 (chemo + Y90) vs 17.1 (chemo); $P = .01$ LSP: 24.6 (chemo + Y90) vs 26.6 (chemo); $P = .3$	RSP: 10.8 (chemo + Y90) vs 8.7 (chemo); $P = .06$ LSP: 11.4 (chemo + Y90) vs 10.8 (chemo); $P = .4$	RSP: No difference in grade ≥ 3 LSP: Y90 group greater odds of grade ≥ 3
White et al (2019)[2]	Prospective, multicenter cohort	None	399	Chemo ± hepatic intervention	7.6 (6.9-8.3)	3.0 (2.8-3.1)	143 (36%) experienced an AE; 8% were ≥ grade 3

AE, adverse event; CRLM, colorectal liver-only or liver-dominant metastases; chemo, chemotherapy; LSP, left-sided primary tumor; NR, not reported; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RSP, right-sided primary tumor; Y90, yttrium-90 selective internal radiation therapy.
*95% CI and/or *P* value not reported.

Failure of the aforementioned phase 3 trials to show definitive superiority of Y90 radioembolization as a first-line treatment has shifted focus away from this locoregional therapy as an option for patients with unresectable CRLM who have failed 1 or more lines of chemotherapy. While several single-arm studies have been published specifically on this topic, the patient populations across studies are markedly variable with respect to previous lines of chemotherapy, prior hepatic resection or ablation, and the presence of extrahepatic metastases. Patients in these studies were generally high-functioning, with 94% to 100% of patients having an ECOG status of 0 or 1 among single-arm studies reporting the statistic.[45-48] In studies regarding the use of salvage Y90 radioembolization for unresectable CRLM, median OS ranged from 7.6 to 11.6 months.[44-49] Only 1 study reported median PFS for salvage Y90 radioembolization, which was 3 months (95% CI, 2.8-3.1).[2] These outcomes are clearly inferior to those obtained with HAIP and SBRT, and thus we infer that Y90 radioembolization should be reserved for salvage therapy only in patients with unresectable CRLM.

Overall, Y90 radioembolization is safe and well tolerated. However, the delivery of Y90 microparticles to tissues other than the tumor can lead to complications.[40] Fortunately, the beta radiation is quite precise, penetrating on average only 2.5 mm from its source and thereby limiting its effects to the intended delivery site.[40] Serious complications can include gastrointestinal ulcers, radiation pneumonitis, and radioembolization-induced liver disease, which includes portal hypertension or damage to the biliary tree.[40] More common postprocedural complaints include nausea, abdominal pain, and generalized fatigue.[47] An analysis of three phase 3 trials reported that less than 6% of patients developed grade ≥ 3 AEs associated with Y90 radioembolization. Another analysis examining the use of Y90 radioembolization in patients who failed previous lines of chemotherapy reported that between 0% and 13% of participants developed grade ≥ 3 AEs.[2,45-48]

In conclusion, Y90 radioembolization is not recommended as a first-line treatment option for patients with unresectable CRLM. However, it is a potentially safe therapy in the salvage setting. While Y90 radioembolization is generally well tolerated, interpretation of the clinical data reported is limited due to the heterogeneous patient populations and lack of comparison groups. Nonetheless, in a patient population with few remaining treatment options, this therapy has the potential to improve OS (within the right-sided metastases population) with a relatively low incidence of serious AEs. Future areas of research may focus on studying Y90 radioembolization as a first-line therapy for unresectable CRLM in patients with right-sided primary tumors and conducting phase 3 trials comparing it to other locoregional treatments or supportive care for patients with unresectable CRLM refractory to chemotherapy. Additionally, other uses of Y90 radioembolization reported in the literature deserve further large-scale scientific inquiry, including its use to downsize CRLM for resection and to induce contralateral liver hypertrophy.[50-51]

Conclusions

Locoregional liver-directed therapies are an attractive option for patients with unresectable CRLM. In general, these therapies are well tolerated and AE profiles are minimal. Unfortunately, the lack of large-scale, prospective phase 3 trials complicates the interpretation of available data. HAIP is considered a safe and effective strategy to control disease progression or expand resectability. However, providers must weigh these potential benefits with risks of toxicity and the need for referral to institutions with HAIP infrastructure and expertise. SBRT may be an attractive option for patients with unresectable CRLM for whom locoregional therapies that require a percutaneous approach are contraindicated. Lastly, although Y90 radioembolization was not shown to be effective as first-line treatment for patients with unresectable CRLM, it has shown some potential in patients with chemotherapy-refractory disease and in those with right-sided primary tumors. Ultimately, for patients with unresectable CRLM, clinical decisions require multidisciplinary discussions that carefully consider the patient's disease process, comorbidities, and functional status in addition to the available clinical expertise at the treating facility. ■

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For references visit cancernetwork.com/McFadden_2.22

Complete Pathologic Response to Neoadjuvant Chemoimmunotherapy and Oxaliplatin-Induced Fever Associated With IL-6 Release in a Patient With Locally Advanced Colon Cancer

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ABSTRACT: Neoadjuvant systemic therapy is a preferred treatment approach for a number of tumor types due to many potential advantages over upfront surgery, including tumor downstaging, early treatment of micrometastatic disease, and providing an in vivo test of tumor biology. For colon cancer, current standard of care is upfront surgery followed by adjuvant systemic therapy in high-risk patients. Concerns about inaccurate radiological staging and tumor progression during preoperative treatment, as well the lack of randomized data demonstrating benefit, are among the reasons for the limited use of neoadjuvant therapy in this disease. Locally advanced colon cancer, defined as primary colon cancer with direct invasion into the adjacent structures or extensive regional lymph node involvement, is not always amenable to pathological complete resection, and when attempted it comes with high incidence of postoperative morbidity and mortality because of the required multivisceral resection. Clinical trials of neoadjuvant chemotherapy for colon cancer to date have been promising with downstaging of disease and higher rates of R0 resection. Here, we report a case of a patient with locally advanced, unresectable, mismatch repair deficient sigmoid colon cancer who was treated with neoadjuvant chemoimmunotherapy followed by surgical resection leading to a complete pathologic response after preoperative systemic chemoimmunotherapy.

Introduction

Colon cancer is the third most common cancer in the United States, with 104,270 new cases in 2021. Colorectal cancer (CRC) is now estimated to be the fourth most common cancer in US men and women aged between 30 and 39 years.[1] Advances in our understanding of pathophysiology of these diseases have increased the array of diagnostic and treatment options leading to individualized treatment plans. Screening for deficient DNA mismatch repair (dMMR) has become a standard of care for all individuals with CRC.[2] dMMR is detected in 15% to 20% of all colon cancer specimens and 10% of rectal cancer specimens. The hallmark of dMMR tumors—microsatellite instability (MSI)—is caused by either a germline mutation in one of the MMR genes (*MLH1, MSH2, MSH6, PMS2*, and deletion of *EPCAM*) or by epigenetic silencing of the MLH1 promoter region.[3] dMMR tumors of colon differ from MMR-proficient (pMMR) tumors in terms of prognosis, response to treatment, and patterns of metastatic spread.[4]

Over the past decade, treatment modalities for CRC have advanced to include endoscopic and surgical local excision; downstaging with preoperative radiotherapy and systemic therapy; extensive surgery for locoregional and metastatic disease; local ablative therapies for metastases; and chemotherapy, targeted therapy, and immunotherapy. Although these new treatment options have doubled overall survival (OS) for advanced disease for up to 3 years, survival is still best for those with nonmetastatic disease. Locally advanced colon cancer (LACC) with direct invasion to the

adjacent structures or with extensive regional lymph node involvement has been difficult to manage because of the difficulties in accomplishing pathological complete resection and high incidence of postoperative morbidity and mortality.[5] Five-year survival rates for patients with stage IIIB and IIIC colon cancer have been reported to be 46% and 28%, respectively.[6] While preoperative chemoradiotherapy is now an established standard treatment option for locally advanced rectal cancer,[7,8] the role of neoadjuvant therapy for LACC is still evolving.

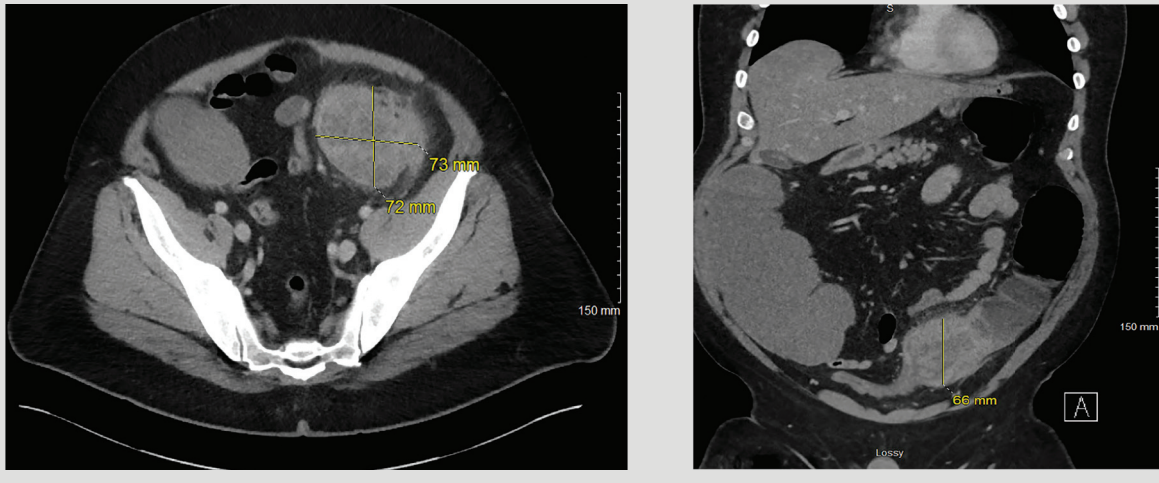
Background

Complete removal of the tumor with negative margins (R0 resection) followed by adjuvant chemotherapy has been the only established curative treatment for localized colon cancer. R0 resection can be challenging for LACC, which is defined as a primary tumor that directly invades adjacent structures with or without extensive nodal involvement. Approximately 26% of patients with colon cancer present with locally advanced disease.[9] In patients with LACC (high-risk stage II or III disease), the current standard of care may not be optimal, as R0 resection is not always possible in patients with T4b, M0 or N2, M0 disease.[10] Neoadjuvant chemotherapy, an appealing concept in many other tumor types, has not been well established in operable colon cancer. Limitations to its widespread use include concerns about inaccurate radiological staging, tumor progression while undergoing preoperative treatment, and a lack of randomized data demonstrating benefit. However, with recent advances in radiological staging and availability of more effective systemic treatment options—including chemotherapy, immunotherapy, and targeted therapy—neoadjuvant treatment in LACC now is being increasingly explored as a promising new strategy.

For an increasing number of cancers in which the treatment goal is cure, neoadjuvant chemotherapy or chemoradiation prior to surgery has shown superior outcomes. The main driver of prognosis for a patient with localized colon cancer is the risk of later distant metastases; therefore, the opportunity to treat any potential distant micrometastatic disease at the time of diagnosis represents a plausible approach to attain long-term cure.[11-13] While chemoradiation prior to resection is a well-established approach for locally advanced rectal cancer, the role of neoadjuvant therapy in LACC remains unclear. Three studies of preoperative chemoradiation in LACC have reported R0 resection rates of as high as 91% to 100% and occasional pathologic complete response rates of 3% to 31% in this setting.[14-16]

A number of single-arm trials have suggested that the use of neoadjuvant fluoropyrimidine oxaliplatin chemotherapy is safe and effective in LACC. In 2 of these studies involving patients with *RAS/RAF* wild type LACC, a minimum of 2 cycles of neoadjuvant capecitabine and oxaliplatin alone or in combination with panitumumab (Vectibix) showed both radiological and pathological responses, with 2% to 4% of patients achieving complete pathological response at surgery.[17,18] In another study, 4 to 6 cycles of 5-fluorouracil, folinic acid, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin neoadjuvant chemotherapy were evaluated, and they were found to be safe and effective with a complete pathological response rate of 4.6%.[19] Triplet neoadjuvant chemotherapy with FOLFOX plus irinotecan (FOLFOXIRI) has also been assessed in a phase 2 study; the results showed a trend to greater tumor volume reduction with each subsequent chemotherapy cycle administered

FIGURE 1. **Large Mass Near the Junction of Descending Colon With Resultant Colonic Obstruction**



compared with patients who received 4 preplanned neoadjuvant cycles.[20] FOLFOXIRI was associated with higher rates of adverse effects (AEs), as expected. In all of these nonrandomized phase 2 studies, neoadjuvant chemotherapy did not appear to delay surgery. Rates of perioperative complications, including length of postoperative hospital stay and rates of anastomotic leak, were similar to published data in patients undergoing surgery alone.

The effect on OS in these single-arm studies is encouraging. Five-year survival in small cohorts with T4 disease ranged from the expected 67% to a very promising 95%.[19,21] A large cohort study utilizing data from the US National Cancer database showed improved survival in patients with T4b colon cancer who received neoadjuvant chemotherapy, but not in patients with T3 or T4a disease, compared with those who received surgery followed by adjuvant chemotherapy.[22]

Case

A White man, aged 45 years, had been experiencing symptoms of intermittent abdominal pain, abdominal distention, and change in bowel habits for the past 2 months. He presented to the emergency department with severe abdominal pain and vomiting. A CT scan of the abdomen and pelvis revealed marked colonic distention and a large (7.2 cm × 7.3 cm × 6.7 cm), heterogeneously enhancing mass in the sigmoid colon involving approximately 13 cm length of the colon; there was moderate infiltration of the surrounding mesenteric fat and mildly enlarged left lower quadrant mesenteric lymph nodes (**Figure 1**). He was taken to surgery with the intent of exploratory laparotomy and resection of the sigmoid colon mass. Due to size, friability, and bleeding from the mass, it was not possible to resect. Therefore, a takedown of splenic flexure with a loop colostomy was performed instead. Pathology

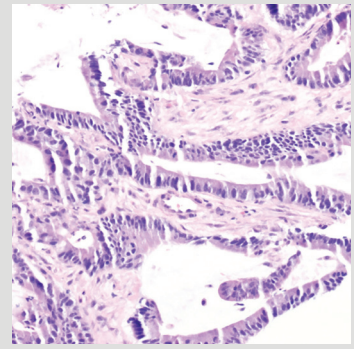


FIGURE 2A. **Evaluation of Colonic Mass by Hematoxylin Eosin Stain Adenocarcinoma (200× magnification)**

of the mass involving colon and adjacent structures came back as moderately differentiated adenocarcinoma.

Immunohistochemical staining for mismatch repair proteins revealed loss of nuclear staining for MLH1 and PMS2, and intact nuclear staining for MSH2 and MSH6 (**Figures 2A & 2B**). Subsequent *BRAF* and *RAS* panel testing was not able to be done due to insufficient tissue for evaluation. A genetic consultation and germline testing was declined by the patient.

After discussion in tumor conference, he was started on FOLFOX chemotherapy regimen plus the immunotherapy pembrolizumab (Keytruda). Approximately 2 to 6 hours after each cycle of the FOLFOX regimen, he developed high temperature (range, 102.5° F to 104.0° F), with shivers, rigors, and chills. He was hospitalized with each episode and underwent extensive work-up for fever of unknown origin. Cultures of blood and urine, cultures from his infuseport, and ultimately removal of his infuseport and cultures of the port, as well as imaging studies, revealed no infectious etiology. Due to the timing of fevers, test trials of holding continuous 5-fluorouracil were undertaken but they did not prevent occurrence of febrile episodes.

Based on rarely published data regarding oxaliplatin-induced fever due to release of interleukin-6 (IL-6), and on an elevated IL-6 level during one of his febrile episodes, his chemotherapy was changed to the FOLFIRI regimen. Consequently, he had no more fever or episodes of shivering with FOLFIRI and completed his planned 6 cycles of neoadjuvant chemotherapy (4 cycles of FOLFOX plus 2 cycles of FOLFIRI) along with 6 cycles of pembrolizumab. Restaging CT scans showed almost complete resolution of his sigmoid colon mass (**Figure 3**). He underwent exploratory laparotomy, sigmoid colon resection with lymph node dissection, reversal of loop colostomy and hernia repair. Pathology showed sigmoid colon resection with no residual tumor, abundant cellular mucin extending from mucosal surface to the serosa consistent with area of treated and destroyed tumor (Figure 3). All 35 mesenteric lymph nodes that were evaluated were negative. There was no lymphovascular or perineural invasion, and pathologic stage was reported as ypT0ypN0.

Discussion

Currently, surgery followed by adjuvant systemic chemotherapy is the standard of care for the curative intent treatment of nonmetastatic colon cancer. R0 surgical resection is among the most important predictors of long-term survival.[23] There is growing interest in exploring the utility of the neoadjuvant approach to convert locally advanced unresectable colon cancer to a resectable stage with the goal of cure. Because radiologic nodal N staging is less accurate than tumor T staging, definition of LACC has been based mostly on the radiological T stage, focusing on high-risk T3 (>5 mm extramural invasion to pericolic fat) and T4 primary tumors.[24,25]

The first phase 3 trial of neoadjuvant chemotherapy for colon cancer from the United Kingdom recruited patients with T3 disease on preoperative staging and randomized them to neoadjuvant

chemotherapy ± panitumumab or to immediate surgery followed by adjuvant chemotherapy.[26] In the pilot phase of this trial, only higher-risk radiological T3 tumors with ≥5 mm extramural extension or T4 tumors were included, and the results showed downstaging of the primary tumor. Further results of this trial, presented at the 2019 American Society of Clinical Oncology Annual Meeting, showed a significantly reduced rate of incomplete surgical resection (R1 or R2) along with reduced pathological staging and decreased 2-year failure rate (HR, 0.77; 95% CI, 0.56-1.06).[27] A subgroup analysis suggested less benefit from neoadjuvant chemotherapy in patients with dMMR tumors.[28] Similarly, neoadjuvant chemotherapy in the second phase 3 trial, FOxTROT, resulted in a 74% pathological response rate in the pMMR group, whereas it was only 27% in the dMMR subgroup.[29]

It is now well established that immune checkpoint inhibitors have increased activity in MSI-high or dMMR solid tumors, and this is true for colon cancer.[30] Evidence for the efficacy of immunotherapy in advanced dMMR CRC is growing, with reported objective response rates up to 31% to 40% for single-agent checkpoint inhibitors and 55% for dual-checkpoint inhibition; however, response rates in metastatic pMMR colon cancer are close to 0%.[31-33]

The role of immunotherapy in the first-line metastatic dMMR CRC setting has now been confirmed with the results of the KEYNOTE-177 study, which led to the FDA approval of pembrolizumab.[34] The role of immunotherapy in the adjuvant setting is currently being studied in the Adjuvant Trial of Deficient Mismatch Repair in Colon Cancer (ATOMIC trial; NCT02912559), which is randomizing patients with stage III dMMR colon cancer to standard chemotherapy alone vs in combination with immunotherapy.[35] Immunotherapy with or without chemotherapy may play a significant role in the neoadjuvant treatment of dMMR LACC. However, there are no definitive data regarding chemoimmunotherapy in the neoadjuvant setting. Although 10% to 15% of patients with early-stage CRC present with dMMR disease, only 4% of patients with metastatic colon cancer test positive for dMMR, making more patients with early-stage disease eligible for immunotherapy.

Neoadjuvant immunotherapy is an evolving strategy in oncology. A phase 2 open-label neoadjuvant immunotherapy trial of 32 patients with MSI-high/dMMR nonmetastatic solid tumors (24 colorectal, 1 endometrial, 1 gastric, 1 meningeal, 2 duodenal, 1 ampullary, and 2 pancreatic) showed that neoadjuvant treatment with pembrolizumab was safe, with encouraging clinical activity.[36] In the first neoadjuvant immunotherapy trial of colon cancer, the phase 2 NICHE trial, 19 patients with resectable, early-stage colon cancer—both dMMR and pMMR—were treated with ipilimumab at 1 mg/kg on day 1 and nivolumab at 3 mg/kg on days 1 and 15.[37] A major pathologic response, defined as <5% residual viable tumor, was observed in 100% (7/7 tumors), and a complete pathologic response was seen in 57% (4/7 tumors) of the dMMR patients. There were no observed major pathologic responses in the pMMR group. More recently, in a final analysis of 35 patients with nonmetastatic resectable CRC (20 with dMMR and 15 with pMMR) treated with neoadjuvant immunotherapy, 12 of 20 patients with dMMR tumors achieved a complete pathologic response; in 19 of 20, a major pathologic response was seen. Interestingly, contrary to other studies, a pathologic response was also noted in 4 of 15 patients with pMMR tumors. In those 4, 3 had a major pathologic response and 1 had a partial response.[38]

Based on the available data and the extent of the tumor, we treated our patient with FOLFOX every 2 weeks and pembrolizumab every 3 weeks, similar to the regimen in the ATOMIC adjuvant trial. The patient tolerated treatments well except for the very interesting and rare AE of oxaliplatin-induced fever with IL-6 release, which led to the change of the chemotherapy component of his neoadjuvant regimen to FOLFIRI. Oxaliplatin, a third-generation platinum analogue, is a novel

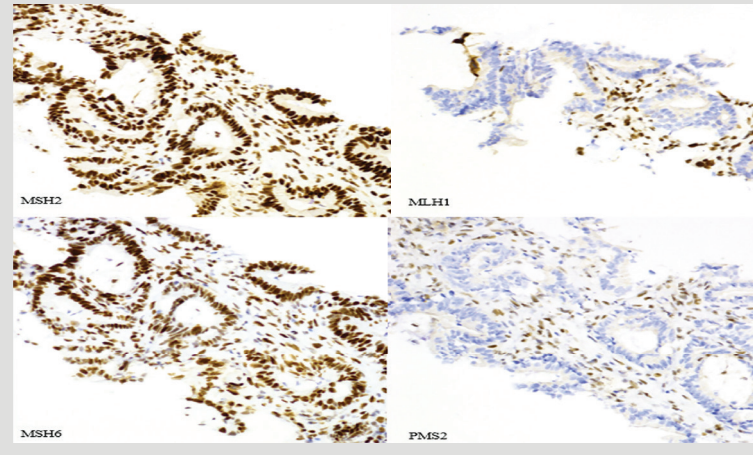
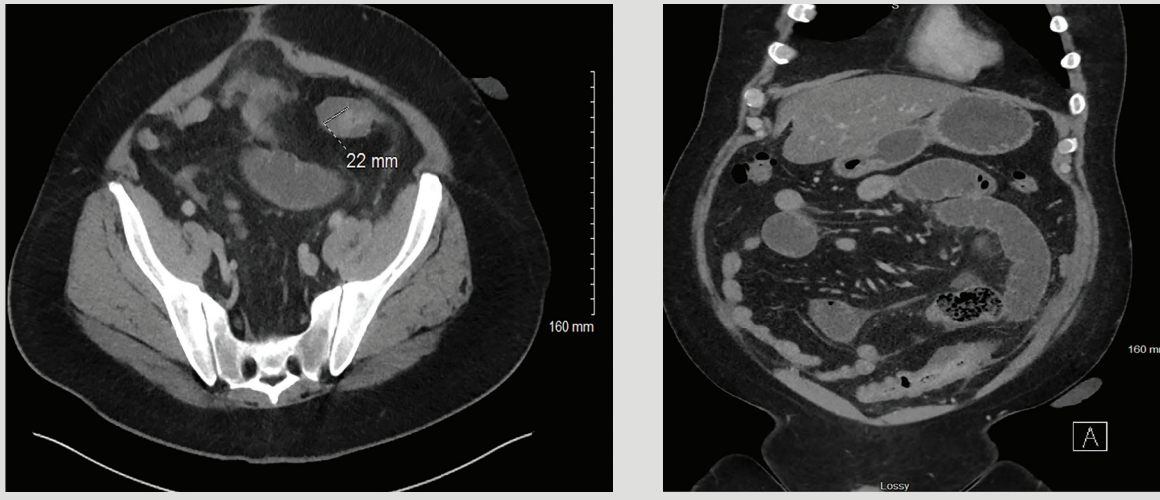


FIGURE 2B. **Evaluation by Immunoperoxidase Stains for Mismatch Repair Enzymes Shows Loss of Staining for MLH1 and PMS2 (200× magnification)**

FIGURE 3. **Large Mass Near the Junction of Descending Colon Significantly Smaller With Resultant Resolution of Colonic Obstruction**



compound with proven antitumor activity in CRC. AEs are generally moderate and include peripheral neuropathy along with mild bone marrow suppression and gastrointestinal AEs. A rare reported AE of oxaliplatin is fever up to 102.2° F starting 2 to 6 hours after administration, persisting for up to 3 days, and recurring at the same interval on following administrations of oxaliplatin. This very rarely reported phenomenon has been associated with IL-6 release.[39] Blood samples taken from our patient disclosed an increase in IL-6 serum levels parallel to the body temperature, while C-reactive protein values remained unchanged. This interesting finding of elevated IL-6 levels during his FOLFOX treatments made us question the available literature data on the possible role of cytokines in predicting the response and AEs related to immune checkpoint inhibitors. The investigations of TNF-α, IFN-γ, IL-6, IL-8, TGF-β and other cytokines as predictors of the responses and AEs to immune checkpoint inhibitors have produced mixed results. While increased levels of IFN-γ and IFN-γ pathway genes have always acted as positive biomarkers for response and AEs, high baseline and increased levels of IL-8, IL-6, and TGF-β have been negative biomarkers for response and AEs.[40] Resolution of fever and elevated IL-6 reaction after changing his chemotherapy to FOLFIRI, as well as complete pathologic response in our patient, further supported this being an oxaliplatin-related AE.

Outcome of the Case

After completion of neoadjuvant chemoimmunotherapy, surgical resection revealed a complete pathologic response. Patient is on follow-up with no evidence of disease.

Conclusions

As data continue to unfold, neoadjuvant chemotherapy and/or immunotherapy will likely find their place in the treatment of locally advanced dMMR and pMMR colon cancer. Molecular characterization of tumors, along with the radiologic and pathologic responses to treatment, will determine which populations are most likely to benefit from this approach. Avoiding operative delays in those with a low likelihood of response to cytotoxic treatment will be imperative in appropriate use of this approach. The inclusion of novel approaches, with immunotherapy or other targeted agents outside of traditional chemotherapy, may provide significant survival advantages. Translational studies will be pivotal in our understanding of this new concept, as will immunomodulation studies using antitumor vaccines and chimeric antigen receptor T cells.[41] Clinicians should closely watch this developing area, consider the option of neoadjuvant chemotherapy, and seek out opportunities for participation in ongoing clinical trials. ■

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For references visit
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INDICATIONS

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA® and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA® and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and 1% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA® , and 2 patients (0.2%) treated with placebo died from a cerebrovascular event. Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® *[see Use in Specific Populations (8.1, 8.3)]*.

ADVERSE REACTIONS

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)

- **Hematology** — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)
- **Chemistry** — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1.0%); hypertriglyceridemia ERLEADA® 67% (1.6%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (1.9%), placebo 22% (0.5%)

Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo.

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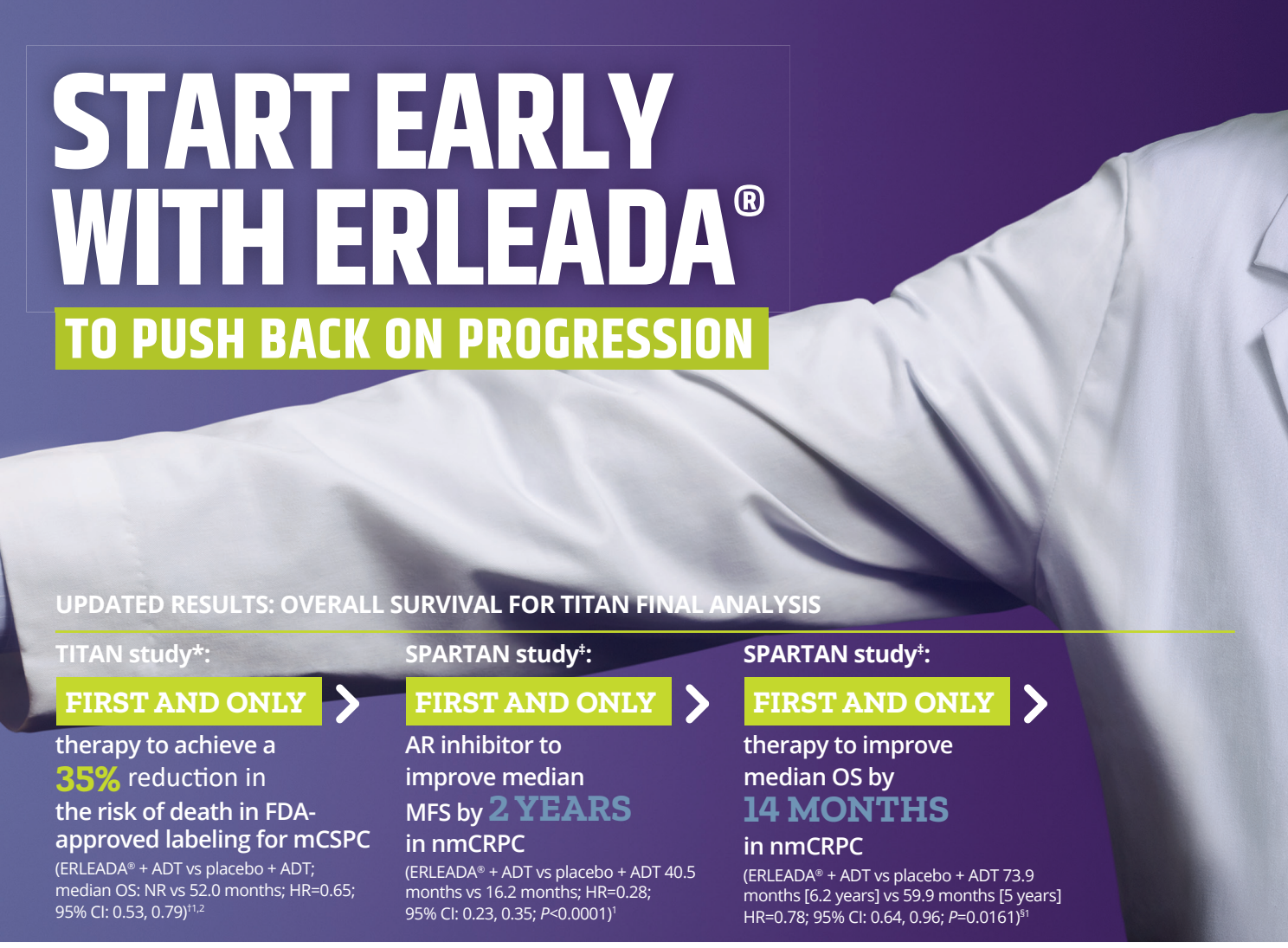

UPDATED RESULTS: OVERALL SURVIVAL FOR TITAN FINAL ANALYSIS

TITAN study*:

FIRST AND ONLY >

therapy to achieve a **35%** reduction in the risk of death in FDA-approved labeling for mCSPC

(ERLEADA® + ADT vs placebo + ADT; median OS: NR vs 52.0 months; HR=0.65; 95% CI: 0.53, 0.79)[†1,2]

SPARTAN study‡:

FIRST AND ONLY >

AR inhibitor to improve median MFS by **2 YEARS** in nmCRPC

(ERLEADA® + ADT vs placebo + ADT 40.5 months vs 16.2 months; HR=0.28; 95% CI: 0.23, 0.35; *P*<0.0001)[1]

SPARTAN study‡:

FIRST AND ONLY >

therapy to improve median OS by **14 MONTHS** in nmCRPC

(ERLEADA® + ADT vs placebo + ADT 73.9 months [6.2 years] vs 59.9 months [5 years] HR=0.78; 95% CI: 0.64, 0.96; *P*=0.0161)[§1]

Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability *[see Dosage and Administration (2.2)]*.

Effect of ERLEADA® on Other Drugs

CYP3A4, CYP2C9, CYP2C19, and UGT Substrates— ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, vBCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

ADT = androgen deprivation therapy; AR = androgen receptor; CI = confidence interval; CT = computed tomography; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; NE = non-estimable; nmCRPC = non-metastatic castration-resistant prostate cancer; NR = not reached; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-509; TITAN = Targeted Investigational Treatment Analysis of Novel Antiandrogen.

*Study Design: TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival and rPFS.[1,4]

†All patients who enrolled in the TITAN study started ADT for mCSPC ≤6 months prior to randomization.[4]

‡Study Design: SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=1207). Patients had a PSA doubling time ≤10 months and serum testosterone levels <50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.[1,3]

§In the SPARTAN study, conventional imaging (technetium-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph nodes <2 cm in short axis (N1) located below the iliac bifurcation at screening were allowed in the study. All patients in SPARTAN had a PSA doubling time ≤10 months at study entry.[1,3]

cp-505076v5

Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

References: 1. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic, castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study [published online April 29, 2021]. *J Clin Oncol.* doi.org/10.1200/JCO.20.03488 **3.** Smith MR, Saad F, Chowdhury S, et al; for the SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med.* 2018;378(15):1408-1418. **4.** Chi KN, Agarwal N, Bjartell A, et al; for the TITAN Investigators. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med.* 2019;381(1):13-24.

Erleada® (apalutamide) 60 mg tablets

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Brief Summary of Prescribing Information for ERLEADA® (apalutamide)
ERLEADA® (apalutamide) tablets, for oral use
See package insert for Full Prescribing Information

INDICATIONS AND USAGE
ERLEADA is indicated for the treatment of patients with

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events
Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA and 1% of patients treated with placebo *[see Adverse Reactions]*. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures
Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 2.7% of patients treated with ERLEADA and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 1.5%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls
Falls occurred in patients receiving ERLEADA with increased frequency in the elderly *[see Use in Specific Populations]*. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure
Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Embryo-Fetal Toxicity
The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA *[see Use in Specific Populations and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:

- Cerebrovascular and Ischemic Cardiovascular Events *[see Warnings and Precautions]*.
- Fractures *[see Warnings and Precautions]*.
- Falls *[see Warnings and Precautions]*.
- Seizure *[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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2.3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

	ERLEADA N=524		Placebo N=527	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Musculoskeletal and connective tissue disorders				
Arthralgia[a]	17	0.4	15	0.9
Skin and subcutaneous tissue disorders				
Rash[b]	28	6	9	0.6
Pruritus	11	0.2	4.6	0.2
Vascular disorders				
Hot flush	23	0	16	0
Hypertension	18	8	16	9

[a] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

[b] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3.1% versus 1.9% on placebo), dysgeusia (3.2% versus 0.6% on placebo), and hypothyroidism (3.6% versus 0.6% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

	ERLEADA N=524		Placebo N=527	
Laboratory Abnormality	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Hematology				
White blood cell decreased	27	0.4	19	0.6
Chemistry				
Hypertriglyceridemia[a]	17	2.5	12	2.3

[a] Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥ 2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3.2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3.4%) in the ERLEADA arm and urinary retention (3.8%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions				
Fatigue[a,b]	39	1.4	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia[b]	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash[c]	25	5.2	6	0.3
Metabolism and nutrition disorders				
Decreased appetite[d]	12	0.1	9	0
Peripheral edema[e]	11	0	9	0
Injury, poisoning and procedural complications				
Fall[b]	16	1.7	9	0.8
Fracture[f]	12	2.7	7	0.8
Investigations				
Weight decreased[b]	16	1.1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1.1	15	0.5
Nausea	18	0	16	0

[a] Includes fatigue and asthenia

[b] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

[c] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

[d] Includes appetite disorder, decreased appetite, early satiety, and hypophagia

[e] Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

[f] Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, and tibia fracture

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (6% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).

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Table 4: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
Laboratory Abnormality	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Hematology				
Anemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	1.8	21	1.6
Chemistry				
Hypercholesterolemia[a]	76	0.1	46	0
Hyperglycemia[a]	70	2	59	1.0
Hypertriglyceridemia[a]	67	1.6	49	0.8
Hyperkalemia	32	1.9	22	0.5

[a] Does not reflect fasting values

Rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of patients treated with ERLEADA and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 4.9% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted *[see Drug Interactions]*.

Post-Marketing Experience

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

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability *[see Dosage and Administration (2.2) in Full Prescribing Information]*. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on ERLEADA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose *(see Data)*.

Data

Animal Data

In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s), and small, incomplete ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients.

Lactation

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. *[see Use in Specific Populations].*

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in Full Prescribing Information].*

Pediatric Use

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

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over.

No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

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

Cerebrovascular and Ischemic Cardiovascular Events

- Inform patients that ERLEADA has been associated with cerebrovascular and ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular or a cerebrovascular event occur *[see Warnings and Precautions]*.

Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures *[see Warnings and Precautions].*

ERLEADA® (apalutamide) tablets

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure *[see Warnings and Precautions].*

Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash *[see Adverse Reactions].*

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Instruct patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman *[see Warnings and Precautions].*

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA *[see Use in Specific Populations].*

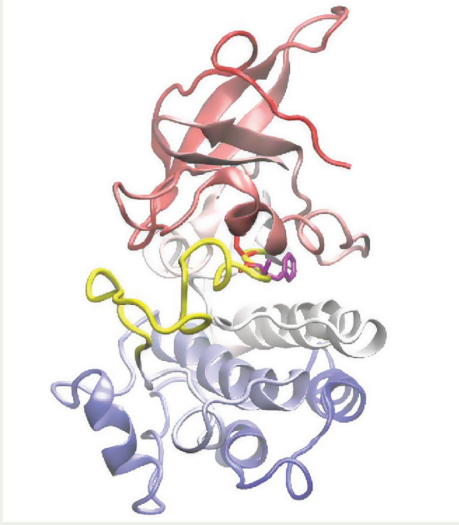
Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

cp-50509v7

EXPERT COMMENTARY ON THE PRODUCT PROFILE OF

Mobocertinib



Drug name: Mobocertinib (Exkivity)

Date of approval: September 15, 2021

Initial indication: For adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) harboring *EGFR* exon 20 insertion mutations and whose disease has progressed following platinum-based therapy.[1]

Dosage and administration: 160 mg orally once daily with or without food.

How supplied: Taken orally

Pivotal clinical trial: Phase 1/2 Study 101 (NCT02716116)[2]

Trial Design of the Pivotal Study 101

ELIGIBLE PATIENTS

- Histologically confirmed, locally advanced or metastatic NSCLC
- Documented *EGFR* exon 20 insertion mutations
- 1 prior line of therapy
- QTc 450 ms or less in males and 470 ms or less in females
- ECOG performance score between 0 and 2

↓

Mobocertinib 160-mg capsule orally once daily for 28-day treatment cycles up to 4 months

↓

Primary end point
Objective response rate assessed by independent review committee

Key secondary end points
safety, tolerability, and efficacy

COMMENTARY BY

Megan May, PharmD, BCOP

Clinical Oncology Pharmacy Specialist Baptist Health Lexington
Lexington, KY

ONCOLOGY®: **Describe the mechanism of action of mobocertinib?**

MAY: Mobocertinib is a small molecule oral EGFR tyrosine kinase inhibitor [TKI], and it was designed specifically to target *EGFR* exon 20 insertion mutations. It binds to and inhibits *EGFR* exon 20 insertion mutations at a lower concentration than the wild-type *EGFR*. It also has inhibitory activity on other EGFR family members, such as HER2 and HER4. *EGFR* exon 20 insertion mutations occur in about 2% of all patients with NSCLC, and they're more common in patients with adenocarcinoma, Asian American [patients], and African American [patients]. Mobocertinib is indicated in [patients with] locally advanced or metastatic NSCLC with the *EGFR* exon 20 insertion mutation whose disease have progressed on or after a platinum-based chemotherapy.

Q: Describe the toxicity profile of mobocertinib. Have any adverse events become more apparent in the real-world setting?

MAY: There is a black box warning for QTc prolongation that everyone needs to be aware of. In the trial, 11% of patients had a 60-ms increase in their QTc from baseline. For example, a patient has a QT change from 350 to 410 ms, which is a huge jump. The average overall increase was 23 ms. If a patient's QTc at baseline was above 470 ms, they were excluded from the study. When we are starting a patient on this medication, we need to make sure we're monitoring QTc and electrolytes at baseline and periodically throughout treatment. In the study, they checked QTc at month 4 and month 12. For my patients, we're going to recommend quarterly monitoring for the QTc prolongation.

Other precautions to be aware of [are that] about 4% of patients in this study developed interstitial lung disease or pneumonitis. We do need to make patients aware of the risk of this and advise patients to report any signs and symptoms to the provider. Cardiac toxicity was also seen in 2.7% of patients. This includes decreased ejection fraction, cardiomyopathy, and congestive heart failure. The package insert says [to monitor this] at baseline and during treatment. In practice, we are going to recommend monitoring quarterly. A reason that we see the cardiotoxicity is because the mobocertinib is also inhibiting those HER kinases.

This is an *EGFR* TKI, so we're going to also think of those classic *EGFR* [adverse] effects [AEs] that we're aware of. By far the most common AE was diarrhea, and this was seen in about 92% of patients in the study. Common AEs were rash, stomatitis, vomiting, and nausea.

As I previously mentioned, 92% of patients had diarrhea of all grades in the study and 21% of them had grade 3 or higher diarrhea. The median time of onset of diarrhea was about 5 days, but it also occurred in as little as 24 hours after taking the first dose. This is usually manageable with dose adjustments and proper treatment. Hopefully these patients will be on treatment long-term, so we want to make sure that we do not have to dose adjust if we don't have to. I advise patients during education to have an antidiarrheal medicine like loperamide on hand before they even start treatment. As soon as they have any diarrhea, they need to start taking that loperamide, increase their fluid intake, and report their symptoms to us.

Depending on the severity of the diarrhea, though, you might have to withhold, reduce, or permanently discontinue the mobocertinib. [Investigators stated] in the protocol to be more proactive with the antidiarrheal medication, so as soon as a patient had grade 1 diarrhea, the protocol did recommend going ahead and using an antidiarrheal medication.

Q: Are dosing modifications common with this agent?

MAY: There are some dose adjustments that are needed with some toxicities. I already mentioned diarrhea, and if you have grade 2 or higher diarrhea, you will need to reduce the dose. If the ejection fraction decreases, or they have a QTc interval prolongation greater than 481 ms, you will need to do a dose adjustment. The FDA-approved dose is 160 mg once a day; the first dose reduction is to 120 mg a day, the next reduction is 80 mg a day, and then you must permanently discontinue if the patient cannot tolerate the toxicities with that reduced dose. One other thing to mention with this is if a patient does develop heart failure or interstitial lung disease, you want to permanently discontinue treatment. You would not want to dose reduce for that.

Q: What are the major drug interactions clinicians should be aware of, if any?

MAY: Mobocertinib is a CYP3A substrate, so we do need to make sure patients are avoiding grapefruit and grapefruit juice. You also must avoid use with strong or moderate CYP3A inhibitors. If you must use a CYP3A inhibitor in combination, you do need to reduce the dose by 50% and monitor that QTc more frequently. Another issue we see in clinic is since patients are staying on these drugs long-term, you want to make sure you're evaluating their current medications at every visit. You might need to adjust the dose depending on if they start a new agent or if they're stopping an agent that they've been on previously. We want to make sure they can stay at the highest dose possible throughout treatment to have the best efficacy.

Q: Have barriers to administration emerged since this agent's approval?

MAY: The biggest issue logistically for this drug is getting insurance coverage. Like most of our oral TKIs, there is a very high price tag for mobocertinib. There is a co-pay assistance program available for commercially insured patients, and the patient can pay as little as $0 per script if they can enroll in that program. If a patient has government insurance, then in my clinic we look for grant funding to assist the patient if they have a high co-pay amount. If a patient is uninsured or under insured, this manufacturer does have a patient assistance program that [may] hopefully get the medication at no charge.

Another unique thing is the manufacturer has a program called the Here2Assist Rapid Start program.[3] If your patient is trying to start the medication and you've had more than a 5-day delay, the patient can get a 1-month supply at no cost from the manufacturer to help you obtain the medication for future use. The manufacturer has contracted with Biologics and Onco360 as their in-network specialty pharmacies. If you are sending this prescription to an outside pharmacy, make sure you're sending it to one of those 2 specialty pharmacies so you don't delay getting the drug to the patient.

Q: Is there anything else you want to add?

MAY: One thing we do need to be aware of is that the indication for mobocertinib is approved under accelerated approval.[4] [The approval] was based on the overall response rate and duration of response data. To continue this approval, it is contingent upon verification of clinical benefit and confirmatory trials. There is an ongoing study looking at this, and it's in patients in a first-line setting. These patients have not had prior systemic therapy, and they're randomizing the patients to mobocertinib compared with standard-of-care chemotherapy. ■

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Best Practices for Mentoring New Physicians

Heidi Moawad, MD

Established physicians often mentor younger physicians within the same field. Recently, formal mentoring has increased, with systemized processes becoming more and more prevalent.

When considering a mentorship, physicians should clarify what guidance they will provide, communicate their availability, and provide transparency about the formality, or informality, of the process.

Establish type of mentoring

Defining the goals of the mentoring relationship can be useful to clarify expectations. If you will spend time guiding a medical student, resident, or a junior physician, you might be happy to do so casually as they navigate their new role. Or you might consider your involvement to be worth the effort only if they will move forward and progress in a specific way. Knowing your own style will help you determine what type of mentoring you are capable of.

Frequency

Another important aspect of setting expectations involves the frequency of your meetings. With an informal mentoring process, you might not necessarily feel the need to provide a set structure. One drawback of this approach is that the physician who you are mentoring might hesitate to contact you—or could end up contacting you more than you would like. Finding a common ground for the frequency and formality of your meetings can be helpful.

Duration

Mentoring another doctor can be a long-term process that lasts for years, but sometimes it isn't possible to continue mentoring someone after they have reached an advanced level in their career. You might not be equipped for guiding someone beyond a particular goalpost that is your niche. After they have reached a given point, you may become more of a peer than a mentor, and you may remain friends for the long term.

Make sure you are up to the task

Mentoring other physicians can feel flattering, but it's best to acknowledge when you aren't the right person to deliver what a potential mentee needs. If a young doctor looking to you for guidance is highly ambitious, it's important that they aren't under the impression that you are more successful than you actually are. And if a young doctor is looking for moral support, you might be able to provide that type of encouragement only if you are a deeply confident person yourself.

To read the full article, visit https://bit.ly/3qf5Dh4

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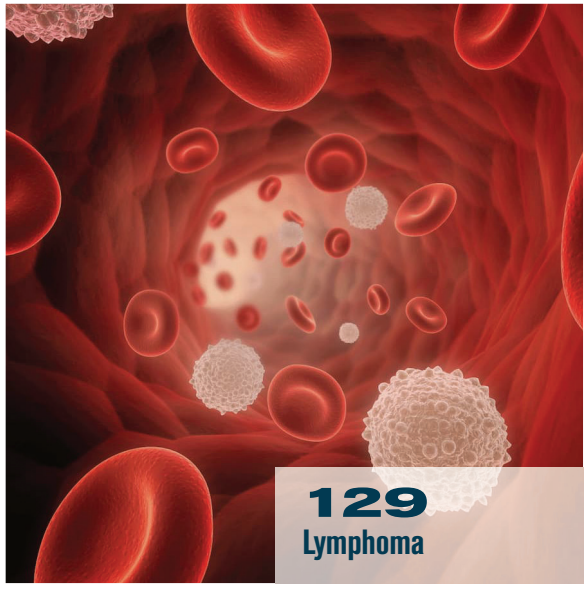

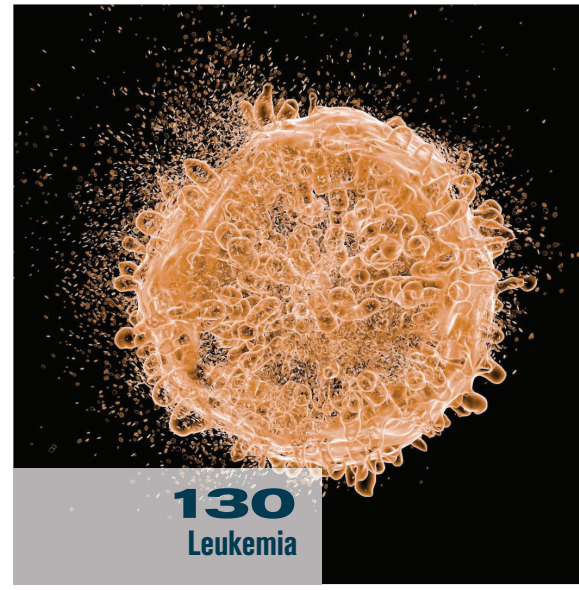

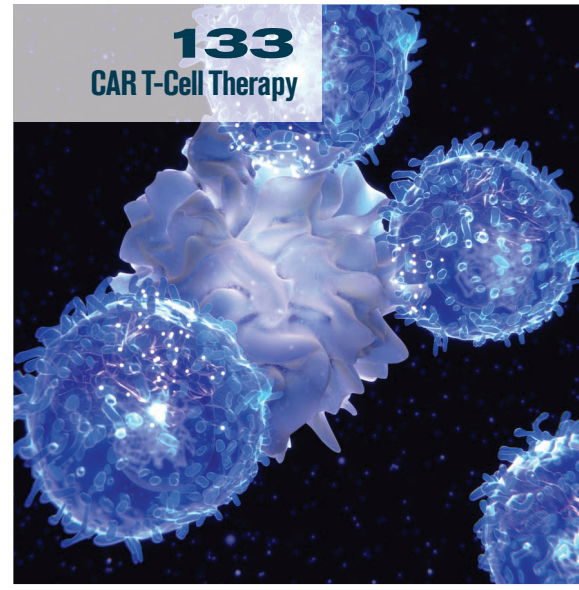

Parsaclisib Provides Rapid and Durable Responses in Marginal Zone Lymphoma

In the phase 2 CITADEL-204 trial (NCT03144674), patients with relapsed or refractory marginal zone lymphoma (MZL) who were treated with parsaclisib monotherapy demonstrated rapid and durable clinical responses.

One hundred patients were evaluated; they experienced an objective response rate (ORR) of 58.3%, duration of response of 12.2 months, and a median progression-free survival of 16.5 months. Parsaclisib proved to induce rapid and durable responses among patients naïve to Bruton tyrosine kinase (BTK) inhibitor therapy, and ORRs were comparable among patients with nodal, extranodal, and splenic MZL.

Information was presented from the BTK inhibitor–naïve cohort of the study, in which patients were allocated 1:1 to a weekly dosing group (n = 28) and a daily dosing group (n = 72). Patients in the weekly group received 20 mg of parsaclisib daily for 8 weeks followed by 20 mg once weekly, and patients in the daily group received 20 mg of parsaclisib daily for 8 weeks followed by 2.5 mg once daily.

The ORR was 58.0% (95% CI, 47.7%-67.8%) for all patients and 58.3% (95% CI, 46.1%-69.8%) for the daily group; ORR by investigator assessment was 72.0% and 69.4%, respectively. In all 81 evaluable patients, there was regression of target lesions or spleen, and 67 of those had greater than 50% reduction as the best percentage change from baseline.

→ **For the full article, visit** cancernetwork.com/ASH21_CITADEL-204

Tafasitamab and Lenalidomide Combo Yields Higher OS vs Standard Options in Relapsed/Refractory DLBCL

Treatment with tafasitamab (Monjuvi) and lenalidomide (Revlimid) provided an overall survival (OS) benefit vs standard options in a population of patients with autologous stem cell transplant–ineligible relapsed/refractory diffuse large B-cell lymphoma (DLBCL), according to findings from an expanded analysis of the RE-MIND2 study (NCT04697160).

There was a statistically significant 56% reduction in the risk of death with tafasitamab plus lenalidomide compared with either polatuzumab vedotin (Polivy) plus bendamustine and rituximab (Rituxan; Pola-BR) or rituximab plus lenalidomide (R2). OS data were similar with tafasitamab plus lenalidomide and chimeric antigen receptor (CAR)–modified T-cell therapies.

For the observational retrospective cohort study, data from the L-MIND trial (NCT02399085) were matched and compared with real-world data, for which the cohorts contained 24, 33, and 37 patient pairs each for tafasitamab plus lenalidomide vs either Pola-BR, R2, and CAR T cells, respectively. The median follow-up duration in L-MIND for tafasitamab plus lenalidomide was 32 months. The median follow-up was 16.6 months, 13.4 months, and 10.2 months in the Pola-BR, R2, and CAR T-cell therapy cohorts, respectively.

The median OS with tafasitamab plus lenalidomide was 20.1 months compared with 7.2 months with Pola-BR in matched patients with DLBCL (HR, 0.441; 95% CI, 0.203-0.956; P = .0340). In the CAR T-cell comparison, the median OS was 22.5 months with tafasitamab plus lenalidomide compared with 15.0 months (HR, 0.953; 95% CI, 0.475-1.913; P = .8915). The median OS was 24.5 months with tafasitamab plus lenalidomide vs 7.4 months with R2 in the real-world setting (HR, 0.435; 95% CI, 0.224-0.847; P = .0122).

→ **For the full article, visit** cancernetwork.com/ASH21_tafasitamab

First-line Axi-Cel Yields Rapid Response in Large B-Cell Lymphoma

In the phase 2 ZUMA-12 trial (NCT03761056), patients with high-risk large B-cell lymphoma treated with axicabtagene ciloleucel (axi-cel; Yescarta) demonstrated rapid and durable responses in the first-line setting, with a high objective response rate of 89% and a complete response (CR) rate of 78%.

With a median follow-up of 17.4 months (range, 6.0-26.7), investigators found among all treated patients (n = 40) an overall response rate (ORR) of 90% (95% CI, 76%-97%) and a complete response (CR) rate of 80% (95% CI, 64%-91%). Among efficacy evaluable patients (n = 37) with a median follow-up of 15.9 months (range, 6.0-26.7), objective response rate was 89% (95% CI, 75%-97%) and the CR rate was 78% (95% CI, 62%-90%). The median overall survival was 24.5 months.

Patients received 30 mg/m^2 of fludarabine and 500 mg/m^2 of cyclophosphamide intravenously on days –5, –4, and –3. On day 0, patients were given 2 x 10^6 of axi-cel chimeric antigen receptor T cells/kg intravenously.

All patients experienced any-grade adverse events (AEs), with grade 3 or higher AEs in 85%. Cytokine release syndrome of grade 3 occurred in 8% of patients. Neurologic events occurred in 73% of patients.

→ **For the full article, visit** cancernetwork.com/ASH21_axi-cel

Sustained Survival Benefit Seen With Oral Azacitidine as Maintenance Therapy for AML in First Remission

Maintenance treatment with oral azacitidine for patients with acute myeloid leukemia (AML) in first remission after intensive chemotherapy sustained a survival benefit over placebo, according to updated results from the phase 3 QUAZAR AML-001 trial (NCT01757535).

At a median follow-up of 51.7 months, the median overall survival (OS) with oral azacitidine was 24.7 months (95% CI, 18.7-30.5) vs 14.8 months (95% CI, 11.7-17.6) with placebo (HR, 0.69; 95% CI, 0.56-0.86; P = .0008). The 3-year OS rates in the investigative and control arms were 37.4% and 27.9%, respectively; these rates at 5 years were 26.2% and 19.2%, respectively.

The data cutoff for the primary analysis was July 2019. Results showed that at a median follow-up of 41.2 months, oral azacitidine significantly prolonged OS vs placebo, with medians of 24.7 months (95% CI, 18.7-30.5) and 14.8 months (95% CI, 11.7-17.6), respectively (P < .001).

In the most recent analysis, at a cutoff of September 2020, 22.7% of patients in the investigative arm were alive and in follow-up vs 15.0% of those in the control arm.

Additional data showed that there was a 9.5% improvement in OS at 3 years with the hypomethylating agent vs placebo, as 37.4% of patients in the investigative arm were alive at that time point vs 27.9% of those in the placebo arm. The 5-year OS rates with oral azacitidine and placebo were 26.2% and 19.2%, respectively, translating to an improvement of 7.0% with the hypomethylating agent.

→ **For the full article, visit** cancernetwork.com/ASH21_azacitidine

Patients With Chronic-Phase CML Achieved Deeper, More Durable Molecular Responses With Asciminib vs Bosutinib

Chronic-phase chronic myeloid leukemia (CP-CML) treated with asciminib (Scemblix) was more likely to reach major molecular response (MMR) vs bosutinib (Bosulif) without any new or worsening adverse effects (AEs), according to updated findings from the phase 3 ASCEMBL trial (NCT03106779).

At a median follow-up of 19.2 months, the MMR rate at 48 weeks was 29.3% with asciminib vs 13.2% with bosutinib, reflecting a 16.1% difference in favor of asciminib. Moreover, the BCR-*ABL1*IS rate of 1% or less was higher with asciminib vs bosutinib, at 42.3% vs 19.4%, respectively.

ASCEMBL enrolled 233 patients with CP-CML who had been previously treated with at least 2 tyrosine kinase inhibitors (TKIs) and had failed or were intolerant to their prior TKI. Patients were randomized 2:1 to receive 40 mg of asciminib twice daily (n = 157) or 500 mg of bosutinib once daily (n = 76) for at least 96 weeks.

Updated analyses, which were performed after all patients had received at least 48 weeks of treatment or discontinued earlier, showed that treatment was ongoing in more than double the percentage of patients receiving asciminib vs bosutinib, at 56.7% vs 22.4%.

Additional findings showed that asciminib led to higher week-48 MMR rates vs bosutinib across lines of therapy. The cumulative incidence and duration of MMR was also consistently higher with asciminib vs bosutinib. The 24-week MMR rates were 25.0% with asciminib vs 11.9% with bosutinib; the 48-week MMR rates were 33.2% vs 18.6%, respectively.

Moreover, fewer grade 3 or greater AEs (50.6% vs 60.5%) and AEs leading to treatment discontinuation (5.8% vs 21.1%) were reported with asciminib vs bosutinib, respectively. The primary reasons for treatment discontinuation in the asciminib vs bosutinib arms were lack of efficacy (23.6% vs 35.5%, respectively) and AEs (5.7% vs 23.7%, respectively).

→ **For the full article, visit** cancernetwork.com/ASH21_asciminib

Adding Ublituximab and Umbralisib to Ibrutinib Produced Strong Undetectable MRD Rate in CLL

Deep remissions and favorable tolerability were seen when ublituximab and umbralisib (Ukoniq; U2) were added to ibrutinib (Imbruvica) for treating patients with chronic lymphocytic leukemia (CLL) who still had detectable minimal residual disease (MRD) after prior ibrutinib treatment, according to results from a phase 2 trial (NCT04016805).

Results indicated that 77% of those who went on to receive the triplet combination achieved undetectable MRD. Moreover, 4% of patients came off treatment after 24 cycles and continued to have undetectable MRD. Nineteen percent of patients remain on therapy with detectable MRD, with the possibility of achieving undetectable levels. The median time to undetectable MRD achievement was 7.4 months (95% CI, 4.6-10.2).

The median time in treatment-free observation was 11 months, and the median time to first undetectable MRD was 6 months. Of the 17 patients who stopped therapy, 53% continue to have undetectable MRD.

The most frequently reported grade 3 or 4 toxicity was hypertension (7%), diarrhea (4%), increased alanine aminotransferase or aspartate aminotransferase (4%), and COVID-19 (4%). Two patients discontinued all treatment because of toxicities, with both having undetectable MRD status at the time of discontinuation.

Investigators continue to enroll patients to the trial. Other cohorts will explore the addition of U2 to agents like acalabrutinib (Calquence) or venetoclax (Venclexta).

For the full article, visit cancernetwork.com/ASH21_ublituximab

Updated CAPTIVATE Data Continue to Show Benefit of Fixed-Duration Ibrutinib-Venetoclax in First-Line CLL

Results of the phase 2 CAPTIVATE trial (NCT02910583) showed that use of ibrutinib (Imbruvica) plus venetoclax (Venclexta) in the first-line setting for patients with previously untreated chronic lymphocytic leukemia (CLL) compared with the placebo continued to result in responses that were deep and durable. Continuous therapy in certain patients based on minimal residual disease (MRD) data showed benefit, as did fixed-duration therapy.

After 12 cycles, patients with confirmed undetectable MRD (uMRD) were randomized to placebo (n = 43) or ibrutinib (n = 43) and those without uMRD to either ibrutinib (n = 31) or ibrutinib plus venetoclax (n = 32).

In patients with confirmed uMRD post randomization, 2-year disease-free survival rates remained unchanged at 95% in the placebo arm and 100% with ibrutinib, for a 4.7% difference (95% CI, –1.6 to 10.9; overall log-rank $P = .1573$).

At a median follow-up of 38 months, the 36-month progression-free survival (PFS) rate in the confirmed uMRD population was 95.3% (95% CI, 82.7%-98.8%) in patients who received placebo and 100% in those assigned to ibrutinib (95% CI, 100%-100%).

In patients without confirmed uMRD, improvements in uMRD rates and in rates of complete response (CR) and CR with incomplete bone marrow recovery were greater with ibrutinib plus venetoclax compared with ibrutinib alone post randomization. The 36-month PFS rates among those patients following randomization were 96.7% in both the ibrutinib (n = 31) and ibrutinib plus venetoclax (n = 32) arms.

Grade 3 or higher adverse events (AEs) were infrequent across randomized arms, with the exception of neutropenia. With median study follow-up of 38 months, AEs remained consistent with known profiles for single agent ibrutinib and venetoclax. With up to 48 months of treatment, 13% of patients had discontinued ibrutinib or venetoclax due to AEs, with no new safety signals emerging in the additional follow-up.

→ **For the full article, visit** cancernetwork.com/ASH21_CAPTIVATE

MRD-Guided Ibrutinib Plus Venetoclax: Feasible Treatment Option for Relapsed/Refractory CLL

Minimal residual disease (MRD)–guided ibrutinib (Imbruvica) plus venetoclax (Venclexta) demonstrated feasibility as an approach for treating relapsed/refractory chronic lymphocytic leukemia (CLL), according to data from the randomized phase 2 VISION HO141 trial (NCT03226301).

Patients received 2 ibrutinib lead-in cycles, then a venetoclax ramp-up during the third cycle. After the first 15 cycles of treatment, MRD was assessed, with ibrutinib maintenance given to those who did not achieve undetectable MRD (uMRD). Patients who achieved at least partial remission and uMRD in both peripheral blood and bone marrow samples at cycle 15 were randomized 1:2 between continuing ibrutinib maintenance (arm A; n = 24) or observation (arm B; n = 48).

At 27 months, 71% of the patients in arm B had uMRD in peripheral blood and 54% in bone marrow compared with 75% and 63% in arm A, respectively.

Moreover, at 27 months, 29% of patients in the nonrandomized ibrutinib arm achieved uMRD in peripheral blood and 13% in bone marrow. The study met the primary end point, with most patients being progression free at 27 months.

For patients who achieved uMRD at cycle 15 and remained on ibrutinib maintenance, no disease progression was reported, with an overall survival rate of 100% at month 27. Although there were some progressors in the group who did not achieve uMRD and continued ibrutinib, the OS rate at 27 months was 92%.

→ **For the full article, visit** cancernetwork.com/ASH21_VISION

Ixazomib/Daratumumab Without Dexamethasone Shows Favorable Safety in High-Frailty Relapsed Myeloma

The phase 2 IDARA trial (NCT03757221) of the combination of daratumumab (Darzalex) plus ixazomib (Ninlaro) without dexamethasone demonstrated safety and preliminary efficacy of the combination in frail, elderly patients with relapsed or refractory multiple myeloma.

In all patients evaluable for response (n = 50), the overall response rate (ORR), composed of partial responses or better, was 72%; 24% of patients overall achieved a very good partial response (VGPR) or better. In the lenalidomide-refractory group (n = 16), the ORR was 75% with VGPRs in 38%.

At a median follow-up of 7.6 months, the median progression-free survival was 16 months (95% CI, 9.9-undefined). Overall survival has yet to be determined.

There were 2 treatment-related deaths, 1 from daratumumab-related bronchospasm and 1 from ixazomib overdose. Other deaths occurred due to infection (7%), disease progression (5%), and second primary malignancy (2%). Grade 3 or higher adverse effects occurred in 23 patients (52%).

→ **For the full article, visit** cancernetwork.com/ASH21_ixazomib

MRD Negativity Improved With Isatuximab Plus RVd in Transplant-Eligible Newly Diagnosed Myeloma

The phase 3 GMMG-HD7 trial (NCT03617731) yielded results of superior minimal residual disease (MRD) when isatuximab (Sarclisa) was added to lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (Isa-RVd) compared with RVd for transplant-eligible newly diagnosed multiple myeloma.

Patients who received Isa-RVd (n = 331) achieved a MRD negativity rate of 50.1% at the end of induction therapy vs 35.6% in those who were given RVd alone (n = 329; odds ratio, 1.83; 95% CI, 1.34-2.51; $P < .001$). Consistent benefit favoring the isatuximab regimen was observed across all clinically relevant subsets.

The addition of isatuximab to RVd did not significantly impact the safety profile or dose intensity of RVd. Results showed that 63.6% of patients who received the isatuximab regimen (n = 330) experienced an any-grade adverse effect vs 61.3% of those who received RVd (n = 328). Additionally, in the investigative and control arms, 34.8% and 36.3% of patients, respectively, reported a serious toxicity with treatment. Four deaths (1.2%) were reported on the Isa-RVd arm vs 8 (2.4%) on the RVd arm.

Furthermore, 26.4% of patients on the investigative arm experienced leukocytopenia or neutropenia vs 9.1% in the control arm. Four patients on the Isa-RVd arm reported infusion-related reactions.

→ **For the full article, visit** cancernetwork.com/ASH21_isatuximab

Selinexor/D-Vd Combo Yields Promising Responses and Safety Profile in Relapsed/Refractory Myeloma

A combination of selinexor (Xpovio) plus daratumumab (Darzalex), bortezomib (Velcade), and dexamethasone (D-Vd) yielded positive responses and safety findings in a population of patients with relapsed multiple myeloma, according to the open-label, multicenter phase 2 GEM-SELIBORDARA trial (NCT03589222).

To analyze the effects of D-Vd and selinexor as a combination, investigators treated 57 patients from July 2018 to March 2021. The study was split into 2 parts. Part 1 examined 24 patients with 3 or more prior lines of treatment who were previously treated with a proteasome inhibitor and immunomodulatory drugs and were either refractory to their last therapy or double refractory. Part 2 looked at 33 patients with relapsed/refractory multiple myeloma who had 1 or more prior lines of treatment.

The overall response rate (ORR) in part 1 was 50%. A total of 3 patients (12%) achieved complete response/stringent complete response (CR/sCR). At a median follow-up of 28.3 months, 18 patients had discontinued treatment (14 due to disease progression). The median progression-free survival (PFS) was 7.1 (95% CI, 3.4-20.0) and median overall survival (OS) was 27.5 months (95% CI, 10.6 to not evaluable [NE]).

At a median follow-up of 9.8 months, 8 patients in part 2 had discontinued treatment (5 due to disease progression). The ORR was 82% and 8 patients (24%) achieved CR/sCR. Median PFS was not yet reached (95% CI, 12.1-NE), while the median PFS in lenalidomide-refractory patients included in this part (n = 15) was 12.1 months. Median OS was also not yet reached (95% CI, NE-NE).

→ **For the full article, visit** cancernetwork.com/ASH21_selinexor

Liso-Cel Results in Long-Lasting Responses in Relapsed/Refractory B-Cell Lymphomas

Lisocabtagene maraleucel (liso-cel; Breyanzi) yielded durable, efficacious responses in a population of patients with relapsed/refractory large B-cell lymphomas, according to 2-year follow-up data of the phase 1 TRANSCEND NHL 001 study (NCT02631044).

Updated study findings indicated that patients treated with liso-cel had a probability of continued response at 2 years of 49.5% (95% CI, 41.4%-57.0%), with a median follow-up of 23.0 months (95% CI, 22.8-23.1). Patients had a median duration of response of 23.1 months (95% CI, 8.6 to not reached). Notably, no patients had relapsed after 23 months on the trial.

At 2 years, the progression-free survival (PFS) rate was 40.6% (95% CI, 34.0%-47.2%) with a median follow-up of 23.9 months (95% CI, 23.7-24.0). Moreover, the median PFS was 6.8 months (95% CI, 3.3-12.7).

The median overall survival was 27.3 months (95% CI, 16.2-45.6). Three deaths were reported after 45 months, with 2 patients experiencing deaths due to unknown causes at 45 and 48 months. Additionally, 1 patient died at 46 months due to disease progression. At 24 months, chimeric antigen receptor (CAR) T-cell persistence was 37%, indicating that CAR T cells were present in peripheral blood for up to 48 months following infusion.

Investigators reported an incidence of any-grade and grade 3/4 cytokine release syndrome of 42% and 2%, respectively. Additionally, the incidence of any-grade and grade 3 or higher neurologic adverse effects was 30% and 10%, respectively.

→ **For the full article, visit** cancernetwork.com/ASH21_liso-cel

Tisagenlecleucel Yields Clinical Improvements in Relapsed/Refractory Follicular Lymphoma

Patients with relapsed or refractory follicular lymphoma who were treated with 2 or more prior lines of therapy and then given tisagenlecleucel (Kymriah) saw an improvement in overall response rate (ORR) and complete responses (CRs), according to a 12-month follow-up extended analysis of the phase 2 ELARA trial (NCT03568461).

Among the 94 efficacy-evaluable patients, the ORR was 86.2% (95% CI, 77.5%-92.4%) and the CR rate was 69.1% (95% CI, 58.8%-78.3%). The 12-month progression-free survival (PFS) rate was 67.0% (95% CI, 56.0%-75.8%) and the 9-month duration of response (DOR) rate was 76.0% (95% CI, 64.6%-84.2%). Notably, among patients who achieved a CR, the 12-month PFS rate was 85.5% (95% CI, 74%-92%) and the estimated 9-month DOR was 86.5% (95% CI, 75%-93%). The median follow-up was 17 months (range, 10-26).

At a longer follow-up of 21 months, the median PFS was 29.5 months (95% CI, 17.9 to not evaluable).

In patients who received at least 3 prior lines of therapy (n = 70) the CR, ORR, and 12-month PFS rates were 72.9%, 88.6%, and 69.4%, respectively. Among patients previously treated with at least 4 lines of therapy (n = 51) the CR, ORR, and 12-month PFS rates were 72.6%, 88.2%, and 68.5%, respectively. Patients who received at least 5 prior lines of therapy (n = 27) had a CR of 59.3%, an ORR of 85.2%, and a 12-month PFS rate of 59.6%.

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Single-Infusion Cilta-cel Produces Strong Response Rate in Heavily Pretreated Myeloma Refractory to Lenalidomide

A single infusion of ciltacabtagene autoleucel (cilta-cel) for patients with multiple myeloma who were lenalidomide (Revlimid) refractory and had undergone a median of 2 previous lines of therapy produced a strong overall response rate of 95%, according to results from cohort A of the phase 2 CARTITUDE-2 trial (NCT04133636).

At a median follow-up of 14.3 months (range, 3.3-19.0), the CAR T-cell therapy elicited responses in 19 of 20 patients (95% CI, 75.1%-99.9%). Of those who responded to treatment, 85% (95% CI, 62.1%-96.8%) achieved a complete response or better, and 90% (95% CI, 68.3%-98.8%) experienced a very good partial response or better.

Additional data indicated that the median time to first response with cilta-cel was 1.0 months (range, 0.7-3.3) and the median time to best response was 2.6 months (range, 0.9-7.9).

Moreover, the progression-free survival rate at 6 months was 95% (95% CI, 69.5%-99.3%) with the CAR T-cell product; at 12 months, this rate was 84% (95% CI, 59.1%-94.7%).

The incidence of initial grade 3 or 4 toxicities that did not recover to at least grade 2 severity by day 60 was 20% for neutropenia, 15% for thrombocytopenia, and 5% for lymphopenia. Additionally, 95% of patients experienced cytokine release syndrome (CRS); with 2 of these patients had grade 3 or 4 CRS. The median time to CRS onset in these patients was 7 days (range, 5-9) and the median duration was 4 days (range, 2-11). ■

→ **For the full article, visit** cancernetwork.com/ASH21_CARTITUDE-2

CONTINUING MEDICAL EDUCATION (CME)

New Targets, New Combinations, New Treatment Goals: Assessing Therapeutic Options to Personalize Care in Multiple Myeloma

FACULTY

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LEARNING OBJECTIVES

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

- Translate patient-specific factors, risk stratification, and treatment history into personalized treatment plans for patients with relapsed or refractory (R/R) multiple myeloma (MM).
- Assess recent results from pivotal trials on current and emerging therapeutic approaches for the treatment of R/R MM
- Implement effective strategies to monitor and mitigate the negative impact of treatment-related toxicities in patients with R/R MM
- Apply recent guidelines in parallel with practice-changing evidence on evolving single agent and combination approaches to real-world case scenarios typically encountered in R/R MM management

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ACTIVITY

Introduction

Multiple myeloma (MM), the second most common hematologic malignancy worldwide, is characterized by the proliferation of malignant plasma cells in the bone marrow.[1,2] Despite active treatments and high response rates to initial therapy, patients diagnosed with MM usually relapse and require further treatment.[3,4] Optimizing treatment strategies is crucial for improved patient outcomes and quality of life.[3-5]

Over the past 10 to 15 years, increased understanding of the biology of MM has led to the development of novel therapies, including immunomodulatory drugs, proteosome inhibitors (PIs), monoclonal antibodies (mAbs), bispecific antibodies, antibody-drug conjugates, small molecule inhibitors, and chimeric antigen receptor (CAR) T-cell therapies.[3,6] These new therapies have prolonged the life expectancy of patients with MM, particularly when these therapeutics are incorporated into treatment regimens before or after the autologous stem cell transplantation (ASCT) in eligible patients.

Patients with newly diagnosed MM usually receive combination induction therapy that includes a PI, immunomodulatory agent, and corticosteroid with or without an anti-CD38 monoclonal antibody followed by an ASCT and maintenance therapy. [6, 7] For patients who are not candidates for ASCT, a triplet regimen is preferred followed by maintenance therapy. In cases of very frail patients who cannot tolerate triplet therapy, doublet regimens are considered initially and the third drug may be added to the regimen if the performance status of the patient improves.[3, 7]

The implementation of maintenance therapy varies by country based on drug availability and approval.[8] Improved progression-free and overall survival have been demonstrated when patients receive maintenance vs no maintenance therapy.[9] Single-agent lenalidomide is most commonly used and a preferred, category 1 maintenance regimen is recommended by the National Comprehensive Cancer Network (NCCN) until disease progression.[7]

Addressing Disparities in MM Care

Inequality across different ethnic and racial groups in cancer care is well documented, and reducing racial and ethnic disparities is an important unmet need.[10]

One factor contributing to racial/ethnic disparities in outcomes for patients with MM is the differential use of anti-myeloma therapy backbones and ASCT.[11,12] According to the Surveillance Epidemiology and End Results data from 2007 to 2013, lenalidomide use among Black patients was significantly lower compared with that of White patients ($P < .01$).[12] Similarly, thalidomide use was higher among Hispanic and Asian individuals ($P < .01$), and bortezomib use was lower among Asian patients ($P < .01$). Early use of ASCT demonstrated prolonged survival in patients with MM; however, Black and Hispanic patients were less likely to receive ASCT within the first year of a diagnosis of MM, and Hispanic patients had the lowest utilization of ASCT when compared with those of other ethnic/racial backgrounds ($P < .01$).[11,12] The time from diagnosis to novel therapy initiation was also longer in Black and Hispanic patients vs White patients (median, 5.2 and 4.6 vs 2.7 months, respectively).[11]

The approval of novel medications resulted in superior response and survival rates in patients with MM However, the cost of MM therapy continues to increase, leading to a cumulative financial burden on patients who have multiple relapses during the course of their disease.[13] The cost of MM care is particularly high among minority groups. Based on an analysis representing patients with MM from 1991 to 2010, claims for drugs during the initial 6 months after diagnosis gradually increased among Hispanic individuals ($P < .001$), whereas claims for total cost of care increased most among Black populations ($P < .001$) when compared with White patients.[14] Drug claims at any time after MM diagnosis were significantly higher among Hispanic ($5400), Asian ($4700), and Black ($3900) patients when compared with White individuals ($3300; $P < .001$). The median total cost of care any time after MM diagnosis was highest, although statistically not significant, in Hispanic patients ($62,100).

Racial and ethnic disparities also exist in clinical trial enrollment. Between July 2008 and June 2013, 56.6% of clinical trials leading to cancer drug approvals reported race as compared with 67.1% of those conducted between July 2013 and June 2018 ($P = .09$).[15] The percentages of clinical trials reporting subgroup analyses during these time periods were 16.1% vs 30.2%, respectively ($P = .03$). Black and Hispanic participants were underrepresented in clinical trials when compared with their expected percentage based on cancer incidence and mortality rate in the United States (22% and 44%, respectively), whereas Asian patients were overrepresented (438%), and, among White patients, clinical trial enrollment occurred at almost the expected rate (98%).

It is critically important to address these disparities. Several organizations, including the American Medical Association and the American Society of Clinical Oncology, have ongoing programs that advocate for equal access to treatment and other resources (eg, clinical trial enrollment), work towards eliminating structural barriers that increase disparities in cancer care, and support a diverse oncology workforce and

members who are committed to addressing equity in healthcare.[16-18] Addressing disparities in health care will allow for patient-centered, equitable care that will not only improve the quality of medical management but also will result in better overall health of the population.

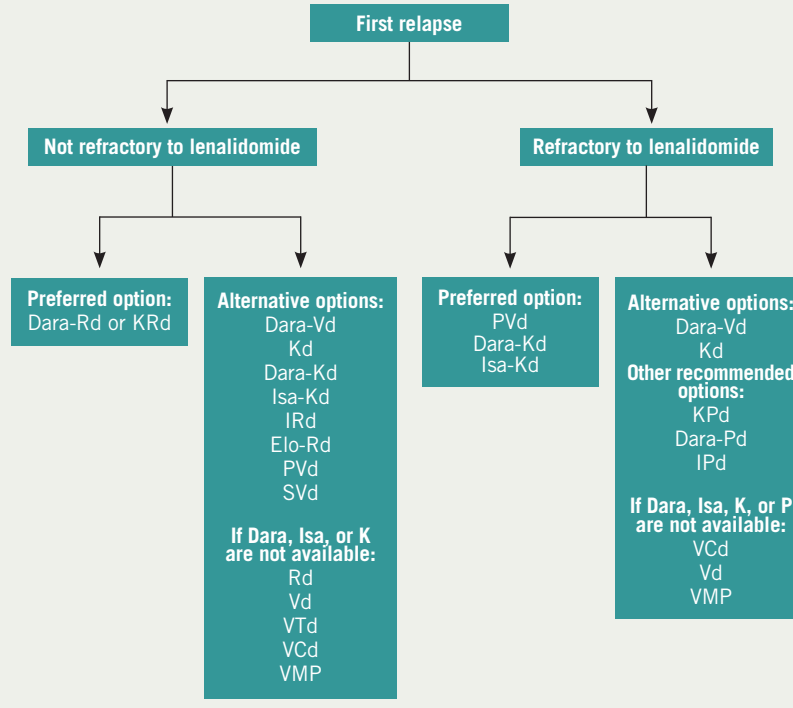
Treating Early Relapse

Despite effective treatment regimens, patients with MM often experience multiple relapses.[3,6,19] Based on the International Myeloma Working Group and NCCN guidelines for MM, selection of appropriate therapy at first relapse depends on several factors. When choosing a treatment regimen for relapsed or refractory (R/R) MM, many factors should be considered, including (1) disease-related factors (eg, nature of relapse, disease burden); (2) treatment-related factors (eg, exposure to different classes of agents, number of prior lines of therapy, depth and duration of response or resistance to previous therapy, treatment-related toxicity); and (3) patient-related factors (eg, age/frailty, history of renal insufficiency, cardiac disease, or hepatic impairment in addition to patient preference). Treatment is indicated if there is clinical relapse (ie, development of hypercalcemia, renal insufficiency, anemia, new bone lesions) as opposed to biochemical progression only.[7,20] In patients who underwent ASCT during initial treatment and had a durable response or stable disease, second transplantation can be considered.[7] In the case of slow biochemical progression (ie, indolent relapse), alternatives to salvage therapy include increasing the dose of maintenance therapy or adding steroids for patients without high-risk disease.[21]

Lenalidomide is generally part of the frontline induction regimen; it is later used for maintenance as a single agent. In this case, response to lenalidomide drives treatment selection at first relapse.[6] In patients with lenalidomide-refractory disease, treatment with a PI-based combination with an anti-CD38 mAb (eg, daratumumab, isatuximab) or the second-generation immunomodulatory agent pomalidomide is preferred.[6,7] Patients who experience first relapse after receiving bortezomib-based frontline therapy without lenalidomide maintenance, or at 6 months or later after completion of lenalidomide-based frontline therapy, are considered not considered to be refractory to lenalidomide. These patients can receive lenalidomide as part of the second-line regimen (**Figure 1**).[6,7]

Venetoclax is a selective, potent BCL2 inhibitor that has shown activity in MM patients with t(11;14) translocations.[22] In the phase 3 BELLINI trial, venetoclax combined with bortezomib and dexamethasone (VenVd) demonstrated superior efficacy compared with placebo plus Vd in patients with t(11;14) R/R MM who had received 1 to 3 prior therapies and had PI-sensitive or -naïve disease (median PFS, 36.8 vs 9.3 months, respectively; hazard ratio [HR], 0.12; 95% CI, 0.03-0.44; P = .0014).[23] The

FIGURE 1. **Treatment Selection at First Relapse in Patients With Multiple Myeloma[6,7]**



Dara-Kd, daratumumab plus carfilzomib plus dexamethasone; Dara-Pd, daratumumab plus pomalidomide plus dexamethasone; Dara-Rd, daratumumab plus lenalidomide plus dexamethasone; Dara-Vd, daratumumab plus bortezomib plus dexamethasone; Elo-Rd, elotuzumab plus lenalidomide plus dexamethasone; IPd, ixazomib plus pomalidomide plus dexamethasone; IRd, ixazomib plus lenalidomide plus dexamethasone; Isa, isatuximab; Isa-Kd, isatuximab plus carfilzomib plus dexamethasone; K, carfilzomib; Kd, carfilzomib plus dexamethasone; KPd, carfilzomib plus pomalidomide plus dexamethasone; KRd, carfilzomib plus lenalidomide plus dexamethasone; P, pomalidomide; PVd, pomalidomide plus bortezomib plus dexamethasone; Rd, lenalidomide plus dexamethasone; SVd, selinexor plus bortezomib plus dexamethasone; VCd, bortezomib plus cyclophosphamide plus dexamethasone; Vd, bortezomib plus dexamethasone; VMP, bortezomib plus melphalan plus prednisone; VTd, bortezomib plus thalidomide plus dexamethasone.

median OS was not reached in either arm (HR, 0.61; 95% CI, 0.16-2.32; *P* =.4654). The most common treatment-emergent adverse events (TEAEs) in the venetoclax vs placebo arms, respectively, included diarrhea (60% vs 50%), nausea (38% vs 23%), constipation (35% vs 31%), and fatigue (33% vs 32%).

Treating Triple Class–Refractory or Penta-Refractory MM

Despite the availability of multiple novel therapeutic agents, most patients with MM experience disease relapse and become refractory to these agents. Patients with MM refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and anti-CD38 mAbs have penta-refractory or triple class–refractory disease (refractory to PIs, immunomodulatory agents, and mAbs).[24] These patients have poor prognosis, with OS of less than a year and response rates to subsequent therapies of 20% to 30%.[25-27]

Several novel agents recently received approval for the treatment of triple class–refractory MM. Selinexor (Sel) is a selective inhibitor of XPO1, an export receptor overexpressed in myeloma cells that induces antitumor actions, such as cell-cycle arrest and apoptosis.[28] Selinexor has been approved in combination with dexamethasone (Sel-d) for the treatment of adult patients with triple class–refractory MM and in combination with bortezomib and dexamethasone (Sel-Vd) for the treatment of adult patients with MM who had received at least 1 prior therapy.[29] In the phase 2 STORM trial, Sel-d resulted in an overall response rate (ORR) of 26%, with a median duration of response (DOR) of 4.4 months, median PFS of 3.7 months, and median OS of 8.6 months in patients with triple class–refractory, R/R MM.[28] Thrombocytopenia (any grade, 73%; grade 3/4, 58%) was the most common hematologic AE noted. Fatigue, nausea, and decreased appetite were the most common nonhematologic toxicities, and grade 3 events were reported in approximately 25% of patients.

In the phase 3 BOSTON trial, the Sel-Vd regimen had a significant benefit in PFS compared with the Vd regimen in patients with R/R MM who were PI-refractory or -sensitive (median PFS, 13.93 vs 9.46 months, respectively; HR, 0.70; *P* = .0075).[30] The ORR was also higher in the Sel-Vd arm vs the Vd arm (76.4% vs 62.3%; *P* = .0012). Median OS was not reached vs 25 months, respectively (HR, 0.84; *P* = .19). The most common AEs noted with Sel-Vd vs Vd included thrombocytopenia (35.9% vs 15.2%), fatigue (11.3% vs 0.5%), and nausea (7.7% vs 0%). Rates of peripheral neuropathy, an AE associated with prolonged bortezomib use, were significantly lower with Sel-Vd vs Vd (grade ≥ 2, 21.0% vs 34.3%; *P* = .0013). Patients receiving selinexor should receive prophylactic antiemetics and have platelet/neutrophil counts monitored during the course of therapy; dose interruptions and/or reductions can help in managing hematologic AEs and gastrointestinal toxicity associated with this agent.[29]

TABLE 1. **Clinical Trials Investigating BCMA-Targeted CAR T-Cell Therapy in R/R MM[40-42]**

	KaRMMa[40] N = 128	CARTITUDE-1[41,42] N = 97
Prior lines of therapy	≥ 3 (median, 6)	≥ 3 (median, 6)
Phase	2	1b/2
CAR T-cell product	ide-cel	cilta-cel
Triple-class refractory population, %	84	88
Pentarefractory population, %	26	42
ORR, %	73	97.9
CR or sCR, %	33	83
Median DOR, months	10.9	NE
Median PFS, months	8.6	NR
Median OS, months	24.8	NR
24-mo PFS, %	—	60.5
24-mo OS, %	51	74
CRS, %	84	95
Grade ≥ 3 CRS, %	5	4
Neurotoxicities, %	18	21
Grade ≥ 3 neurotoxicities, %	4	9

CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; HD, highest dose; ide-cel, ide-cabtagene vicleucel; NE, not estimable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed/refractory multiple myeloma; sCR; stringent complete response.

Belantamab mafodotin (belamaf) is an ADC that targets BCMA. It is approved by the United States Food and Drug Administration (FDA) for patients with R/R MM who have received at least 4 prior therapies, including an anti-CD38 mAb, a PI, and an immunomodulatory agent.[31] The phase 2 DREAMM-2 trial enrolled patients with R/R MM refractory to both Immunomodulatory and PIs who were refractory and/or intolerant to an anti-CD38 mAb.[32] Patients were randomized 1:1 to receive 2.5 mg/kg or 3.4 mg/kg of belamaf every 3 weeks until disease progression or unacceptable toxicity occurred. The ORR was 31% in the 2.5-mg/kg cohort and 35% in the 3.4-mg/kg cohort.[32] Median PFS was 2.8 months vs 3.9 months, respectively, and the median DOR was not reached vs 6.2 months, respectively. The most common grade 3 or greater AEs in the 2.5-mg/kg cohort vs the 3.4-mg/kg cohort, respectively, were keratopathy (29% vs 24%), thrombocytopenia (21% vs 32%), anemia (20% vs 27%), pneumonia (6% vs 13%), and neutropenia (11% vs 16%). Belamaf, which carries an FDA warning for ocular toxicity, may cause changes in vision, dry eyes, corneal ulcers, and severe vision loss. A risk evaluation and mitigation strategy program is required to manage ocular toxicity; it requires performance of ophthalmic exams before starting treatment, prior to each dose, and promptly for worsening symptoms.[33]

New and Emerging T Cell–Directed Therapies

Despite recent developments in MM therapy, there is still an unmet need for more tolerable, effective treatments that promote better clinical outcomes, such as stringent complete responses (sCR) and minimal residual disease (MRD) negativity.[34,35] Furthermore, patients have developed resistance to treatment with successive lines of therapy.[36] Several treatment options addressing these challenges are in development.

As previously noted, belamaf is a therapeutic that targets BCMA, a transmembrane glycoprotein that is only expressed in plasma cells and mature B cells and that is almost universally expressed on myeloma cells.[37] BCMA activation induces myeloma cell growth and survival through upregulation of antiapoptotic proteins and several molecular pathways associated with angiogenesis, metastasis, and adhesion. BCMA expression is significantly upregulated with disease progression in patients with MM. Changes in CD38 levels are less well-characterized, and this makes BCMA a more favorable target than CD38 for the treatment of MM.[38] Some BCMA-targeted strategies for treatment of R/R MM are discussed below.

CAR T-cell therapy

CAR T cells have been used to effectively treat B-cell malignancies and are being studied for the treatment of R/R MM.

Based on outcomes of the KarMMa

TABLE 2. **Clinical Trials Investigating BCMA x CD3 Bispecific Antibodies in R/R MM[48-53]**

Bispecific antibody	AMG 701[48] N = 85	Teclistamab[49] N = 165	CC-93269[50] N = 30	Elranatamab[51] N = 55	REGN5458[52] N = 73	TNB-383B[53] N = 118
Clinical trial	—	MajesTEC-1	—	Magnetismm-1	—	
Phase	1	1/2	1	1	1	1
No. of prior lines of therapies, median	6	5	5	6	5	5
Triple-class refractory, %	68	78	77	91	95	61
ORR, %	Overall, 36, ≥ VGPR, 24% At 9 mg, 83	62 ≥ CR, 29 ≥ VGPR, 58	43 ≥ CR, 17 At 10 mg, 89	69 (1 mg/kg Q1W)	75 ≥ VGPR, 58 (200 - 800 mg)	60 ≥ VGPR, 40
CRS, %	65	72	77	87	38	54
Grade ≥ 3 CRS, %	9	< 1	3	0	0	3
Neurotoxicity, %	—	13	—	16	4	5
Grade ≥ 3 neurotoxicity, %	—	0	—	0	0	0

CR, complete response; CRS, cytokine release syndrome; ORR, overall response rate; Q1W3, once every 3 weeks; R/R MM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

trial, idecabtagene vicleucel (ide-cel) is the first BCMA-targeted CAR T-cell therapy that received approval from the FDA for the treatment of adult patients with R/R MM who have received 4 or more prior lines of therapy.[39] In the phase 2 KarMMa trial, ide-cel therapy led to deep, durable responses in patients with R/R MM who had received 3 or more prior lines of treatment (**Table 1**).[40] Ciltacabtagene autoleucel (cilta-cel) is another CAR T-cell therapy that is in development for the treatment of MM. Ciltacel contains 2 BCMA-targeting, single-domain antibodies. In the phase 1b/2 CARTITUDE-1 study, cilta-cel yielded deep, durable responses in patients with R/R MM (**Table 1**).[41,42]

Several other CAR T-cell therapies are being evaluated in clinical trials for the treatment of R/R MM, including CT103A, ARI0002h, P-BCMA-101, CT053.[43-46]

Bispecific antibodies for treatment of R/R MM

Bispecific antibodies are composed of antigen-binding sites from 2 antibodies connected by a peptide linker, with 1 antibody targeting CD3 expressed on T cells and the other targeting a tumor-specific antigen, such as BCMA on myeloma cells.[47] Currently, there are several BCMA-targeting bispecific antibodies in early clinical development for the treatment of R/R MM (**Table 2**).[48-53] To improve the efficacy and duration of response, some of these agents are also being evaluated in combination with other agents in heavily treated patients with R/R MM.[51,54,55]

Despite their efficacy in treatment of R/R MM, T cell–directed therapies are associated with increased cytokine release syndrome (CRS) and neurotoxicity.[47,56] These toxicities can result in end-organ damage and compromise the patient acutely. It is important to balance the management of AEs while maintaining the antitumor effect of therapy.

The interleukin (IL) -6 antibody tocilizumab effectively treats CRS; it has been approved by the FDA for the treatment of CAR T cell–induced severe or life-threatening CRS.[57] High-dose corticosteroids, such as dexamethasone, are considered to be the alternative option for managing serious CRS.[56] However, corticosteroids have the potential to suppress CAR T-cell function and are only recommended when the patient is unresponsive to tocilizumab. For patients presenting with CAR T cell–associated neurotoxicity without CRS, high-dose corticosteroids are recommended as the first line of treatment. Dexamethasone is prioritized over methylprednisolone; however, specific circumstances can apply. As a general approach, management of neurotoxicity should be managed independently of CRS.[56] Cytopenias are also common after the receipt of T cell–directed therapies and can be managed via dose interruptions and/or reductions, as clinically appropriate.[56] ■

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