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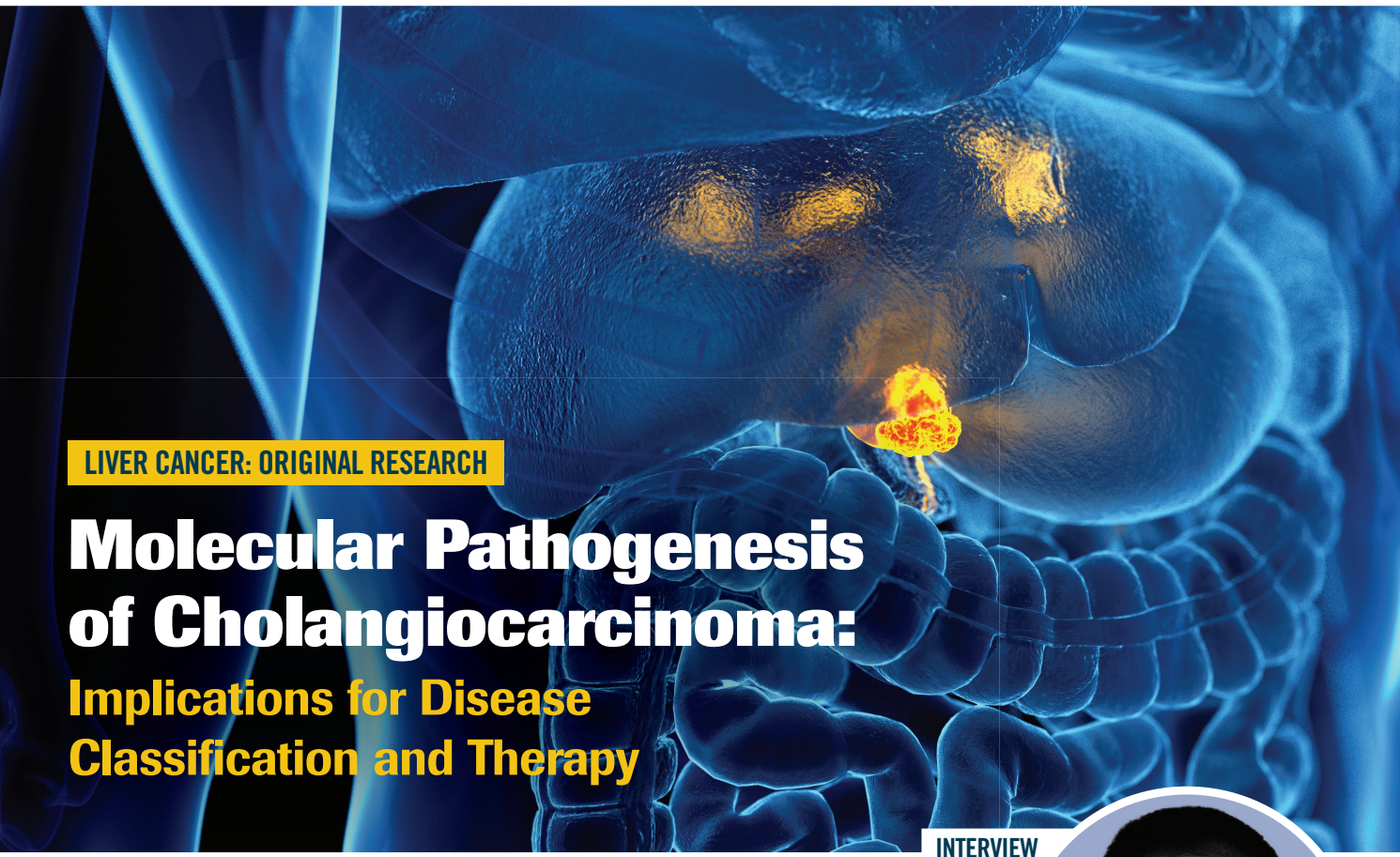

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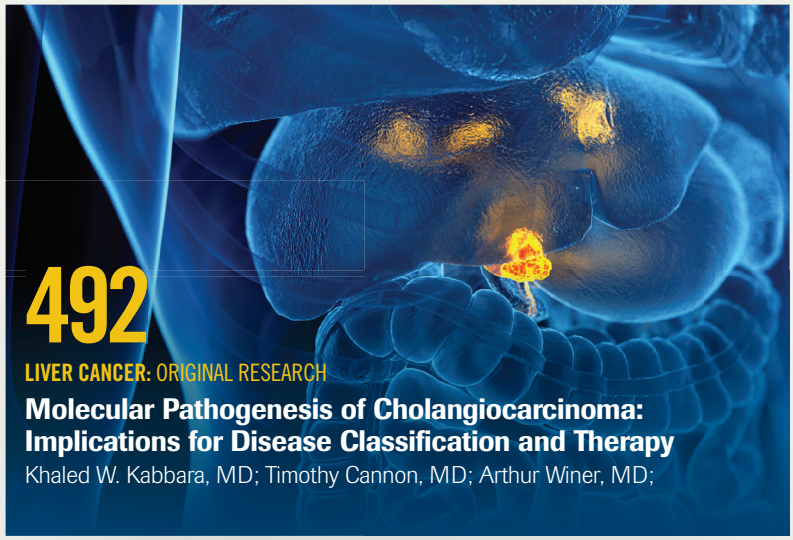
WEIJING SUN, MD, FACP



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ONCOLOGY®

AUGUST 2022 ▪ VOL. 36 ▪ NO. 8

LEADING A NEW ERA IN BTK INHIBITION

CALQUENCE®
(acalabrutinib) 100 mg capsules

MORE PATIENTS START WITH CALQUENCE THAN ANY OTHER BTKi IN 1L CLL*[1]

SCAN HERE TO DISCOVER MORE

*Based on IMS claims data as of 2/2022.
1L=first-line; BTKi=Bruton tyrosine kinase inhibitor; CLL=chronic lymphocytic leukemia.

Indication and Usage
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Select Safety Information
Serious adverse events, including fatal events, have occurred with CALQUENCE, including serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, and atrial fibrillation and flutter. The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

Please see Brief Summary of full Prescribing Information on adjacent pages.

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

Reference: 1. Data on File, REF-63120. AstraZeneca Pharmaceuticals LP.

INTENDED FOR US AUDIENCE ONLY.

AstraZeneca

CALQUENCE® (acalabrutinib) capsules, for oral use
Initial U.S. Approval: 2017

Brief Summary of Prescribing Information.
For full Prescribing Information consult official package insert.

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

DOSAGE AND ADMINISTRATION

Recommended Dosage

CALQUENCE as Monotherapy

For patients with CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

CALQUENCE in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE prior to obinutuzumab when given on the same day.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time.

Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

Recommended Dosage for Hepatic Impairment
Avoid administration of CALQUENCE in patients with severe hepatic impairment.

Dose modifications are not required for patients with mild or moderate hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 *[see Drug Interactions (7) in the full Prescribing Information]*.

Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg approximately every 12 hours.

Concomitant Use with Gastric Acid Reducing Agents

Proton Pump Inhibitors: Avoid concomitant use *[see Drug Interactions (7) in the full Prescribing Information]*.

H2-Receptor Antagonists: Take CALQUENCE 2 hours before taking a H2-receptor antagonist *[see Drug Interactions (7) in the full Prescribing Information]*.

Antacids: Separate dosing by at least 2 hours *[see Drug Interactions (7) in the full Prescribing Information]*.

Dose Modifications for Adverse Reactions
Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE.

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious and Opportunistic Infections
Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dose Modifications for Adverse Reactions (2.4) in the full Prescribing Information]*.

Second Primary Malignancies
Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter
Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Hemorrhage *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Cytopenias *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Atrial Fibrillation and Flutter *[see Warnings and Precautions (5.5) in the full Prescribing Information]*

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

The data in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

Chronic Lymphocytic Leukemia

The safety data described below reflect exposure to CALQUENCE (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.2) in the full Prescribing Information]*.

The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

ELEVATE-TN

The safety of CALQUENCE plus obinutuzumab (CALQUENCE+G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomized, multicenter, open-label, actively controlled trial in 526 patients with previously untreated CLL *[see Clinical Studies (14.2) in the full Prescribing Information]*.

Patients randomized to the CALQUENCE+G arm were treated with CALQUENCE and obinutuzumab in combination for six cycles, then with CALQUENCE as monotherapy until disease progression or unacceptable toxicity. Patients initiated obinutuzumab on Day 1 of Cycle 2, continuing for a total of 6 cycles. Patient randomized to CALQUENCE monotherapy received CALQUENCE approximately every 12 hours until disease progression or unacceptable toxicity. The trial required age ≥ 65 years of age or 18 to < 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min, hepatic transaminases ≤ 3 times upper limit of normal (ULN) and total bilirubin ≤ 1.5 times ULN, and allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

During randomized treatment, the median duration of exposure to CALQUENCE in the CALQUENCE+G and CALQUENCE monotherapy arms was 27.7 months (range 0.3 to 40 months), with 95% and 92% and 89% and 86% of patients with at least 6 months and 12 months of exposure, respectively. In the obinutuzumab and chlorambucil arm the median number of cycles was 6 with 84% of patients receiving at least 6 cycles of obinutuzumab, 70% of patients received at least 6 cycles of chlorambucil. Eighty-five percent of patients in the CALQUENCE+G arm received at least 6 cycles of obinutuzumab.

In the CALQUENCE+G and CALQUENCE monotherapy arms, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE+G arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (2.8% to 7%).

In the CALQUENCE+G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE in 7% of patients. In the CALQUENCE monotherapy arm, adverse reactions led to discontinuation in 10% and dose reduction in 4% of patients.

Tables 5 and 6 presents adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

Table 5: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ELEVATE-TN)

Body System Adverse Reaction*	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection†	69	22‡	65	14‡	46	13‡
Upper respiratory tract infection[a]	39	2.8	35	0	17	1.2
Lower respiratory tract infection[b]	24	8	18	4.5	7	1.8
Urinary tract infection	15	1.7	15	2.8	5	0.6
Blood and lymphatic system disorders§						
Neutropenia[c]	53	37	23	13	78	50
Anemia[d]	52	12	53	10	54	14
Thrombocytopenia[e]	51	12	32	3.4	61	16
Lymphocytosis[f]	12	11	16	15	0.6	0.6
Nervous system disorders						
Headache	40	1.1	39	1.1	12	0
Dizziness	20	0	12	0	7	0
Gastrointestinal disorders						
Diarrhea	39	4.5	35	0.6	21	1.8
Nausea	20	0	22	0	31	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[g]	37	2.2	32	1.1	16	2.4
Arthralgia	22	1.1	16	0.6	4.7	1.2
General disorders and administration site conditions						
Fatigue[h]	34	2.2	23	1.1	24	1.2
Skin and subcutaneous tissue disorders						
Bruising[i]	31	0	21	0	5	0
Rash[j]	26	2.2	25	0.6	9	0.6
Vascular disorders						
Hemorrhage[k]	20	1.7	20	1.7	6	0

* Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia

‡ Includes 3 fatal cases in the CALQUENCE plus obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm
§ Derived from adverse reaction and laboratory data
[a] Upper respiratory tract infection, nasopharyngitis and sinusitis
[b] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
[c] Includes neutropenia, neutrophil count decreased, and related laboratory data
[d] Includes anemia, red blood cell count decreased, and related laboratory data
[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data
[f] Includes lymphocytosis, lymphocyte count increased, and related laboratory data
[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain
[h] Includes asthenia, fatigue, and lethargy
[i] Includes bruise, contusion, and ecchymosis
[j] Includes rash, dermatitis, and other related terms
[k] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:
- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

Table 6: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)

Laboratory Abnormality*,[a]	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	29	29	22	22	37	37
ALT increase	30	7	20	1.1	36	6
AST increase	38	5	17	0.6	60	8
Bilirubin increase	13	0.6	15	0.6	11	0.6

*Per NCI CTCAE version 4.03
[a] Excludes electrolytes

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) *[see Clinical Studies (14.2) in the full Prescribing Information]*. The trial enrolled patients with relapsed or refractory CLL after at least one prior therapy and required hepatic transaminases ≤ 2 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and an estimated creatinine clearance ≥ 30 mL/min. The trial excluded patients having an absolute neutrophil count < 500/µL, platelet count < 30,000/µL, prothrombin time or activated partial thromboplastin time > 2 times ULN, significant cardiovascular disease, or a requirement for strong CYP3A inhibitors or inducers. Patients were allowed to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonist.

In ASCEND, 154 patients received CALQUENCE (100 mg approximately every 12 hours until disease progression or unacceptable toxicity), 118 received idelalisib (150 mg approximately every 12 hours until disease progression or unacceptable toxicity) with up to 8 infusions of a rituximab product, and 35 received up to 6 cycles of bendamustine and a rituximab product. The median age overall was 68 years (range: 32-90); 67% were male; 92% were white; and 88% had an ECOG performance status of 0 or 1.

In the CALQUENCE arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE, permanent discontinuation due to an adverse reaction occurred in 10% of patients, most frequently due to second primary malignancies followed by infection. Adverse reactions led to dosage interruptions of CALQUENCE in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and dose reduction in 3.9% of patients.

Selected adverse reactions are described in Table 7 and non-hematologic laboratory abnormalities are described in Table 8. These tables reflect exposure to CALQUENCE with median duration of 15.7 months with 94% of patients on treatment for greater than 6 months and 86% of patients on treatment for greater than 12 months. The median duration of exposure to idelalisib was 11.5 months with 72% of patients on treatment for greater than 6 months and 48% of patients on treatment for greater than 12 months. Eighty-three percent of patients completed 6 cycles of bendamustine and rituximab product.

Table 7: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND)

Body System Adverse Reaction*	CALQUENCE N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection†	56	15‡	65	28‡	49	11
Upper respiratory tract infection[a]	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection[b]	23	6	26	15	14	6
Blood and lymphatic system disorders §						
Neutropenia[c]	48	23	79	53	80	40
Anemia[d]	47	15	45	8	57	17
Thrombocytopenia[e]	33	6	41	13	54	6
Lymphocytosis[f]	26	19	23	18	2.9	2.9
Nervous system disorders						
Headache	22	0.6	6	0	0	0
Gastrointestinal disorders						
Diarrhea[g]	18	1.3	49	25	14	0
Vascular disorders						
Hemorrhage[h]	16	1.3	5	1.7	6	2.9
General disorders						
Fatigue[i]	15	1.9	13	0.8	31	6
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[j]	15	1.3	15	1.7	2.9	0

*Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia
‡ Includes 1 fatal case in the CALQUENCE monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm
§ Derived from adverse reaction and laboratory data
[a] Upper respiratory tract infection, rhinitis and nasopharyngitis
[b] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection.
[c] Includes neutropenia, neutrophil count decreased, and related laboratory data
[d] Includes anemia, red blood cell decreased, and related laboratory data
[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data
[f] Includes lymphocytosis, lymphocyte count increased and related laboratory data
[g] Includes colitis, diarrhea, and enterocolitis
[h] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis
[i] Includes asthenia, fatigue, and lethargy
[j] Includes back pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, pain in extremity, myalgia, spinal pain and bone pain

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:
- *Skin and subcutaneous disorders*: bruising (10%), rash (9%)
- *Neoplasms*: second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders*: arthralgia (8%)
- *Cardiac disorders*: atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection*: herpesvirus infection (4.5%)

Table 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)

Laboratory Abnormality [a]	CALQUENCE N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	15	15	11	11	23	23
ALT increase	15	1.9	59	23	26	2.9
AST increase	13	0.6	48	13	31	2.9
Bilirubin increase	13	1.3	16	1.7	26	11

Per NCI CTCAE version 5
[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to animals during organogenesis resulted in dystocia in rats and reduced fetal growth in rabbits at maternal exposures (AUC) 2 times exposures in patients at the recommended dose of 100 mg approximately every 12 hours (*see Data*). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breast-feed while taking CALQUENCE and for at least 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.

Contraception

Females

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Pediatric Use

The safety and efficacy of CALQUENCE in pediatric patients have not been established.

Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

Hepatic Impairment

Avoid administration of CALQUENCE in patients with severe hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment *[see Recommended Dosage for Hepatic Impairment (2.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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The High Cost of Oral Anticancer Drugs: What Does the Future Hold?

An increasing number of exciting new oral medications are being discovered for the treatment of various types of malignancies, including breast cancer, lung cancer, chronic lymphocytic leukemia, and multiple myeloma, among many others. Such drugs often have benefits for patients, such as improved activity, limited toxicities, and easier administration, which allows for decreased time in the infusion center. For patients with a traditional insurance prescription drug benefit plan, the annual limits and out-of-pocket caps would normally apply.

However, patients with a traditional Medicare Part D pharmacy benefit plan could face very high and unlimited out-of-pocket costs for these very effective and convenient oral medications. For example, a common maintenance dose of lenalidomide (Revlimid) is 10 mg daily for 21 of 28 days. The price per monthly prescription filled would be $17,262, according to the 2020 Centers for Medicare & Medicaid Services Dashboard. Beneficiaries often reach catastrophic coverage with the first refill, and subsequent refills typically are capped at 5% coinsurance. Even with these safeguards, the yearly out-of-pocket expenses in this example of lenalidomide would be $12,652. This needs to be put into context of the median annual income for patients in the 65-to-69 age group of $53,951 per year and $34,951 per year for those older than 75. In this example, 24% of the patient's income in the 65-to-69 age group and 36% in those older than 75 would have to pay for this anticancer medication.

In addition to the stress of the cancer diagnosis, discussion of this financial burden for the patient and family is an additional factor, which often increases a stressful situation, known as financial toxicity. Manufacturers are legally able to provide co-pay assistance to patients with commercial insurance. However, manufactures are not able to legally provide assistance with cost sharing for patients who have government-sponsored insurance such as Medicare Part D. Therefore, the only mechanism for patients on Medicare Part D to get assistance for co-pays are through grants from various nonprofit foundations or through manufacturer-sponsored patient assistance programs (free drug programs). These programs provide the drug, free of charge from the manufacturer, and bypass Medicare Part D altogether. Patients typically must meet a very low-income level to qualify for the free drug program.

Several foundations, such as the CancerCare Co-Payment Assistance Foundation, and disease-specific programs, such as the Leukemia and Lymphoma Society Co-Pay Assistance Program, assist many patients each year with this process. These grants are supported indirectly by the drug manufacturers and private donations and are capped at varying levels by agent or disease type. They often run out quickly each year and leave many patients with a tough decision to either pay for their oral anticancer medication or other everyday expenses.

With these very real issues surrounding financial toxicity for our patients with cancer, it is not uncommon that hematology/oncology physicians must choose medications that are administered intravenously or subcutaneously so the patients are not faced with such high out-of-pocket medical bills for oral medications. However, this choice is not always the best option for treatment of the patient's cancer, which creates a dilemma for the physician as well as the patient and family.

As prices of oral anticancer therapeutics continue to increase, where will this vicious cycle end? Manufacturers must recoup their investments made in the new medications and plan for the next breakthrough. However, the current process is unable to support as many co-pay assistance programs each year as are needed for the number of patients prescribed the oral anticancer agents. Hopefully a reset of this vicious cycle with lower price points for these oral anticancer medications can be a goal for the near future. The recent approval of H.R.5376 by the Congress will push toward this goal. ■

REFERENCE

Dusetzina SB. Your money or your life - the high cost of cancer drugs under Medicare Part D. *N Engl J Med*. 2022;386(23):2164-2167. doi:10.1056/NEJMp2202726

MEET OUR EXPERT

Weijing Sun, MD, FACP, is director of the Medical Oncology Division, Sprint Professor of Medical Oncology, and professor of medical oncology and cancer biology at the University of Kansas School of Medicine; associate director of the University of Kansas Cancer Center; and president of the International Society of Gastrointestinal Oncology®.

Weijing Sun, MD, FACP, Reviews Trends in Gastrointestinal Cancer

"…we don't focus on survivorship enough. It's important to understand the other factors involved in surviving besides just a treatment."

Current treatment options in gastrointestinal cancer continue to evolve, with longer survival times leading investigators to focus more and more on patients' quality of life and survivorship care.

Weijing Sun, MD, FACP, discussed new treatments, trends in the space, diversity in clinical trials, and how an increased focus on survivorship is changing the needs of patients and investigators in an interview with *ONCOLOGY*®.

Q: Can you give a brief overview of updates in the gastrointestinal space?

SUN: Cholangiocarcinoma [had seen a lot of progress recently, with treatments for] molecular markers or mutation drivers, such as *FGFR* and *IDH1* mutations becoming standardized to a certain level after the FDA approved some drugs. Most studies show the advantage of those [precision] approaches, so it's an important [characteristic] we're looking for. There's not a huge [amount of data] with these studies, but that information is important because each mutation allows for a personalized medicine [approach]. For gastric and esophageal cancer, over the past 2 or 3 years we confirmed that immune checkpoint inhibitors are playing a major role in metastatic disease.

Q: What trends have you observed?

SUN: One would be quality of life vs treatment [outcomes]. In some diseases like stomach disease or gastric cancer, [guidelines] are updated all the time. We focus on the overall survival and the response rate. Nowadays, we have data showing quality of life makes people survive longer. I'm glad to see [survival increasing in] many of these studies, through all different kinds of support. This type of research is important for the future because the longer the patient is surviving, the quality of life [increasingly becomes a concern]. I see it as something to focus on.

An area is in gastrointestinal cancer we don't talk about much is diversity, which means [we end up with] underrepresented or underserved populations. We want to make a difference; we see more research heading in that direction. With this information, we can deliver better care, we can deliver more focus for those underserved populations, and their outcomes can catch up with [those in the overall populations].

Q: What are some unmet needs in the gastrointestinal cancer field?

SUN: Pancreatic cancer is a [lesser investigated malignancy than other] diseases. We still don't know everything; we are far away from [uncovering it all] compared with other diseases. We need to put in more effort, especially regarding tumor biology and the tumor microenvironment because this can tell us the mutations that are important and play an important role.

The other thing is we need a more comprehensive understanding of the diseases, even in survivorship. It's important because certain patients are living [longer lives], and we don't focus on survivorship enough. It's important to understand the other factors involved in surviving besides just a treatment. ■

For full interview and references, visit cancernetwork.com/Sun_8.22

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

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

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

ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

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

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

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

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

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

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

*Range: 0.0-41.4 months.[4]

†Kaplan-Meier estimate.

‡Range: 0.03-69.52 months.[3]

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

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

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

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

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

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

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

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

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

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

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

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

See the latest data rolling out.
Visit FrontlineMomentum.com

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

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

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

DARZALEX *FASPRO*®: Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE

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

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

Local Reactions

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

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

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

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

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

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

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

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

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

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

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

DARZALEX®: ADVERSE REACTIONS

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

DARZALEX *FASPRO*®: ADVERSE REACTIONS

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

INDICATIONS

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

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

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

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

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

cp-248517v3

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

Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

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

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

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

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

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

Interference with Serological Testing

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

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

Infections

Grade 3 or 4 infections were reported as follows:

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

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

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

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

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

Fatal infections (Grade 5) were reported as follows:

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

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

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

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

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

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

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

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

Postmarketing Experience

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

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

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

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

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

cp-271933v2

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

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

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

Interference with Serological Testing

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

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

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

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

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

Postmarketing Experience

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

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

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

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

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Product of Switzerland

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

cp-267681v2

Molecular Pathogenesis of Cholangiocarcinoma: Implications for Disease Classification and Therapy

Khaled W. Kabbara, MD; Timothy Cannon, MD; Arthur Winer, MD; and Raymond Wadlow, MD

ABSTRACT

Cholangiocarcinomas are an aggressive group of heterogeneous malignancies that affect over 210,000 individuals globally each year. Their incidence is rising, particularly in Western countries. Traditionally, cholangiocarcinomas are classified based on anatomic location of the tumor and are treated with similar cytotoxic chemotherapy despite significant molecular and genomic differences. With the rise of genetic and molecular sequencing, several driver mutations have been identified and targeted as novel therapeutic approaches. The most common genomic alterations include changes in *FGFR2, IDH1, KRAS, BRAF, HER2,* and the tumor suppressor p53. In addition, increased understanding of the cellular and molecular constituents of the tumor microenvironment (TME) has created opportunities for further novel therapeutic approaches. New strategies using combination therapies targeting driver mutations and various components of the TME hold promise for improved patient outcomes. This review covers the evolving molecular and therapeutic landscape of cholangiocarcinoma.

Introduction

Cholangiocarcinomas (CCAs) comprise a rare and aggressive group of heterogeneous malignancies that combined with gallbladder cancers affect more than 210,000 individuals globally on an annual basis.[1] Well-characterized risk factors include primary sclerosing cholangitis, cirrhosis, Caroli disease, viral hepatitis, cholelithiasis or choledocholithiasis, hepatolithiasis, and nonalcoholic fatty liver disease. CCA is 40 times more common in East Asia than in Western countries because of endemic infection with the liver flukes *Opisthorchis viverrini, Clonorchis sinensis*, and *Schistosomiasis japonica* as well vertical transmission of hepatitis B virus. Western countries have witnessed a 6-fold increase in incidence over the past 30 years, with some evidence suggesting a causal role for diabetes, obesity, and metabolic syndrome.[2-4] Arising from malignant transformation of epithelial cholangiocytes lining biliary ducts,[5] CCAs are classified anatomically by their site of origin within the biliary tree. Intrahepatic tumors arise proximal to the bifurcation of the right and left hepatic ducts. Extrahepatic tumors are divided into perihilar tumors, also known as Klatskin tumors, originating from between the bifurcation and the confluence of the cystic and hepatic ducts and distal tumors arising between the origin of the cystic duct and the ampulla of Vater. Klatskin tumors are further classified using the Bismuth-Corlette classification based on location and extension within the hilar confluence.[6] Although anatomic classification has implications for locoregional therapy, approximately 80% of patients with CCA are diagnosed at an advanced stage associated with a median survival between 6 and 18 months.[7] Alternative classifications based on cell of origin or growth pattern may be more relevant to disease biology but have not yet led to distinct therapeutic strategies in the advanced setting. Cytotoxic chemotherapy, based on data from clinical trials that included patients with CCA,

gallbladder, and ampullary cancer, represented the only treatment option for these patients until the FDA approved pemigatinib in 2020 for patients with associated *FGFR* gene fusions or other gene rearrangements.[8,9] The success of pemigatinib as well as the recent approval of ivosidenib for *IDH1*-mutated CCA represent landmark developments in the era of real-time comprehensive genomic profiling of advanced CCA for the identification of therapeutically actionable driver mutations. Furthermore, recently reported results from the phase 3 TOPAZ-1 trial (NCT03875235) revealed an overall survival (OS) benefit from the addition of the PD-L1 checkpoint inhibitor durvalumab to combination chemotherapy for patients with advanced CCA, illustrating the promise of strategies targeting intercellular interactions within the tumor microenvironment (TME).[10] Thus, although anatomically classified CCAs have traditionally been grouped together as 1 entity in clinical trials, these examples highlight how increasing knowledge of the molecular basis of disease phenotypes promises a reclassification of CCA into subtypes with greater therapeutic relevance. Herein we review the most recent data associated with a molecular classification of CCA, focusing on clinically actionable targets within the cancer genome and the functional components of the TME.

Driver Mutations

The identification of mutations in oncogenes functionally relevant to the initiation and progression of CCA has led to the development of targeted therapies that are now approved for routine clinical use (**Table**). Next-generation sequencing platforms are commonly used to select therapy for driver mutations in CCA. In addition, companion diagnostics, including the Oncomine Dx Target Test and FoundationOne CDx, are FDA approved for drugs that target activating *IDH1* mutations and *FGFR* fusions, respectively.[11,12]

FGFR2: Four of the 5 known isoforms of FGFR function as transmembrane tyrosine kinases that exert pleiotropic effects on cell proliferation and survival in response to cognate ligand binding. *FGFR* mutations, amplification, and gene rearrangements including translocations and intragenic deletions have been described in a wide variety of human malignancies.[13] Clonal *FGFR2* gene fusions in CCA lead to ligand-independent activation of multiple signaling networks including the MAPK, PI3K-AKT, JAK-STAT, and protein kinase C pathways that in turn promote tumor progression through enhanced malignant cell proliferation, migration, and survival, as well as angiogenesis. Over 100 fusion partners of *FGFR2* have been described, many unique to individual patients, and are present in 10% to 16% of intrahepatic CCAs but are rare in extrahepatic tumors.[14] Pemigatinib, a selective competitive inhibitor of FGFR1/2/3, was associated with a 35% objective response rate and a median OS of 21.1 months in 107 patients with *FGFR2* fusions or rearrangements enrolled in the phase 2 FIGHT-202 trial (NCT02924376), leading to FDA approval for patients with advanced CCA and *FGFR2* gene fusions or rearrangements after progression on chemotherapy.[15,16] Notably, none of the 20 patients in FIGHT-202 with other *FGF/FGFR* gene alterations achieved a response, demonstrating the specific oncogenic function of enhanced receptor dimerization resulting from gene fusion. Toxicities of pemigatinib include hyper/hypophosphatemia (12% grade 3, a class effect of FGFR inhibitors due to FGFR1 inhibition in the renal tubule) and serous retinal detachment due to subretinal fluid accumulation (4%). The role of pemigatinib in first-line therapy is being evaluated by an ongoing phase 3 clinical trial comparing the drug with gemcitabine and cisplatin chemotherapy.[16,17] Infigratinib, another ATP-competitive inhibitor of FGFR1/2/3, was associated with similar results and has also been granted regulatory approval[18,19]; the first-line PROOF 301 trial (NCT03773302) comparing infigratinib to chemotherapy in patients with *FGFR2* translocations is in progress. Multiple mutations in the kinase domain of FGFR2 confer drug resistance by interfering with the binding of competitive inhibitors. These mutations have been detected in circulating cell-free DNA and demonstrated to promote intra- and intertumoral clonal heterogeneity that evolves in parallel with resistance driven by FGFR-independent mechanisms such

TABLE. **Efficacy of Targeted Therapy by Molecular Marker in Cholangiocarcinoma**

Drug	Molecular target	Activity
Pemigatinib	FGFR2 (ICCA)	35% RR[12]
Futibatinib	FGFR2 (ICCA)	42% RR[22]
Infigratinib	FGFR2 (ICCA)	23% RR[15]
Ivosidenib	IDH1	51% DCR[23]
Selumetinib	MEK	12% RR[34]
Selumetinib with cisplatin and gemcitabine	MEK	80% DCR[36]
Trastuzumab and pertuzumab	HER2	23% RR[55]
Adagrasib	KRAS G12C	50% RR in pancreatic cancer; ongoing studies in CCA[42]
Dabrafenib with trametinib	BRAF and MEK	56% RR[46]

CCA, cholangiocarcinoma; DCR, disease control rate; ICCA, intrahepatic cholangiocarcinoma; RR, response rate.

as loss of phosphatase and tensin homolog.[20,21] The FGFR1/2/3/4 inhibitor futibatinib retains activity despite mutations that confer resistance to ATP-competitive inhibitors by binding covalently and irreversibly to the P-loop of the receptor kinase domain. Futibatinib was associated with an overall response rate of 41.7% and a median OS of 20 months in the phase 2 FOENIX-CCA2 trial (NCT02052778) and is being compared with gemcitabine and cisplatin chemotherapy in previously untreated patients with *FGFR2* gene rearrangements in the ongoing phase 3 FOENIX-CCA3 trial (NCT04093362). Drugs that mitigate off-target effects by selectively inhibiting FGFR2 are in development.[20-22]

IDH1: IDH1 and IDH2 are metabolic enzymes that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate and are mutated in a variety of human malignancies.[23] Missense mutations in the R132 codon of *IDH1* are present in 13% to 20% of intrahepatic CCAs (ICCAs) and rarely in extrahepatic CCAs (ECCAs) and perihilar CCAs, resulting in excess production of the oncometabolite R-2-hydroxyglutarate (R-2HG).[3] R-2HG accumulation modifies the epigenetic state of tumor progenitor cells by altering DNA and histone methylation patterns, thereby inhibiting cellular differentiation and promoting oncogenesis.[3,24] The phase 3 ClarIDHy study (NCT02989857) investigated the role of the IDH1-selective inhibitor ivosidenib in patients who had progressed on up to 2 lines of prior systemic therapy. Compared with placebo, ivosidenib significantly prolonged median progression-free survival (PFS; 2.7 vs 1.4 months; HR, 0.37; P <.0001) and OS adjusted for crossover (10.8 vs 5.1 months; HR, 0.49; P <.001).[25-27] The percentage of patients treated with ivosidenib who were progression free at 6 and 12 months was 32% and 22%, respectively, whereas no patients in the placebo arm remained progression free at 6 months. Ivosidenib is administered orally and is well tolerated; low-grade nausea, diarrhea, and fatigue were the most common treatment-emergent adverse events, and there were low rates of drug discontinuation and dose reduction. Ivosidenib is FDA approved for patients with previously treated locally advanced or metastatic CCA with an *IDH1* mutation. Resistance-promoting receptor tyrosine kinase mutations as well as secondary *IDH1* mutations that inhibit drug binding and restore cellular R-2HG levels have been described in acute myeloid leukemia, but mechanisms of ivosidenib resistance in CCA have yet to be elucidated.[28]

MAPK/KRAS: The MAPK pathway includes several intermediaries that play a central role in carcinogenesis, and mutated forms are common drivers of CCA.[29] These protein kinases, which include Ras, Raf, MEK, and ERK, are involved in signal transduction pathways that modulate a variety of processes that impact cellular pathophysiology. Mutations of *KRAS* and *BRAF* that result in constitutive activation of the protein kinase are particularly common.[3,30] *RAS* mutations, particularly in *KRAS*, are found in 38% of ECCAs,[31] but in less than 10% of ICCAs. These activating mutations are most commonly found in exon 2 and less commonly in exons 3 and 4.[32]

Differences in the genomic makeup between ICCA and ECCA are likely partially related to differences in the cell of origin. Periductal glandular epithelial cells surrounding larger bile ducts, including the common bile duct, may constitute the more common cell of origin for ECCA. These cells are associated with distinct molecular alterations, specifically *RAS* mutations, which are linked to lower PFS and OS.[33-37] The high frequency of *RAS* mutations in ECCA may be related to the poor response to chemotherapy that characterizes ECCA, with outcomes similar to *RAS*-mutated pancreatic adenocarcinoma.

Targeting the MAPK pathway in CCA has not yet led to consistent therapeutic benefit. Strategies that target MEK, an intermediary downstream of Ras, have been investigated. Bekaii-Saab et al reported a 12% response rate with selumetinib monotherapy among 28 patients with metastatic biliary cancers (not selected for specific alterations), but to our knowledge no other studies have since shown high response rates with this strategy.[38] Selumetinib in combination with gemcitabine and cisplatin chemotherapy was associated with a disease control rate of 80% and median OS of 9.8 months.[29,39,40] Although pan-KRAS inhibitors have been elusive, mutation-specific KRAS G12C inhibitors have shown high response rates in *KRAS* G12C–mutated lung cancer.[41,42] *KRAS* G12C mutations comprise up to 7.1% of *KRAS* mutations in CCA.[43] Although CCAs have not been heavily represented in KRAS G12C inhibitor clinical trials, at least 1 patient had stable disease with sotorasib in the CodeBreaK 100 trial (NCT03600883).[44] Adagrasib, an irreversible covalent inhibitor that binds to KRAS G12C, is now being investigated, and a partial remission was reported in a patient with CCA in the KRYSTAL-1 trial (NCT03785249).[45,46] Other inhibitors of specific *KRAS* mutations are now in development, including inhibitors of KRAS G12D.[47]

BRAF: *BRAF* mutations occur in approximately 5% of CCA and are mutually exclusive from KRAS.[29] They have been more commonly described in ICCAs.[48] BRAF is downstream of KRAS, with the most common mutation at V600E, resulting in strong activation of RAF kinase and RAS-independent signaling. Other less common mutations include class 2 mutations, which result in intermediate RAF kinase activation, and the "kinase-dead" class 3 mutations that result in BRAF activation through a negative feedback loop.[3] Extrapolating from treatment trials in cancer subsets where *BRAF* V600

mutations are more common, such as melanoma and colorectal cancer, has led to the investigation of MEK and BRAF inhibition in this subset of CCA. The phase 2 ROAR trial (NCT02034110), for example, demonstrated that combination therapy with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor)[49] resulted in a response rate of 56% and a median OS of 15 months.[50] Several basket trials, including TAPUR (NCT02693535) and NCI-Match (NCT02465060), are also investigating combination therapy in *BRAF*-mutated CCA.[51,52]

HER2: HER2, encoded by the *ERBB2* gene, is a member of the human epidermal growth factor receptor family and is a plasma membrane-bound receptor tyrosine kinase.[53] It interacts with multiple signaling nodules and initiates multiple different signaling pathways. Targeting of this pathway has changed the landscape of breast, gastric, and colorectal cancers.[54,55] Ligand binding causes dimerization of the HER receptor, leading to activation of the tyrosine kinase and downstream signaling cascades including the MAPK pathway, which in turn results in enhanced cellular proliferation.[56,57] Deregulation of these receptors plays a role in tumorigenesis. In a meta-analysis, HER2 overexpression was seen in 20% of patients with ECCA and is rarely found in ICCA.[57]

The combination of trastuzumab and pertuzumab resulted in a response rate of 23% in HER2-amplified or -overexpressed metastatic biliary tract cancer previously treated, which included CCA.[58] The median duration of response was 10.8 months, and the median OS was 10.9 months. Several other investigations of HER2-targeted agents in CCA are ongoing in basket trials, as well as a Korean study of trastuzumab combined with folinic acid, fluorouracil, and oxaliplatin, or FOLFOX, in pretreated HER2-amplified metastatic biliary tract cancer.[59,60]

p53: *TP53* is a tumor suppressor gene that is also present in different types of CCA.[29] Lowery et al observed *TP53* mutations, common in multiple biliary tract malignancies and pancreatic cancer, in 49% of ECCAs and less than 20% of ICCAs.[31] *TP53* mutations are seen at a higher prevalence in fluke-related CCA and hepatitis B antigen seropositive patients.[29,61-63] Strategies targeting p53 include degradation of mutant p53, restoration of wild-type p53 through epigenetic modification and clustered regularly interspaced short palindromic repeats technology, and immunotherapy targeting cells expressing mutant *TP53*.[64] Although these strategies are currently under various stages of investigation, their potential application to patients with CCA remains uncertain.[64]

The Tumor Microenvironment

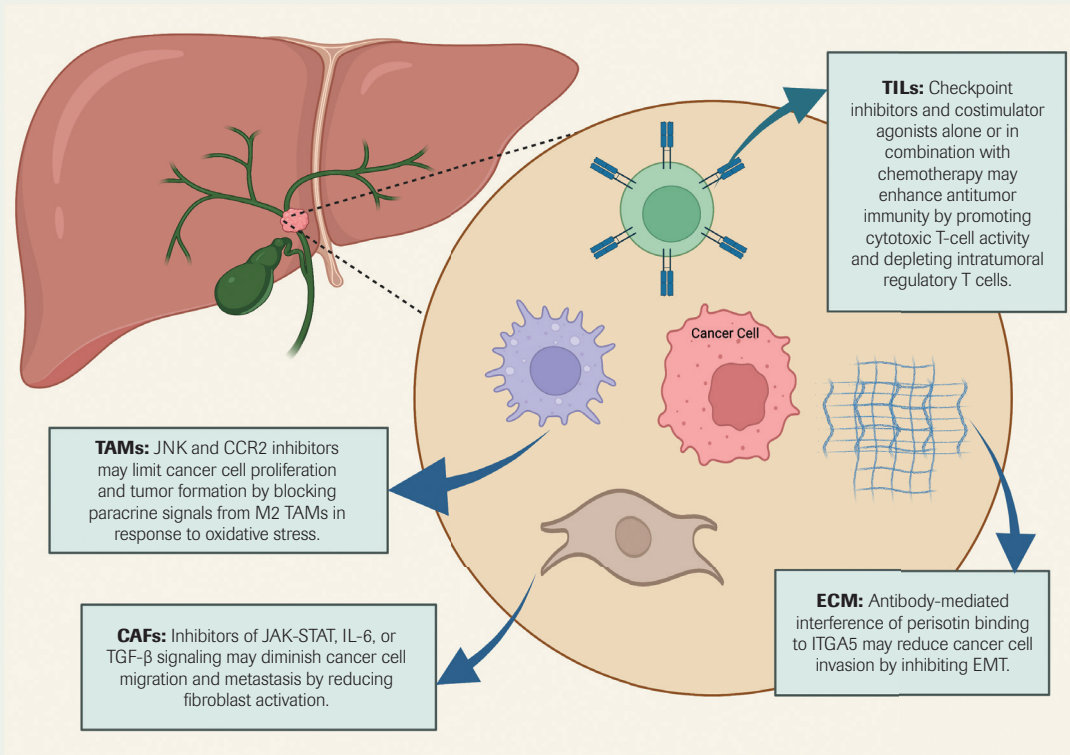
The TME consists of heterogeneous cell types including tumor-infiltrating lymphocytes (TILs) and natural killer cells; cancer-associated fibroblasts (CAFs); tumor-associated macrophages (TAMs) and myeloid cells; endothelial cells and pericytes; and a desmoplastic extracellular matrix (ECM) consisting of proteoglycans and soluble factors. A variety of treatment strategies directed against various constituents of the TME are being explored, and here we highlight efforts to target TILs, CAFs, TAMs, and the ECM.[23,65]

TILs: Interactions between malignant cells and TILs promote tumor progression in part through the activation of immune checkpoints including PD-1 (and its ligand PD-L1) and CTLA-4 that result in exhaustion of cytotoxic CD8+ lymphocytes and upregulation of CD4+CD25+FOXP3+ regulatory T cells.[66] The aforementioned global phase 3 TOPAZ-1 trial established the efficacy of combining the PD-L1 checkpoint inhibitor durvalumab with chemotherapy in previously untreated patients, improving survival at 2 years from 10.4% with chemotherapy alone to 24.9% with combined therapy. TOPAZ-1 enrolled 685 patients with ICCA (56%), ECCA (19%), and gallbladder cancer (25%), and benefit was reported in all subtypes.[10]

Dual checkpoint therapy with the PD-1 antibody nivolumab and the CTLA-4 antibody ipilimumab has also demonstrated early efficacy in this disease type, but with differential responses depending on anatomic location of the tumor, with associated objective responses in 5 of 16 patients with advanced ICCA but 0 of 10 patients with ECCA.[67] The combination of nivolumab and ipilimumab is now being compared with nivolumab, gemcitabine, and cisplatin in a multicenter, randomized phase 2 study of previously untreated patients with advanced CCA.[68]

PD-L1, microsatellite instability (MSI), and high tumor mutational burden (TMB) have all been explored as biomarkers for selecting patients for immunotherapy.[69-71] A phase 2 trial reported PD-L1 expression in 43% of CCAs, and consistent with cumulative experience across a broad variety of malignancies, TOPAZ-1 reported greater relative benefit in patients with PD-L1 expression with a hazard ratio for OS of 0.79 in 58% of patients with PD-L1 tumor area positivity (TAP) of 1% or greater vs 0.86 in 30% of patients with PD-L1 TAP of less than 1%.[10] However, given the observation of responses even in patients without protein expression, PD-L1 immunohistochemistry is an imperfect biomarker for patient selection. MSI and high TMB are postulated to predict responses to checkpoint inhibitor therapy by increasing neoantigen expression and immune activation.[72] Both are FDA-approved biomarkers for selecting patients for the PD-1 antibody pembrolizumab agnostic of tumor type. MSI (or its correlate, deficient DNA mismatch repair protein expression) has been reported in 1% to 10% of CCAs, with greater prevalence in ICCAs vs ECCAs.[67,70] The KEYNOTE-158 trial (NCT02628067)

FIGURE. **Therapeutic Strategies for Targeting the Cholangiocarcinoma Microenvironment**



TILs, CAFs, TAMs, and the ECM contain a variety of therapeutic targets undergoing investigation. Biomarkers (eg, target protein expression or markers of enhanced neoantigen presentation for TIL therapies), FAP for CAF-directed therapies, and rational combinations with drugs targeting cancer cell mutations hold promise for future clinical use.

CAF, cancer-associated fibroblast; CCR2, chemokine receptor type 2; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FAP, fibroblast activation protein; IL-6, interleukin 6; ITGA5, integrin α-5; JAK-STAT, Janus kinase/signal transducer and activator of transcription proteins; JNK, c-Jun N-terminal kinase; TAM, tumor-associated macrophage; TGF-β, transforming growth factor β; TIL, tumor-infiltrating lymphocyte.

included 22 patients with CCA, of whom 9 (41%) had an objective response to pembrolizumab.[73] High TMB is seen in less than 5% of CCAs, but there is scant evidence that it predicts response to checkpoint inhibitors.[74] Genomic approaches combining laser-capture microdissection of tumor stroma with functionally validated computational annotation of TME components may offer improved disease classification and identification of an immunogenic subtype sensitive to checkpoint inhibitor therapy.[70] Moreover, strategies targeting immune checkpoints beyond PD-1/PD-L1 including LAG3, TIM-3, TIGIT, and BTLA as well as costimulatory receptors including OX40, 4-1BB, GITR, and ICOS remain under investigation across a broad variety of malignancies and may provide additional benefit as well as markers for improved patient selection.[69,70]

CAFs: Comprising the majority of cells within the tumor stroma, CAFs in CCAs are thought to arise from a variety of normal precursors including hepatic stellate cells, portal fibroblasts, and bone marrow–derived mesenchymal cells.[75,76] Far from representing a passive reaction of normal host tissue to malignant tumor development, the pleiotropic mechanisms whereby CAFs actively enhance cancer cell migration, metastasis, and chemoresistance have been elucidated using a variety of model systems across a broad range of solid tumors and present opportunities for therapeutic intervention.[75-81] For example, inflammatory cytokines within the TME including IL-6 and TGF-β promote stromal remodeling and cancer cell migration through JAK-STAT–dependent activation of actomyosin contractility within CAFs.[82-85] IL-6 antibodies and JAK inhibitors that have been FDA

approved for autoimmune and myeloproliferative diseases are in clinical trials for solid tumors including CCA, and novel small molecule inhibitors of JAK-STAT signaling including S63845 and AZD1480 are being investigated in preclinical studies.[85,86] Strategies targeting TGF-β have been complicated by incomplete understanding of its distinct tumor-suppressive and tumor-promoting functions mediated through canonical SMAD and non-SMAD signaling cascades. The bifunctional fusion protein bintrafusp-α, composed of the extracellular domain of the TGF-β receptor TβRII and human IgG1 antibody targeting PD-L1, demonstrated an objective response rate of 10.1% in patients previously treated with platinum chemotherapy, but a first-line trial evaluating the drug in combination with chemotherapy was discontinued due to futility.[87,88] Additional strategies targeting CAFs using antibodies or CAR T cells directed against the serine protease fibroblast activation protein as well as other CAF markers hold promise but remain in need of further development, including the identification of biomarker-defined subsets with a higher likelihood of benefit.[89]

TAMs: TAMs are derived from resident hepatic macrophages known as Kupffer cells and from circulating CD14+/CD16+ monocytes that infiltrate the TME in response to chemoattractant proteins including MCP/CCL2 and CSF1.[76,90-93] Similar to CAFs, TAMs synthesize stromal remodeling enzymes including matrix metalloproteinases to create a suitable environment for tumor growth and cancer cell migration.[94] In addition, TAMs play a dual role in modulating the immune response through CCR2/CCL2-mediated polarization into M1 and M2 subsets promoting inflammation and immunosuppression, respectively.[95,96] M2 TAMs inhibit cytotoxic T cells and facilitate angiogenesis by expressing PD-L1, CTLA-4, and VEGF, fostering an immunosuppressive milieu conducive to tumor growth and metastasis.[71,80,81,97,98]

Preclinical studies have investigated strategies for reducing TAM infiltration, M2 TAM polarization, and cooperative signals between TAMs and malignant cells.[96,99] For example, mouse models of ICCA demonstrate that Kupffer cells produce tumor necrosis factor (TNF) in response to oxidative stress within the liver, and that TNF in turn leads to paracrine activation of JNK-mediated cholangiocellular overgrowth and tumor formation.[100] Small molecule inhibition of JNK abrogated tumor growth in mice and the proliferation of human ICCA cell lines. Further supported by the observation that JNK activation has been reported in 80% of human ICCAs, targeting TNF-JNK signaling between TAMs and malignant cells with JNK inhibitors is of interest for clinical development.[100,101]

In addition, early clinical efforts in pancreatic cancer targeting TAMs by inhibiting CCR2 in combination with cytotoxic chemotherapy may hold similar promise for patients with CCA.[102] However, a study using a genetically engineered mouse model of CCA demonstrated that inhibition of TAM CCR2 led to a compensatory increase in granulocytic myeloid-derived suppressor cells and that dual inhibition of both cell types in combination with immune checkpoint blockade was required to potentiate tumor regression.[71] Clinical strategies that leverage a more sophisticated understanding of the immune response to CCAs will require careful patient selection based on personalized characterization of the TME.

ECM: ECM components, including fibrillar proteins, glycoproteins, and proteoglycans, contribute to tumor formation and progression through a variety of mechanisms that suggest potential therapeutic targets.[103] For example, the CAF-secreted matricellular protein periostin contributes to cell migration and metastasis in CCAs by promoting malignant cell epithelial-to-mesenchymal transition (EMT).[104] Antibody-mediated blockade or inhibition of the periostin receptor integrin alpha 5 on CCA cells reduced CCA proliferation and invasion by downregulating the EMT-promoting transcription factor TWIST2, and higher expression levels of TWIST2 in human CCA samples are associated with poor prognosis.[104,105] Nonetheless, ECM-targeting strategies in patients based on promising preclinical data have largely fallen short in the clinical setting, as exemplified by the negative phase 3 trial in patients with pancreatic cancer evaluating the addition of recombinant human hyaluronidase PEGPH20 to gemcitabine and nanoparticle albumin-bound paclitaxel.[106] Thus, indiscriminate efforts to target the ECM in CCA similarly may fail without improved patient selection via enhanced mechanistic understanding of ECM components in different disease subsets and stages of tumor development.

Conclusion

To date, CCA has generally been treated as a single entity in clinical trials. Treatment paradigms have not significantly varied based on location in the biliary tree. However, the advancement of molecular diagnostics including genomic sequencing has shed new light on the unique subtypes within the broad classification of CCA. Indeed, extrahepatic and intrahepatic CCA differ so greatly in molecular findings that it seems reasonable to consider them as separate diseases, for which unique clinical trials should be performed. Intrahepatic CCA has been associated with longer OS per stage and often has clear driver mutations, such as *FGFR* fusions or *IDH1* mutations, whereas extrahepatic and hilar CCA share genomic similarities with pancreatic adenocarcinoma.

Molecular profiling has been a cornerstone for new therapeutic endeavors and personalized medicine. In addition, increased understanding of all

components of the TME and their pleiotropic effects on tumor progression will allow for new avenues of therapeutic discovery. Combination therapy that targets the tumor stroma in conjunction with actionable mutations represents a promising strategy, which in turn may enhance clinically relevant molecular classification and patient selection. For example, the attenuating effect of pharmacologic IDH1 inhibition on ICCA in a genetically engineered mouse model was limited by immune checkpoint activation and recruitment of regulatory T cells; combination therapy with an anti–CTLA-4 antibody and IDH1 inhibitor led to synergistic antitumor effects meriting further investigation.[107]

Rapidly expanding technology for characterizing circulating tumor DNA (ctDNA) and metabolites using liquid biopsies may circumvent the need for tumor sequencing, although the utility of ctDNA in the clinic may be limited by the absence of spatial resolution for characterizing the outgrowth of resistant clones.[108] Moreover, ctDNA alone will not permit real-time analysis and tailored targeting of the TME. Investigational molecular imaging using novel tracers coupled to radioisotopes, bioluminescent probes, and fluorescent reporters holds promise for improved diagnosis and in vivo target validation in early drug development trials.[109] Finally, ongoing efforts to characterize the role of host genetic background through genome-wide association studies of cancer predisposition as well as the gut microbiome may further aid in the molecular classification and treatment of patients with CCA.[39,110] ■

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REVIEW

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Current Treatment of Burkitt Lymphoma and High-Grade B-Cell Lymphomas

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ABSTRACT

Purpose of Review: This article reviews the current data and future directions in the management of Burkitt lymphoma (BL) and high-grade B-cell lymphoma (HGBL).

Recent Findings: BL is a rare, mature B-cell lymphoma molecularly defined by translocation of the proto-oncogene *MYC*. Multiple intensive combination chemoimmunotherapy regimens have demonstrated excellent efficacy in this disease, although treatment toxicity remains a challenge in many patients. Double-hit lymphoma (DHL) represents HGBL with translocations of the oncogene *MYC* along with either *BCL2* or *BCL6*, or both. In 2016, the World Health Organization update of this classification was revised to a new entity defined by cytogenetics: HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements. Recent prospective data using dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab has demonstrated encouraging treatment efficacy in these patients. HGBL, not otherwise specified (NOS) is a heterogeneous, aggressive, mature B-cell lymphoma that does not meet criteria for BL, DHL, or diffuse large B-cell lymphoma NOS. Therapy for this entity is not well established.

Summary: The aggressive B-cell lymphomas BL, DHL, and HGBL, NOS are unique diseases with specific pathogenesis and biology. Insights into the molecular biology of these diseases have enabled new classifications and personalization of therapy.

Key Words: non-Hodgkin lymphoma; diffuse large B-cell lymphoma; high-grade B-cell lymphoma; Burkitt lymphoma; double-hit lymphoma

Introduction

Non-Hodgkin lymphoma (NHL) is the seventh most common cancer in the United States, with approximately 77,000 new cases and 20,000 deaths in 2020.[1] A significant minority of these cases were the especially aggressive B-cell lymphomas Burkitt lymphoma (BL) and high-grade B-cell lymphoma (HGBL), the latter of which includes the histologic subtypes HGBL with *MYC* and *BCL2* and/or *BCL6* translocations (conventionally referred to as double-hit lymphoma [DHL]) and HGBL, not otherwise specified (NOS).[2] The understanding of the molecular pathogenesis of these diseases continues to expand, which has permitted changes in classification and further personalization of therapy in these diseases.[2] In this article, we review the pathogenesis and management of BL and HGBL.

Burkitt Lymphoma

Histology and molecular biology

BL is an uncommon mature B-cell NHL, accounting for approximately 1% of all cases of NHL. It is one of the most aggressive malignancies in existence, with a rapid growth pattern, and it is uniformly fatal if untreated.[3,4] BL is classified into

3 variant forms: the "endemic" variant, which is associated with Epstein-Barr virus (EBV) and has a geographic pattern of incidence; an "immunodeficiency-associated" variant, which is typically associated with HIV; and a "sporadic" variant, which most frequently occurs in young adults.[5-7] Morphologically, BL involves monomorphic medium-sized B cells with basophilic cytoplasm, numerous mitotic figures, rounded nuclei with finely clumped chromatin, myriad apoptosis, and tingible body macrophages, which result in a classic "starry sky" pattern. Immunophenotypically, the cells express membrane IgM with light chain restriction, CD19, CD20, CD22, CD79a, PAX5 (B-cell antigens), the germinal center markers CD10 and BCL6, and strong MYC expression with a Ki-67 of nearly 100%. The molecular hallmark of the disease is the translocation of the proto-oncogene *MYC* at band 8q24 to the IGH region on chromosome 14q32, t(8;14)(q24;q32) or, less frequently, to the IGK locus on 2p12, t(2;8), or the IGL locus on 22q11, t(8;22). In a minority of cases, no *MYC* rearrangement can be identified, but gene-expression profiling has identified identical signatures to the typical *MYC* translocated cases.[8] Additionally, the 2016 revision of the World Health Organization (WHO) Classification of Lymphoid Tumors added a provisional entity called Burkitt-like lymphoma with 11q aberration, which lacks a MYC rearrangement but instead has a chromosome 11q alteration with interstitial gains in 11q23.2-23.3 and losses of 11q24.1-qter.[8]

Clinical presentation and prognostic factors

Each variant of BL has distinct clinical features. The endemic variant typically occurs in children aged 4 to 7 years, with a male predominance and a predilection for jaw involvement, although other extranodal sites can be involved; it is uniformly associated with EBV.[3,9] Endemic BL classically occurs in equatorial Africa and Papua New Guinea. The immunodeficiency variant typically occurs in patients with HIV infection, usually with preserved CD4 counts, and often presents with abdominal disease and extranodal involvement, and is associated with EBV in 25% to 40% of cases.[7,8] Sporadic BL has a median age at diagnosis of 30 years and also frequently presents with abdominal involvement, most classically the ileocecal valve; 20% to 30% of cases are associated with EBV.[8,10,11] Recently, a large multicenter study created an adult BL prognostic model, identifying age greater than or equal to 40 years, an ECOG performance status greater than or equal to 2, a lactate dehydrogenase (LDH) level exceeding 3 times the institutional upper limit of normal (ULN), and central nervous system (CNS) involvement as independent prognostic factors. The BL International Prognostic Index (IPI) comprises these 4 risk factors and places patients into categories of low risk (0 risk factors; 3-year progression-free survival [PFS] rate, 92%), intermediate risk (1 risk factor; 3-year PFS rate, 72%), and high risk (≥ 2 risk factors; 3-year PFS rate, 53%).[12]

Management

BL is a highly curable disease, with a recent real-world study demonstrating a 3-year overall survival (OS) rate of approximately 70%.[13] Historically, commonly used regimens included intensive therapies such as CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, cytarabine, intrathecal methotrexate, and cytarabine) or Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine), although more recent data have emerged with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab).[14-16] The backbone of many active regimens in this disease includes cyclophosphamide, doxorubicin, and vincristine, as well as CNS-penetrating agents.[17,18] Commonly used contemporary regimens include modified R-CODOX-M/R-IVAC,[16,19-21] R-Hyper-CVAD,[14,22] the CALGB-10002 trial (NCT00039130) regimen,[23,24] DA-EPOCH-R,[15,25] and European LMBA02 (NCT00180882)[26,27] and GMALL05 (NCT00199082) trial regimens.[28] No randomized clinical trials have been conducted to identify a single preferred regimen. Maintaining treatment intensity is challenging, and treatment-related mortality is a critical problem, most notably in older or frail adults and immunocompromised individuals.

Magrath and colleagues initially published data using CODOX-M/IVAC with intrathecal methotrexate and cytarabine. Patients with low-risk disease, defined as a single site less than 10 cm with a normal LDH (or completely resected abdominal disease), received 3 cycles of CODOX-M; all others received 4 courses of alternating therapy with CODOX-M and IVAC. In a patient population with a median age of 25 years, the 2-year event-free survival (EFS) rate was 92%.[16] Because of the high rates of toxicity with this regimen, investigators established a modified-Magrath regimen with reduced doses of methotrexate and cytarabine, demonstrating a 2-year PFS rate of 64%, including a 2-year PFS rate of 49% in high-risk patients.[19] The addition of rituximab to CODOX-M/IVAC is associated with enhanced PFS and OS,[29] and a phase 2 study including mostly high-risk patients that included rituximab with CODOX-M/IVAC reported a 2-year PFS rate of 80% and 2-year OS rate of 80%.[30] Hyper-CVAD demonstrated a 3-year OS rate of 49%,[14] and the addition of rituximab was associated with improved outcomes, including a 3-year EFS rate of 80% and 3-year OS rate of 89%.[14] A regimen developed by the Cancer and Leukemia Group B incorporating prephase therapy of cyclophosphamide and

prednisone followed by 3 cycles of ifosfamide, methotrexate, vincristine, cytarabine, etoposide, and dexamethasone alternating with cyclophosphamide, methotrexate, vincristine, doxorubicin, and dexamethasone, as well as intrathecal chemotherapy, demonstrated a 5-year OS rate of 52% (of note, a portion of these patients also received cranial irradiation).[23] As with other regimens, the inclusion of rituximab was associated with improved outcomes, with a prospective study noting a 4-year EFS rate of 74% and 4-year OS rate of 78%.[24] The French Lymphomes Malins B (LMB) regimen administered cyclophosphamide, doxorubicin, vincristine, and prednisone (COPAD) to low-risk patients (resected stage I and abdominal stage II disease). For high-risk patients (bone marrow and/or CNS involvement) and intermediate-risk patients (all others), prephase therapy included cyclophosphamide, vincristine, and low-dose steroids. The intermediate group received 5 additional cycles of COPADM/CYM, which also included high-dose methotrexate, cytarabine, and intrathecal methotrexate, and high-risk patients received 8 cycles with augmented doses of methotrexate, cytarabine, etoposide, and intrathecal methotrexate and cytarabine, or COPADM, CYVE. Those with CNS involvement also received cranial radiotherapy to 24 Gy. The 2-year EFS rate with this regimen was 65% in a cohort with a median age of 33 years.[26] The addition of rituximab was evaluated in a phase 3 randomized controlled trial, with its incorporation resulting in improved 3-year EFS (75% vs 62%) and no difference in adverse events.[27]

More recently, prospective data using the less intensive DA-EPOCH-R regimen have emerged. Investigators at the National Cancer Institute treated 30 patients, including a cohort of HIV-negative patients receiving DA-EPOCH-R and a cohort of HIV-positive patients treated with short course (SC)-EPOCH-RR (2 rituximab doses per cycle). The median age was 33 years in this study, with a median follow-up of 86 months and 73 months in the respective groups; the freedom from progression was 95%.[25] A multicenter follow-up study enrolled 113 patients, with a median age of 49 years. Low-risk patients, defined as having stage I or II disease with normal LDH, no mass greater than or equal to 7 cm, and an ECOG performance status of 0 or 1, received 3 cycles of DA-EPOCH-RR without CNS prophylaxis, and high-risk patients received 6 cycles of DA-EPOCH-R with intrathecal CNS prophylaxis on days 1 and 5 of cycles 3 through 6 (or with extended intrathecal treatment twice weekly for at least 4 weeks, weekly for 6 weeks, and then monthly for 6 months if active CNS involvement). At a median follow-up of 58.7 months, the EFS rate was 84.5% and OS rate was 87.0%, including EFS rates of 100% and 82% in low- and high-risk patients, respectively. Among 11 patients with cerebrospinal fluid involvement at presentation, 6 experienced disease progression or died, with a 4-year EFS rate of 45.5% compared with 89.9% in those with high-risk disease but no CNS involvement, suggesting that intensive regimens with augmented CNS penetration may be preferable in this subset of patients. Inferior outcomes were also seen in those with blood and/or marrow involvement, for whom more intensive strategies can be considered in young, fit patients.[15]

Relapsed BL, although uncommon, remains an unmet medical need, as the prognosis remains extremely poor, with a median survival of approximately 2.8 months.[31-33] Salvage regimens using hyper-CVAD reinduction, high-dose cytarabine, R-ICE (rituximab, ifosfamide, carboplatin, and etoposide), and R-GDP (rituximab, gemcitabine, dexamethasone, and cisplatin) have all been used with limited data for long-term efficacy, and patients who do achieve remission should be considered for transplant.[33] Given the unmet need for rationally designed therapies, a phase 2 study investigating CPI-613, an analogue of lipoic acid and inhibitor of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, in relapsed BL is currently ongoing (NCT03793140), and other effective agents in chemotherapy-refractory aggressive B-cell lymphomas such as chimeric antigen receptor (CAR) T-cell therapy warrant further evaluation.[34]

Double-Hit Lymphomas

Histology and molecular biology

DHL is the conventional terminology for an HGBL with translocations of the oncogene *MYC* along with either *BCL2* or *BCL6*, or both. The 2008 WHO classification previously classified this entity morphologically as either diffuse large B-cell lymphoma (DLBCL) or B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLu). However, in the 2016 WHO update, this entity was revised to a new entity defined by cytogenetics, called HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements.[8] DHLs usually have germinal center B-cell–like (GCB) cell of origin, particularly DHL with rearrangements of *MYC* and *BCL2*, which is the most common variation of DHL, although a minor fraction of cases can be non-GCB (usually *MYC* and *BCL6* DHL). Most cases have high Ki-67 proliferation fractions and immunohistochemical coexpression of *MYC* and *BCL2* and/or *BCL6*.[35-40]

Clinical presentation and prognostic factors

The clinical presentation of DHL is often in older adults; it typically presents at an advanced stage of disease with frequent extranodal involvement and elevated LDH.[41] Bone marrow and peripheral blood involvement is more common with DHL than with DLBCL, and the risk of CNS involvement is high at initial

diagnosis or relapse. Historically, the prognosis of DHLs has been poor, with a median OS of less than 1 year,[42-45] but these data have been affected by selection bias, in which only the most aggressive-appearing cases (either clinically or histologically) were evaluated via fluorescence in situ hybridization for the presence of *MYC* translocations.[46] A prospective series of DHLs that were morphologically classified as DLBCL and uniformly treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP–like chemoimmunotherapy demonstrated a 5-year PFS of approximately 60%, suggesting that the prognosis is indeed more favorable than initially reported in retrospective studies and highlighting that good clinical outcomes can be achieved in a significant proportion of patients with morphologic DLBCL with *MYC* and *BCL2* and/or *BCL6* translocation utilizing standard R-CHOP.[47] With respect to prognostic factors, the IPI is associated with outcome,[37,48] and in a large retrospective analysis, advanced stage, LDH level greater than 3 times the institutional ULN, leukocytosis, and CNS involvement were all adverse factors with respect to OS.[48]

Management

Management of DHL remains relatively controversial in the absence of randomized trials, but historically poor outcomes with R-CHOP have prompted investigations of more intensive treatment strategies. Retrospective data demonstrated a 2-year PFS rate of less than 20% with R-CHOP compared with approximately 50% with more intensive treatment regimens, such as DA-EPOCH-R, R-Hyper-CVAD, or R-CODOX-M/R-IVAC.[48] However, multiple recent studies, including a cohort of patients from prospective clinical trials and population registries with morphologic DLBCL and the presence of *MYC* and *BCL2* and/or *BCL6* rearrangements, have shown better outcomes with R-CHOP than previously reported, with a 2-year PFS rate of approximately 60%.[47,49] These findings underscore that initial retrospective data were likely affected by significant selection bias and that some patients, particularly those with morphologic DLBCL, may have superior clinical outcomes with R-CHOP than was previously thought. A multicenter study of DA-EPOCH-R in *MYC*-rearranged aggressive B-cell lymphomas given for 6 cycles and administered with prophylactic intrathecal methotrexate demonstrated an overall response rate (ORR) of 87%, a 48-month EFS rate of 71%, and a 48-month OS rate of 77%; 45% of patients had DHL, with a 4-year EFS rate of 73%.[50] A recent multicenter Alliance for Clinical Trials in Oncology randomized clinical trial investigated DA-EPOCH-R with or without the BCL2 inhibitor venetoclax in DHLs. Although the addition of venetoclax resulted in excess toxicity and death, the control arm of DA-EPOCH-R demonstrated an ORR of 73%, a complete response rate (CRR) of 67%, and a 15-month PFS rate of approximately 65%. This prospective clinical trial is the largest conducted to date in DHL and provides prospective clinical trial data for the use of DA-EPOCH-R in this disease with favorable outcomes compared with historical studies.[51] Consolidation with high-dose chemotherapy has been utilized at some centers, but retrospective analyses have not demonstrated a survival advantage.[37,48,52] Limited-stage disease is uncommon but is associated with a much more favorable prognosis, with a 2-year PFS rate approaching 75% and 2-year OS rate of approximately 80% with R-CHOP or DA-EPOCH-R.[48,53,54] R-CHOP may be sufficient systemic therapy in patients with limited-stage disease, although many practitioners still prefer DA-EPOCH-R in the absence of a contraindication. In the absence of definitive data, our preference is to include consolidative radiation therapy for localized disease, given that this disease has exhibited an increased risk of chemoresistance.[53]

In the relapsed setting, salvage chemoimmunotherapy regimens have been associated with dismal outcomes,[37,48] and the most effective therapy to date in the relapsed setting is anti-CD19 CAR T-cell therapy, with response rates of approximately 80% and durable PFS in approximately 40% of patients.[55-58] Notably, outcomes with CAR T-cell therapy appear to mirror that of other non-DHL disease subtypes, in stark contrast to chemotherapy.

Additional novel therapies have been developed primarily in DLBCL but have included a small number of HGBL cases in pivotal trials. Loncastuximab tesirine-lpyl, an antibody-drug conjugate containing a humanized CD19 antibody conjugated to a pyrrolobenzodiazepine dimer cytotoxin, SG3199, was evaluated in relapsed/refractory DLBCL, including 15 cases of DHL. The ORR for the entire study was 48%, with a 24% CRR, median duration of response (DOR) of 10.3 months, and manageable safety profile. Among DHL cases, the ORR was 33%, with a CRR of 33% and median DOR of 13 months.[59] Polatuzumab vedotin-piiq, a CD79B-targeting antibody-drug conjugate with monomethyl auristatin E, a microtubule inhibitor, was evaluated in combination with rituximab and bendamustine in a cohort of patients with DLBCL that included 5 with HGBL. The ORR for the entire study was 62.5%, with a CRR of 52.5% and DOR of 10.9 months.[60] Tafasitamab-cxix, an anti-CD19 monoclonal antibody, was evaluated in combination with lenalidomide in the L-MIND trial (NCT02399085), a phase 2 trial of adults with relapsed/refractory DLBCL. The regimen demonstrated durable remissions in a subset of patients and an encouraging safety profile, but patients with DHL were excluded from this

study.[61] Selinexor, a novel oral selective inhibitor of nuclear export, was examined in patients with relapsed/refractory DLBCL, including 5 patients with DHL. Among all 127 patients evaluated in the study, the ORR was 28%, with a CRR of 12% and median DOR of 9 months.[62] Finally, multiple bispecific antibodies with binding to CD20 on B cells and CD3 on T cells have emerged as promising therapeutics in relapsed/refractory aggressive B-cell NHLs, including DHL. Mosunetuzumab in aggressive B-cell NHLs demonstrated an ORR of 35%, CRR of 19%, and median DOR of 23 months in patients with a complete response.[63] Glofitamab in aggressive B-cell NHLs demonstrated an ORR of 48%, CRR of 33%, and overall median DOR of 5.5 months.[64] Epcoritamab in patients with relapsed/refractory DLBCL showed an ORR of 68% and a CRR of 45%,[65] and odronextamab administered to patients with relapsed/refractory DLBCL demonstrated an ORR and CRR of 60%, with a median DOR of 10 months in those without prior CAR T-cell therapy versus an ORR of 33%, CRR of 24%, and median DOR of 3 months in those with prior CAR T-cell therapy.[66]

CNS prophylaxis has historically been routinely incorporated into upfront therapy, given the increased risk of CNS involvement; however, multiple recent large retrospective studies have called into question the utility of CNS prophylaxis in DLBCL, demonstrating similar CNS relapse rates as a series without prophylaxis incorporated.[48,67-69] Whether CNS prophylaxis is effective at reducing CNS events specifically in DHL is unknown, but it has been associated with improved outcomes in a multicenter retrospective analysis and is routinely included by many practitioners. Novel targets continue to be explored in this disease, including venetoclax in combination with R-CHOP, and inhibition of PLK1, which promotes MYC protein stability.[70,71]

High-Grade B-Cell Lymphoma, NOS

Histology and molecular biology

HGBL, NOS is a biologically heterogeneous aggressive mature B-cell lymphoma that does not meet criteria for DHL, DLBCL, NOS, or BL.[8] In the previous 2008 WHO classification, HGBL, NOS cases were included alongside DHL in the category of B-cell lymphoma, unclassifiable, with features intermediate between those of DLBCL and BL. Given the separation of DHL into its own classification, HGBL, NOS encompasses the remaining cases of this prior classification category, such as blastoid-appearing mature B-cell neoplasms that do not meet a diagnosis of mantle cell lymphoma. The morphologic appearance of HGBL, NOS mimics BL, with a diffuse proliferation of medium to large cells with no stromal reaction or fibrosis. Starry-sky macrophages, mitotic figures, and apoptosis are common. There can be greater morphologic heterogeneity than in a typical BL. The immunophenotype is not distinctive, given the heterogeneity of the category, but is typically CD20 positive, BCL6 positive, IFR4/MUM1 negative, and variable with respect to CD10 expression, Ki-67 positivity, and *MYC* expression. The molecular and cytogenetic profile includes a *MYC* rearrangement in 20% to 35% of cases, and by definition, a *MYC* rearrangement must not be present with either a *BCL2* and/or *BCL6* rearrangement.[8] Recent work using gene expression profiling of a set of centrally confirmed cases showed a high rate of reclassification as DLBCL and did not identify any shared molecular features among cases, suggesting that this entity does not necessarily denote a truly distinct disease and may be changed in future classification updates.[72]

Clinical presentation and prognostic factors

HGBL, NOS is poorly characterized given its recent reclassification, but it is commonly a disease of older adults, with a median age at presentation of 70 years. Adverse IPI risk factors are also frequently observed, as a prior series of B-cell lymphoma, unclassifiable/HGBL demonstrated that most cases had advanced-stage disease, elevated LDH, and IPI greater than or equal to 3, and one-third of cases involved more than 1 extranodal site. Two-year PFS rates range from 23% to 69% in published series, with 2-year OS rates ranging from 30% to 77%.[73-78]

Management

Therapy for HGBL, NOS is not well established, as prior clinical trials mostly included these lymphomas with other aggressive B-cell lymphomas. A retrospective study that included a portion of HGBL, NOS cases as well as DHL cases reported a CR rate of 43% and a 5-year EFS rate of 23%, with most patients receiving R-CHOP.[74] Moreover, a series of 52 patients with the former entity B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, found that the PFS of patients treated with R-CHOP was significantly inferior to those receiving the more intensive R-Hyper-CVAD regimen, highlighting concern that more intensive regimens are needed, at least for patients with high-risk features.[75] A small number of HGBL, NOS cases were included in the FLYER trial (NCT00278421) of low-risk aggressive B-cell lymphomas (IPI of 0 and no tumor size ≥ 7.5 cm); the 3-year PFS rate for the overall study cohort was 96% with 4 cycles of R-CHOP with 2 additional rituximab doses.[79] Similarly, the S1001 trial (NCT01359592) included 17% HGBL, NOS cases and reported a 5-year PFS rate of 87% for the overall study cohort. In the S1001 trial, patients with nonbulky (< 10 cm) stage I/II disease received 4 cycles of R-CHOP if an interim PET/CT after 3 cycles was negative vs 3 cycles plus involved-field radiation therapy and ibritumomab

TABLE. **Summary of Burkitt Lymphoma, Double-Hit Lymphoma, and High-Grade B-Cell Lymphoma, Not Otherwise Specified**

Characteristics	BL	DHL	HGBL, NOS
Molecular features	*MYC* translocated at band 8q24 to the IGH region on chromosome 14q32 in the context of a simple karyotype	*MYC* rearrangement and *BCL2* and/or *BCL6* translocation, usually in the context of a complex karyotype	Variable, *MYC* rearrangement in 20% to 35% of cases
Histologic findings	Monomorphic medium-sized B cells with numerous mitotic figures, rounded nuclei with finely clumped chromatin, myriad apoptosis, and tingible body macrophages	Heterogeneous, with approximately half of cases having DLBCL, NOS morphologic features, and others having Burkitt-like or blastoid histology	Diffuse proliferation of medium-large cells with no stromal reaction or fibrosis, starry-sky macrophages, mitotic figures, and apoptosis
Immunohistochemistry	Express membrane IgM with light chain restriction, CD19, CD20, CD22, CD79a, PAX5, the germinal center markers CD10 and BCL6, and strong MYC expression with a Ki-67 of nearly 100%	Germinal center cell of origin, high Ki-67 proliferation fractions, and coexpression of *MYC* and *BCL2* and/or *BCL6*	Typically CD20 positive, *BCL6* positive, *IFR4/MUM1* negative, and variable with respect to CD10 expression, Ki-67 positivity, and *MYC* expression
Notable clinical features	Sporadic BL presents at median age of 30 years, commonly has abdominal involvement and extranodal involvement	Presents in older adults, typically advanced-stage disease with extranodal site involvement and elevated LDH	Presents in older adults, typically advanced-stage disease, elevated LDH, IPI ≥3
Prognostic factors	Aged ≥40 years, ECOG PS ≥2, LDH >3 × ULN, CNS involvement	Advanced-stage IPI, LDH >3 × ULN, leukocytosis, CNS involvement	IPI
Frontline therapy	Low risk: R-CODOX-M, DA-EPOCH-R, R-Hyper-CVAD High risk: R-CODOX-M/R-IVAC, DA-EPOCH-R, R-Hyper-CVAD	DA-EPOCH-R, R-CODOX-M/R-IVAC, R-Hyper-CVAD	No clear standard, DA-EPOCH-R, R-CODOX-M/R-IVAC, R-Hyper-CVAD, R-CHOP

BL, Burkitt lymphoma; CNS, central nervous system; CODOX-M, vincristine, doxorubicin, cyclophosphamide, cytarabine, and methotrexate; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; IGH, immunoglobulin heavy chain; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CODOX-M/R-IVAC, rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, cytarabine, intrathecal methotrexate, and cytarabine; R-Hyper-CVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine; ULN, upper limit of normal.

tiuxetan.[80] Collectively, these studies highlight the possibility that R-CHOP can be associated with good clinical outcomes in patients with early-stage, nonbulky disease and an IPI of 0.

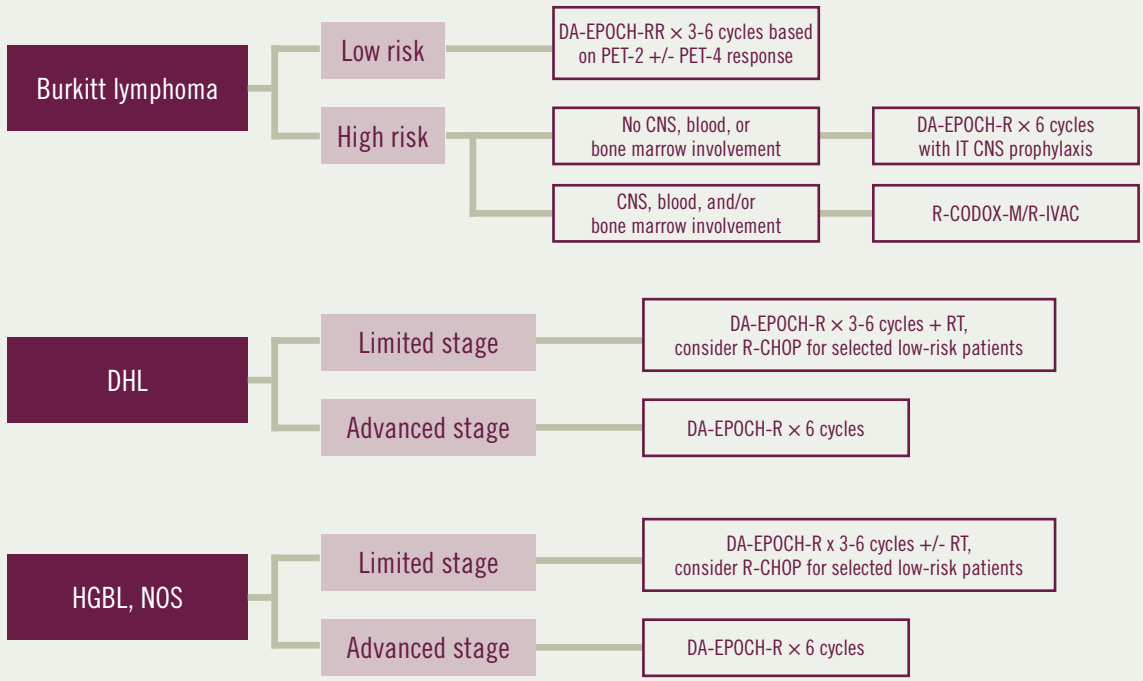
The more intensive BL regimen R-CODOX-M/IVAC demonstrated a 2-year PFS rate of 68% in a phase 2 clinical trial that also enrolled patients with CNS involvement at presentation.[81] The aforementioned multicenter study of DA-EPOCH-R in aggressive B-cell lymphomas enrolled 10 patients (19% of the cohort) with HGBL, NOS; overall, the 4-year EFS of the cohort was 71.0%.[50] Notably, patients up to 80 years of age could enroll in this trial, emphasizing that DA-EPOCH-R is feasible in older adults despite its dose intensity. The role of CNS prophylaxis in HGBL, NOS is unclear, given a paucity of data, although notably R-CODOX-M/IVAC includes multiple agents with CNS activity, and DA-EPOCH-R was given with intrathecal methotrexate prophylaxis in the multicenter trial. Given that DA-EPOCH-R is as effective as R-CHOP in DLBCL,[82] our preference in the absence of more definitive data is to treat these patients with DA-EPOCH-R, as this appears more effective than R-CHOP in the high-grade histologies of DHL and BL and not inferior to R-CHOP in DLBCL. We still consider use of R-CHOP in select low-risk and older patients.

Salvage therapy for relapsed/refractory HGBL, NOS is extrapolated from DLBCL treatment paradigms, given that little data exist specifically for HGBL, NOS.[83,84] Anti-CD19 CAR T-cell therapy represents a promising treatment strategy for relapsed/refractory disease, given its excellent outcomes in other aggressive B-cell NHLs, including DHL. ZUMA-1 (NCT02348216) did include 2 patients with HGBL, NOS, and a real-world study included 17 patients with HGBL, NOS who received CAR T-cell therapy with axicabtagene ciloleucel, with a response rate of 88%.[55,85] We hope that future work will evaluate other novel agents such as tafasitamab, polatuzumab vedotin, loncastuximab tesirine, and bispecific antibodies, as well as expand the role of CAR T-cell therapy in this disease.

Conclusion

The aggressive B-cell lymphomas BL, DHL, and HGBL, NOS are unique

FIGURE. **How We Treat High-Grade B-Cell Lymphomas**



CNS, central nervous system; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DA-EPOCH-RR, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (the latter given as 2 doses per cycle); DHL, double-hit lymphoma; HGBL, NOS, high-grade B-cell lymphoma, not otherwise specified; IT, intrathecal; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PET-2/PET-4, positron emission tomography scan after cycle 2/positron emission tomography scan after cycle 4; R-CODOX-M/R-IVAC, rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, cytarabine, intrathecal methotrexate, and cytarabine; RT, radiotherapy.

diseases, each with specific pathogenesis and biology (**Table**). Insights into the molecular biology of these disease have enabled new classifications and personalization of therapy. Prospective multicenter studies have established multiple intensive regimens as viable therapeutic options for BL as well as DA-EPOCH-R for DHL. HGBL, NOS remains a disease with limited data to guide treatment selection, but at this juncture, more intensive regimens are often favored (**Figure**). Additional studies are warranted to optimize therapy in these aggressive diseases, especially for older adults and in the relapsed setting. ■

DISCLOSURE: **JSA** reports consulting for AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Century, Epizyme, Genentech, Genmab, Incyte, Kite Pharma, Kymera, Lilly, MorphoSys, Mustang Bio, Ono Pharma, and Regeneron; **PCJ** reports consulting for AstraZeneca.

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Recent Advances in Multiple Myeloma: Applying Real-world Evidence to Clinical Practice

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Following on the heels of the 2022 American Society of Clinical Oncology Annual Meeting, several experts in multiple myeloma sat down to discuss real-world evidence as it applies to the treatment of patients with multiple myeloma in today's treatment landscape. **Rafael Fonseca, MD**, professor of medicine and director for Innovation and Transformational Relationships at Mayo Clinic in Phoenix, Arizona, led the discussion, joined by **Luciano Costa, MD, PhD**, professor of medicine–hematology and oncology in the Department of Medicine at University of Alabama at Birmingham O'Neal Comprehensive Cancer Center; **Ajay K. Nooka, MD, MPH**, director of the Myeloma Program and an associate professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine, and medical director of the Winship Data and Technology Applications Shared Resource at Winship Cancer Institute of Emory University in Atlanta, Georgia; and **Matthew James Pianko, MD**, a clinical assistant professor at the University of Michigan Health in Ann Arbor.

"Randomized controlled trials [RCTs] are done specifically for a reason: regulatory approvals and to clearly identify the safety [profile] of the specific drug in evaluation. This is done in a cohort of patients that is preselected. These patients must qualify for all the inclusion criteria. Unfortunately, that patient population does not reflect those we treat daily," Nooka said. "There are guiding principles from the RCTs in terms of the regulatory aspects, but when we treat real patients, there's complexity and diversity."

Nooka offered the experience of 1000 real-world patients treated at Emory University from January 2007 through August 2016 who were consecutively treated with induction lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVd) therapy followed by risk-adapted maintenance. At the time the data were published, the median overall survival (OS) was 78.2 months (95% CI, 62.2-94.2) for high-risk patients and had not been reached for standard-risk patients. Rates of OS at 5 years were 57% and 81%, respectively, and 10-year rates were 29% and 58%.[1]

"If you look at the SEER [Surveillance, Epidemiology, and End Results] data set, the 5-year survival [rate in multiple myeloma is] 58%.[2] Clearly, there's a discrepancy [in outcomes]," said Nooka. "Offering the right treatments to patients and understanding where to intensify and where to pull back is important. These could all be evaluated now that we do have long follow-up of greater than 10 years."

Real-world Use of Systemic Therapy for Transplant-Eligible Disease

In patients with frontline transplant-eligible multiple myeloma, the panel agreed that few circumstances justify opting for a 3- vs a 4-drug regimen, with many clinicians being early and enthusiastic adopters of monoclonal antibodies plus traditional therapy backbones.

Limitations of adding that fourth drug, such as daratumumab (Darzalex) or isatuximab (Sarclisa), may relate to reimbursement issues or the potential risk of infections, but panelists agreed that the risk-benefit ratio favors quadruplets.

Digging Into Optimal Therapy Cycles

One main consideration when using any frontline regimen in this setting is the number of cycles of induction therapy necessary to induce a favorable response prior to proceeding to transplant. Nooka said the key is to balance the duration of therapy with an adequate response, as adverse effects (AEs) are liable to increase in step with the likelihood of an adequate response.

"The response flattens after a few cycles, so there should be a desired target response to go to consolidation with the transplant," he said. "I limit these to between 4 [and] 6 cycles and if the desired response is greater than a partial response, I'm ready to move forward."

Fonseca echoed this sentiment, stating that the use of 4 cycles is informed by real-world experience and is relatively standard unless patients experience suboptimal response. Similarly, Costa agreed that 4 cycles of induction are typical before pushing to transplant but added that the use of minimal residual disease (MRD) data following successful induction may stand to influence how clinicians approach this going forward.

Harnessing Minimal Residual Disease to Inform Treatment

Considering the use of MRD in a response-adaptive treatment approach is being tested in numerous ongoing RCTs, with positive results potentially standing to inform future drug indications. However, for some on the panel, use of MRD as a predictive tool to guide treatment selection is still far from reality.

For one thing, Pianko said MRD can serve to inform a conversation about treatment decisions with patients, but in an era with clear treatment pathways, its use as a definitive tool to guide therapy is still "murky." Nooka said looking at MRD results is great for prognosis, but a single outcome at any given time should not be weighted too heavily into decision-making because MRD dynamics are liable to change at varying time points throughout treatment.

Costa detailed trials that are using MRD by next-generation sequencing to shape response-adapted approaches, such as the phase 2 MASTER trial (NCT03224507) examining daratumumab, carfilzomib (Kyprolis), lenalidomide, and dexamethasone (Dara-KRd) for the management of frontline multiple myeloma. In 80% of study participants treated with the regimen, MRD negativity defined as 10^{-5} was achieved, and nearly all patients were able to stop therapy after autologous transplant without disease progression or MRD resurgence.[3]

Another ongoing phase 3 trial called MIDAS (NCT04934475) will determine whether MRD data can inform the use of isatuximab plus KRd with or without transplant in patients with multiple myeloma who are younger than 66 years.

> "There are guiding principles from the randomized clinical trials in terms of the regulatory aspects, but when we treat real patients, there's complexity and diversity."
>
> AJAY K. NOOKA, MD, MPH

Key Considerations in Transplant-Ineligible Disease

To kick off the discussion of treating transplant-ineligible multiple myeloma, Fonseca reviewed trials that led to approved therapies in the space (**FIGURE**), namely SWOG S0777 (NCT00644228), ALCYONE (NCT02195479), MAIA (NCT02252172), and TOURMALINE-MM2 (NCT01850524).[4-7]

He then pivoted to real-world data on attrition rates between lines of therapy for patients who are not eligible for transplant showing that of 22,062 patients, fewer than half (43%) went on to receive subsequent therapy after their first treatment. Those receiving only 1 line of therapy were significantly older, with higher mean Charlson Comorbidity Index (CCI) scores and incidences of comorbidities.[8]

Compounding this effect, the ability of patients to achieve a deep response drops off from first to later lines of therapy, with evidence from a study in 2016 showing that complete responses and very good partial responses occur in up to three-fourths of patients (74%), but tail off in the second (58%), third (43%), fourth (32%), and fifth line and beyond (11%).[9]

Top Considerations for Choosing First-line Therapy

These data combined with therapy effects of each approved regimen beg the question of whether the most effective regimen should be used up front or saved for later lines of therapy.

To answer this question, Fonseca reviewed data presented by his team at the 2021 American Society of Hematology

Annual Meeting and Exposition showing that first-line use of daratumumab, lenalidomide, and dexamethasone (DRd) led to better OS vs waiting for second-line treatment. This correlation was seen using attrition rate scenarios of 58.8% and 27.2%. The most optimal sequence examined was DRd, then a regimen containing pomalidomide (Pomalyst) or carfilzomib in the second line, followed by frontline RVd and a second-line daratumumab-containing regimen, and then frontline Rd and a second-line daratumumab regimen.[10]

"The first treatment is so important because a significant number of these patients may not be receiving the second treatment. What your modeling had shown was if you're able to give them the best treatment, [you may induce up to 9 years of survival or more], similar to what you can get with transplant-eligible patients," said Nooka. "The best treatment is so important because the same treatment given at 2 different times in myeloma may yield 2 different responses or 2 different outcomes. Why not use it at the right time in the first place?"

With these data taken together, Pianko said his number 1 priority in the absence of transplant is finding out what his patients prefer, as quality of life in this setting is the most significant factor to many. "Patients want to have good quality of life for as long as possible. That's our goal of therapy in transplant-ineligible multiple myeloma. There's a balance between toxicities of therapy and goals you're trying to achieve in this population, particularly when patients are frail, elderly, and unfit. You can run into the issue where you're interfering with your own goal of therapy if there are adverse effects of the treatments," he said.

For those patients whose frailty needs to be considered, Nooka said he is still giving a 3-drug regimen but with significantly dose-reduced schedules of each agent. For example, he will still administer DRd to a patient in their 90s but takes the dose of lenalidomide down to 5 mg because the progression-free survival (PFS) results from the MAIA trial are so compelling. Additionally, he tapers off the dexamethasone after the first year and continues maintenance with daratumumab, lenalidomide, or both.

> **"There is a real need to understand both the burden of infectious outcomes as well as the consequences to patients who suffer from these infections. This is, unfortunately, a common and severe problem to date in our field."**
>
> MATTHEW JAMES PIANKO, MD

Pianko's strategy for choosing maintenance at this point comes back to considering what is best for the patient's quality of life. "If everything is going well, the relative benefit is to simplify treatment and go to an all-oral maintenance program where possible. For some patients, there may be value to continue 2-drug maintenance. But I'm also weaning off all steroids for my transplant-eligible patients at somewhere between 8 and 12 cycles to avoid all the consequences of that."

On the other side of that coin, Fonseca said some of his patients prefer coming in for monthly infusions rather than relying on a daily pill for their maintenance strategy. Regardless, he said, most patients make it to 2 years of maintenance and then tail off rather than receiving continuous therapy.

Comparing Doublet and Triplet Therapy

Nooka said when he is delivering treatment in the transplant-ineligible setting, he almost always opts for use of 3 drugs over 2 unless there are true contraindications for one of the agents in the regimen.

To back that up, Fonseca revisited previously reported data from the MAIA trial showing that DRd was superior to Rd alone in terms of PFS for both nonfrail (HR, 0.48; 95% CI, 0.34-0.68; $P < .0001$) and frail individuals (HR, 0.62; 95% CI, 0.45-0.85; $P = .0003$).

To back this up, Pianko went as far as to question the reason for patients' frailty and whether withholding more efficacious treatment for the sake of avoiding AEs offers an advantage or a disadvantage to patients. "You can really salvage those patients who are frail from myeloma. Of course, there are situations where it's impossible, but these data lend toward pushing for a third drug."

Considering Patient-Specific Factors in a Real-world Setting

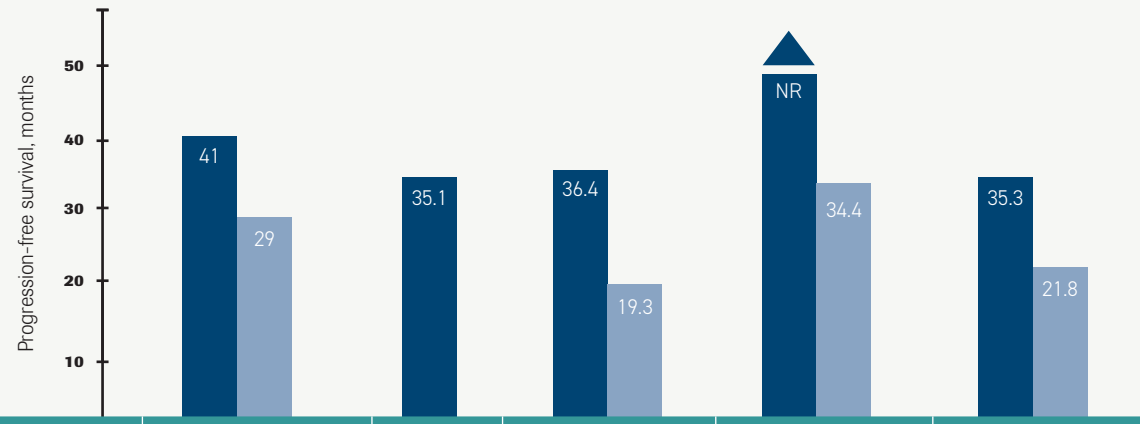
Frailty

To determine frailty in a patient who is ineligible for transplant but may be able to receive systemic therapy for their disease, Pianko considered current approaches to establishing a patient's status.

International Myeloma Working Group (IMWG) frailty score, age, CCI score, and ECOG performance status can all factor in, but the challenge in the clinic is finding time to use these tools. Pianko went on to say he used more of a "functional approach," such as observing how the patient gets around the office or performs a 6-minute walk test. Although it's a subjective measure, it may offer a more practical approach to treatment "given the pressures on time" that are limiting factors in some environments.

"In the transplant-ineligible setting, refining our frailty assessments are key,

FIGURE. **Pivotal Data in Newly Diagnosed Transplant-Ineligible Multiple Myeloma**



Therapy arms	RVd vs Rd	RVd-lite	Dara-VMP vs VMP	DaraRD vs Rd	IRd vs Rd
Trial	SWOG S0777	NCT01782963	ALCYONE	MAIA	TOURMALINE-MM2
Patients, N	225 vs 235	50	350 vs 356	368 vs 369	351 vs 354
Median age, years	63	73	71	73	73
Median follow-up, months	84	30	40	56	54
HR for PFS	0.742 (96% CI, 0.594-0.928)	N/A	0.42 (95% CI, 0.34-0.51)	0.53 (95% CI, 0.43-0.66)	0.83 (95% CI, 0.676-1.018)
HR for OS	0.71 (95% CI, 0.54-0.93)	N/A	0.60 (95% CI, 0.46-0.80)	0.68 (95% CI, 0.53-0.86)	0.998 (95% CI, 0.790-1.261)

Dara, daratumumab; IRd, isatuximab, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; RVd, lenalidomide, bortezomib, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

and there are clear arguments for optimizing your myeloma therapy and trying to get your patients on the best therapy possible," said Pianko.

Nooka confirmed this, expressing frustration in quantifying frailty that is aggravated by the 7 or so scales that are commonly used. Additionally, he pointed out limitations of frequently used measures, such as the automatic classification of patients over 75 years of age as frail by the IMWG frailty score, which may not properly characterize patients in the real-world setting.

"We can't just group them into buckets and start making dose reductions when they don't need them or giving them doublets when they would benefit from triplets," said Nooka.

Infectious Outcomes

According to Pianko—who attested to his primary interests in infections, immunity, and the potential impacts of the microbiome on outcomes in myeloma—results of RCTs underestimate the potential risks of some standard treatments in more frail, older populations or in those who would not otherwise qualify for clinical trials.

"There is a real need to understand both the burden of infectious outcomes as well as the consequences to patients who suffer from these infections. This is, unfortunately, a common and severe problem to date in our field," Pianko said. "There have been some interesting data out of the UK looking at antibiotic prophylaxis, but there are some challenges there [because they] don't necessarily reflect what we use in real practice in the United States."

Some of the most pressing concerns with using antibiotic prophylaxis in this patient population stem from their possible impact on treatment outcomes and survival. In some data sets, broadly applying antibiotic prophylaxis reduced the rates of fever and death, yet more patients died of progressive myeloma than did those of a standard-of-care group. Additionally, Pianko said some evidence from his own research has pointed to potentially more abundant microbiota in patients who are MRD negative, which could have implications for who ends up receiving prophylaxis.

"A randomized clinical trial to understand that seems like a tall order," Pianko said. "There's a need for real-world data to understand how infections interact with treatments that we use."

Cytogenetics and Risk Status

No conversation regarding real-world outcomes would be complete without also looking at risk stratification, with the panelists first visiting the use of cytogenetic risk factors such as deletion (del)17p; translocations t(4;14), t(14;16), t(14;20); and 1q gain (1q+). However, not all classification systems consider these factors equally. In his experience, Fonseca noted, patients presenting with those cytogenetic risk factors rarely have good outcomes in the clinic.

Pianko had concerns with classification of disease risk using only cytogenetics, as he has seen patients with favorable baseline characteristics who still behave as though they harbor these genetic biomarkers. "You meet your patient and treat them with what you think is the best therapy based on their presentation. Over time, a standard-risk patient behaves in a functionally high-risk way. They have an early relapse, and you are surprised," he said, adding that MYC amplification always makes him "raise an eyebrow" about disease prognosis.

Another challenge that may limit the use of cytogenetics in risk assessment is the lack of standardization in the reporting of pathology results, which is particularly poignant in the evaluation of 1q+. The number of copies of 1q is important in determining risk, but most patients have their bone marrow evaluated several months prior to seeing their medical oncologist and the appropriate information is lacking.

Future Directions

To conclude, the panelists considered what is needed in the immediate future to clarify some of their outstanding questions. "If you look at the RVd data set from the Emory group [discussed by Nooka earlier], we can't [always] wait 10 years to get those data to be offering the best therapy to our patients. Because there has been adoption of 4-drug regimens both in academia and the community, there's an opportunity to look at real-world data and the impact of those therapies outside sometimes too-rigid confines of randomized clinical trials to observe the potential benefits," Pianko concluded. ■

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CONTINUING MEDICAL EDUCATION (CME)

Advanced Renal Cell Carcinoma: Tyrosine Kinase Inhibitors Versus Immune Checkpoint Inhibitors

FACULTY

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LEARNING OBJECTIVES

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

- Compare the mechanisms of action (MOA) of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs), and how the MOA apply to treatment of advanced renal cell carcinoma (RCC)
- Outline phase 3 clinical trial data demonstrating the efficacy and safety of ICIs and TKIs in patients with advanced RCC
- Review the outcomes of clinical trials studying ICIs and TKIs as combination therapy in patients with advanced RCC

RELEASE DATE: August 1, 2022
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It is estimated that in 2022, there will be approximately 79,000 new cases of renal cell carcinoma (RCC) diagnosed and 13,920 related deaths reported in the US.[1] It is among the 10 most common neoplasms in the US, and it is more prevalent among men than women. The 5-year survival rate is 93% for patients given a diagnosis of localized disease, and it decreases based on stage at diagnosis. (regional disease, 72.3%; metastatic disease, 15.3%; unknown, 45.1%).[1]

RCC often is discovered accidentally, and its primary treatment often includes partial or radical nephrectomy, tumor ablation, or active surveillance, depending upon disease stage.[2] Various therapies for relapsed or stage IV disease include tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) are given as monotherapy or in combination.[1] Treatment selection is typically based on the risk of recurrence. Although TKIs and ICIs are generally considered less toxic than systemic chemotherapy, these new drugs can cause significant unanticipated adverse effects (AEs).[3]

In this article, Brian Rini, MD, chief of clinical trials at Vanderbilt-Ingram Cancer Center and Ingram Professor of Medicine in the division of hematology/oncology at Vanderbilt University Medical Center in Nashville, Tennessee, discusses the use of ICIs and TKIs for the treatment of patients with advanced RCC.

Q: What is the mechanism of action of ICIs, and what is the rationale for using them to treat advanced RCC?

RINI: As I explain to my patients, ICIs work by removing the brakes on the immune system. They inhibit proteins that are present on the surface of T cells, which are the functional arm of antitumor immunity.[4] Broadly speaking, ICIs increase inflammation against tumor cells. The overarching goal is to increase the amount of antitumor T cells that are present and active in a given patient. In kidney cancer, which has long been considered very responsive to immunotherapy (IO) dating back decades to treatment with interleukin and interferon, the rationale for using ICIs is that kidney cancer is susceptible to manipulation of the immune system. Along with melanoma, kidney cancer was the first disease involving the testing of novel IO.

Q: What is the mechanism of action of TKIs, and what is the rationale for using them to treat advanced RCC?

RINI: TKIs used to treat kidney cancer include cabozantinib, axitinib, and sunitinib; they are commonly directed against the VEGF receptor (VEGFR). The VEGFR is a protein associated with angiogenesis that is often upregulated in kidney cancer.[5] It is one of the fundamental drivers of disease, and it has been recognized as such for a long time. VEGFR TKIs have been in common use in kidney cancer for at least 15 to 20 years. They're very good at controlling and shrinking disease. They are generally not considered to be curative, but they were really the first wave of active drugs to be developed after cytokines. VEGFR TKIs provide good disease control; they can be given in sequence, but they have the downside of chronic toxicity. These medications are one of the fundamental pillars upon which our modern therapy is based.

Q: What is the rationale for combining ICIs and TKIs for the management of RCC?

RINI: There are several regimens that combine an IO and a TKI in the frontline treatment of advanced clear cell RCC (ccRCC).[2] There are probably 2 main rationales for combining these medications. The first rationale is empirical, in that the drugs have different mechanisms of action. Giving a patient 2 drugs, each with different mechanisms that inhibit the tumor, might give them 2 chances of responding as opposed to 1 drug. The more mechanistic explanation is that VEGF is an immunosuppressive molecule.[6,7] So if we inhibit the action of VEGF with TKIs, then we may allow IO to work better. There's a fair amount of clinical controversy in this case. When the drugs are given together, they are at least additive. I'd probably stop short of saying that they're synergistic.

Q: What AEs are common with ICI/TKI combinations, and what is your approach to managing them?

RINI: As you can imagine, common AEs associated with TKI combinations are those that are common with each agent alone. The TKI component brings fatigue, diarrhea, hand-foot syndrome, and hypertension.[8] Again, the AEs with TKIs are typical of this drug, and we've known about and managed them for years. IO creates inflammatory AEs. I tell patients that it's meant to inflame your T cells against the tumor, but it can also inflame normal organs, such as the skin (ie, rash), or the gut (ie, diarrhea), or, really, any organ. You can see some of the toxicities are overlapping, and some aren't, but, taken together, the most common AEs are fatigue, diarrhea, and rash.

In terms of IO management, the therapy has been around long enough that people understand how to manage immune-mediated toxicity and how to manage TKI toxicity. In these particular combinations, sometimes, there's some overlap of toxicity. For example, in a given patient having diarrhea or liver function abnormalities, you don't necessarily know if it's 1 agent or the other. It is a generally accepted maneuver to just hold the TKI unless the patient is very ill-appearing.[9] Those toxicities should resolve sooner because of the much shorter half-life, depending on the agent. If they don't resolve, then it could be immune-mediated, and you would act appropriately

by prescribing steroids. Because IO/TKI regimens have been around for bit, that sort of general approach is fairly common, but it's not always easy in clinical practice. It's not always easy to differentiate. Sometimes, you think it's 1 drug, and then it's the other. If a patient's critically ill, you're not going to have the time or luxury for this maneuver. You're going to have to admit them and give them steroids and presume it's immune-mediated, because those toxicities can be much more life-threatening.[9]

Q: Can you briefly describe the outcomes of the CheckMate 214 study?

RINI: CheckMate 214 studied ipilimumab (a CTLA-4 inhibitor) and nivolumab (a PD-1 inhibitor) as combination therapy compared with sunitinib (a VEGF TKI), which was the old standard of care.[10] This established the double IO regimen with superiority in terms of overall survival (OS) as the most important end point. More importantly, as we now have 5 years of follow-up from the initial data, it is the hallmark of IO associated with a durable response. There is a higher tail of the curve in both survival, progression-free survival (PFS), and durability of response.

It's the only trial that has looked at an all-immune regimen versus an all-VEGF–inhibiting regimen. Sunitinib, especially in certain populations (eg, patients with favorable risk), has advantages in terms of response rate, PFS, or what we call tumor shrinkage end points. Ipilimumab plus nivolumab has advantages in its durability, in that some patients are able to stop therapy and maintain control.[11] What this really speaks to is that there are different populations of patients, with some benefiting from one drug and some benefiting from another. We've not yet done a good job of teasing out which patient may benefit from which regimen prior to giving therapy.

VEGF is an immunosuppressive molecule. So if we inhibit the action of VEGF with TKIs, then we may allow IO to work better. When the drugs are given together, they are at least additive.

Q: What were the overall results of the KEYNOTE-426 study?

RINI: KEYNOTE-426 studied pembrolizumab (a PD-1 inhibitor) plus axitinib (a small molecule VEGFR inhibitor) against sunitinib control.[12] The results showed advantages in response rates of up to 60% for PFS and OS. This is a common theme to all the IO/TKI regimens. You get the typical outcomes from TKIs (eg, good tumor shrinkage), but you also get the immune component, which, presumably, is contributing to some of the longer-term outcomes, like OS. Pembrolizumab plus axitinib was the first IO/TKI regimen approved by the FDA, and it remains in common use. It is a very well tolerated by patients as well, and it may be among the best tolerated of the IO/TKI regimens.[12]

Q: What is currently known about the utility of lenvatinib plus pembrolizumab for RCC?

RINI: Lenvatinib plus pembrolizumab is the most recently developed and FDA-approved IO/TKI combination. Lenvatinib is a multitargeted TKI that has a broader spectrum of activity than axitinib.[13] Data from the CLEAR trial was impressive in terms of the tumor shrinkage end points.[14] The response rate was 71%, and the PFS was nearly 2 years, with a complete response rate of 16%. It's difficult to compare across trials of different combination regimens (eg, nivolumab plus ipilimumab, nivolumab plus cabozantinib, avelumab plus axitinib) for a variety of reasons, but, at least on the surface looking at those end points, it is the most impressive. The survival signal against sunitinib monotherapy has been extremely consistent across all of these doublets, with a hazard ratio of about 0.7.[12,15-18]

Lenvatinib plus pembrolizumab was recently approved by the FDA; it is fairly commonly used in the community.[19] The 1 caveat would be that lenvatinib can be a difficult drug to give, as it is dosed at 20 mg in this combination, which is a challenging dose for most patients. The vast majority of patients in the trial needed to go down a dose, and that's true in practice, as well.[14] In terms of which IO/TKI double regimen to use—they're all good regimens, as they all extend survival. It's very much the clinician's choice with a balancing of efficacy and toxicity.

Q: Can you briefly discuss the outcomes of the Checkmate 9ER study?

RINI: CheckMate 9ER investigated another IO/TKI combo, cabozantinib and nivolumab, versus sunitinib control.[15] This combination had outcomes similar to those of the other IO/TKI combos in terms of higher response rates and longer PFS and OS compared with sunitinib monotherapy. The toxicity profile is probably in the middle between pembrolizumab monotherapy and the lenvatinib/pembrolizumab combination. So, again, it's really the clinician's choice in regard to their familiarity with and their preference in terms of managing TKI-related toxicities. It is also FDA approved and used relatively commonly.[20]

Q: What is your approach to the use of adjuvant therapy in frontline RCC?

RINI: Historically, there have not been any

approved drugs for the management of kidney cancer in the adjuvant setting. A few years ago, there was a wave of TKIs tested in the adjuvant setting that produced largely negative results, except for a single study of sunitinib.[21] This study showed disease free–survival (DFS) advantages. Sunitinib is not commonly used because of limited clinical benefit and toxicity; in addition, many other trials demonstrated negative results. The single study mentioned was an outlier. Then, last year, a trial of adjuvant pembrolizumab in resected high-risk kidney cancer showed a DFS advantage that has persisted in follow-up.[22] There's no OS advantage yet. Pembrolizumab was FDA approved in that setting, and it is commonly used.[23]

There are other trials of IO that have been done or that are finishing accrual; results will be reported over the next year or so. We'll see how this story evolves in terms of the use of adjuvant IO. Clearly, pembrolizumab is a standard, and it will be the control arm of our future trials pending the outcome of these other studies. I do give pembrolizumab in practice, but I certainly do caution patients against the relatively small percentage of patients who experience significant, or even lifelong, toxicities. Decision-making in an adjuvant setting is very different than in a metastatic setting because many of those patients are not destined for recurrence, so you can't possibly help them—you can only hurt them. However, in the right patient who understands the benefit and risks, I would use pembrolizumab.

Q: How do you manage patients with refractory RCC?

RINI: The vast majority of patients, including those whom I treat, are getting an immune-based doublet up front. We don't yet know if sequential IO has activity in kidney cancer. There are ongoing trials, but I don't do it in practice yet. Somewhat TKI monotherapy is the default standard in refractory kidney cancer.[2] Participation in a clinical trial is always the right answer for patients with refractory disease. In my opinion, if you've moved away from immune-based therapy, you are no longer able to cure that patient, and you are just aiming for disease control. I use TKI monotherapy, including cabozantinib, in the second line, because I tend to give axitinib plus pembrolizumab or lenvatinib plus pembrolizumab in the front line. Lenvatinib plus everolimus is a doublet that has activity, although it has a fair amount of toxicity.[24] I'm fairly sensitive to the toxicities of therapy in the refractory setting. As patients move through lines of therapy, they become less able to tolerate toxicity. Again, if I'm not curing that patient, I'm personally reluctant to accept higher levels of toxicity, even if it buys me a little more response rate or another scan interval or the patient to be without progression. This is just knowing the patient and the drugs and then deciding when you might be a little more aggressive and not. It's hard to put into words, but there is an art to applying these therapies. Refractory kidney cancer changed dramatically when IO moved up front. We are now just starting to do trials in the IO-refractory setting. Over the next few years, we'll redefine the landscape, but, for now, we're kind of stuck with TKI monotherapy.

> **We've not done a great job of developing biomarkers in RCC, but there are efforts ongoing using some newer gene-expression profiles and other tools. The field is ripe and ready to do prospective trials that are biomarker-based.**

Q: How does the management of ccRCC compare with that for non–ccRCC (nccRCC)?

RINI: All of the really good data tends to be in ccRCC, because it's a much more prevalent histologic subtype. In all, nccRCC makes up about 10% of total RCC cases.[25] We tend to borrow the data from trials in ccRCC and apply them to nccRCC. There are very few large, randomized trials in nccRCC, which is not the greatest approach, but it tends to be what we do. These studies have very limited data sets, and they are often single-arm studies. There was a small study report of cabozantinib versus sunitinib in papillary kidney cancer that showed advantages to cabozantinib.[26,27] Many clinicians have used that set of data to either give cabozantinib by itself or the combination of cabozantinib and nivolumab up front to papillary kidney cancer patients, a subtype of nccRCC.

We struggle to understand the biology of nccRCC. There are no nccRCC-specific drugs. Again, we borrow from the ccRCC experience. It is a very common question I hear from clinicians, who ask, "How do I manage nccRCC?" I tend to give cabozantinib plus nivolumab up front based on that small study I mentioned. I believe that all patients should get IO up front, because it provides durable control. After that, clinical trials are always an option for nccRCC. Again, we've done a better job recently of enrolling patients in nccRCC trials and trying to discover drugs, but it's still way behind ccRCC management.

Q: The treatment of other tumor types are further ahead; it has incorporated biomarkers and targeted therapies. Why do you think biomarkers are not used in the management of RCC?

RINI: The reason is that with kidney cancer, we're targeting the stroma,

immune cells, and blood vessels versus the tumor.[28] Unlike lung cancer, where you have EGFR and guiding tumor-directed therapy, RCC does not offer similar factors to clinicians.[29] It appears to be much trickier to find biomarkers for the types of drugs we're giving, because we're not giving directly tumoricidal drugs.

Q: Where do you see the field of treatment for kidney cancer going in the future?

RINI: I hope kidney cancer treatment in the future is much more biologic-based and biomarker-driven. So far, we have not discussed anything about biomarkers or how we select patients, as it currently is empiric and up to the clinician. It seems to depend on what trial the clinician was involved in or what their favorite drug is, which is not really a great way to treat patients. It's certainly not an individualized way to treat patients. We've not done a great job of developing biomarkers in RCC, but there are efforts ongoing using some newer gene-expression profiles and other tools. The field is sort of ripe and ready to do prospective trials that are biomarker-based. We're doing one such trial at Vanderbilt. I know there are other efforts going on in cooperative groups and industry to really try to define patients by biologic signatures instead of by clinical risk factors.

We're a long way from that being a reality, but we're finally starting to move toward it. That would be one main aspect of where we need to go, and the other, of course, is novel mechanisms. Our drugs fall into basically 2 buckets, IO and antiangiogenic therapy. However, there is a whole group of patients with other biologic drivers of their disease that we're not helping with those drugs. We just haven't developed those drugs yet, but it's a whole untapped area that could involve tumor cell metabolism, antimyeloid compounds, or other mechanisms. In the next 5 years, we're going to see, perhaps, a third bucket of therapy. ■

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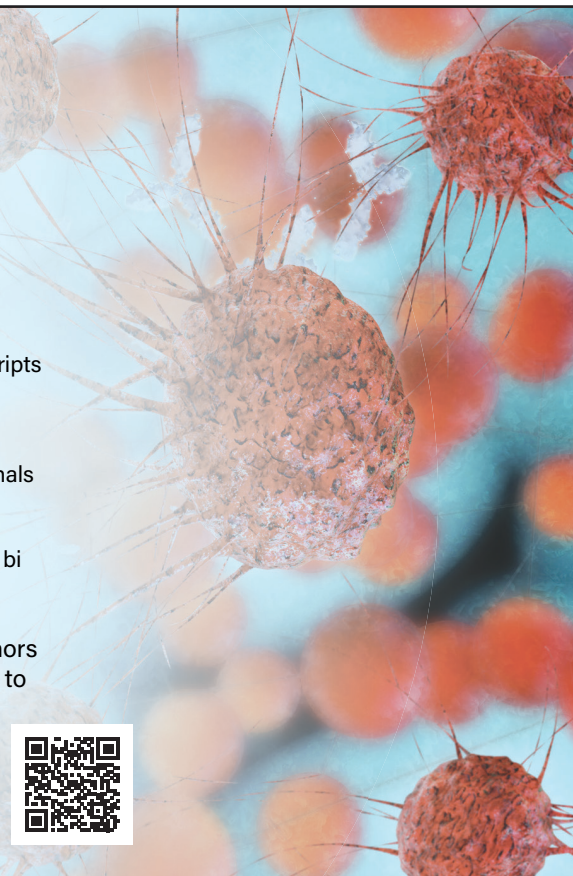


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Your mental health partner

We take the guesswork out of mental health care referrals, with insurance accessible care that treats the whole person — not just the diagnosis. We're a trusted leader in mental health, and your partner in patient care.

Our Services

- Psychiatric Evaluation
- Medication Management
- Therapy
- Pediatric Mental Health Care
- Family/Marital Counseling

We are adding access to more services frequently.

mindpath.com/referrals

Fax: 855-420-6402

MINDPATH HEALTH

Offering same-day appointments

Introducing Mindpath On Demand, offering a fast and convenient way to get a same-day appointment, providing patients with rapid care.

Three easy steps:

1. Call 866-386-1445
2. Enter waiting room and complete documentation https://portal.mendfamily.com/
3. See provider quickly, allowing patients to get a new prescription or refill that same day

Mon–Thurs: 8am–4pm for Therapy
Tues: 1pm–4pm for Medication Management
Wed: 7am–11am for Medication Management

MINDPATH ON DEMAND

We're here to help. Refer *today.*

Fax or complete our online referral form.

In-network with most patients' insurance

More accessible care - new insurance plans are added regularly. Visit our website to learn more.

BlueCross BlueShield
Cigna
friday health plans
Humana
United Behavioral Health
OPTUM