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PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

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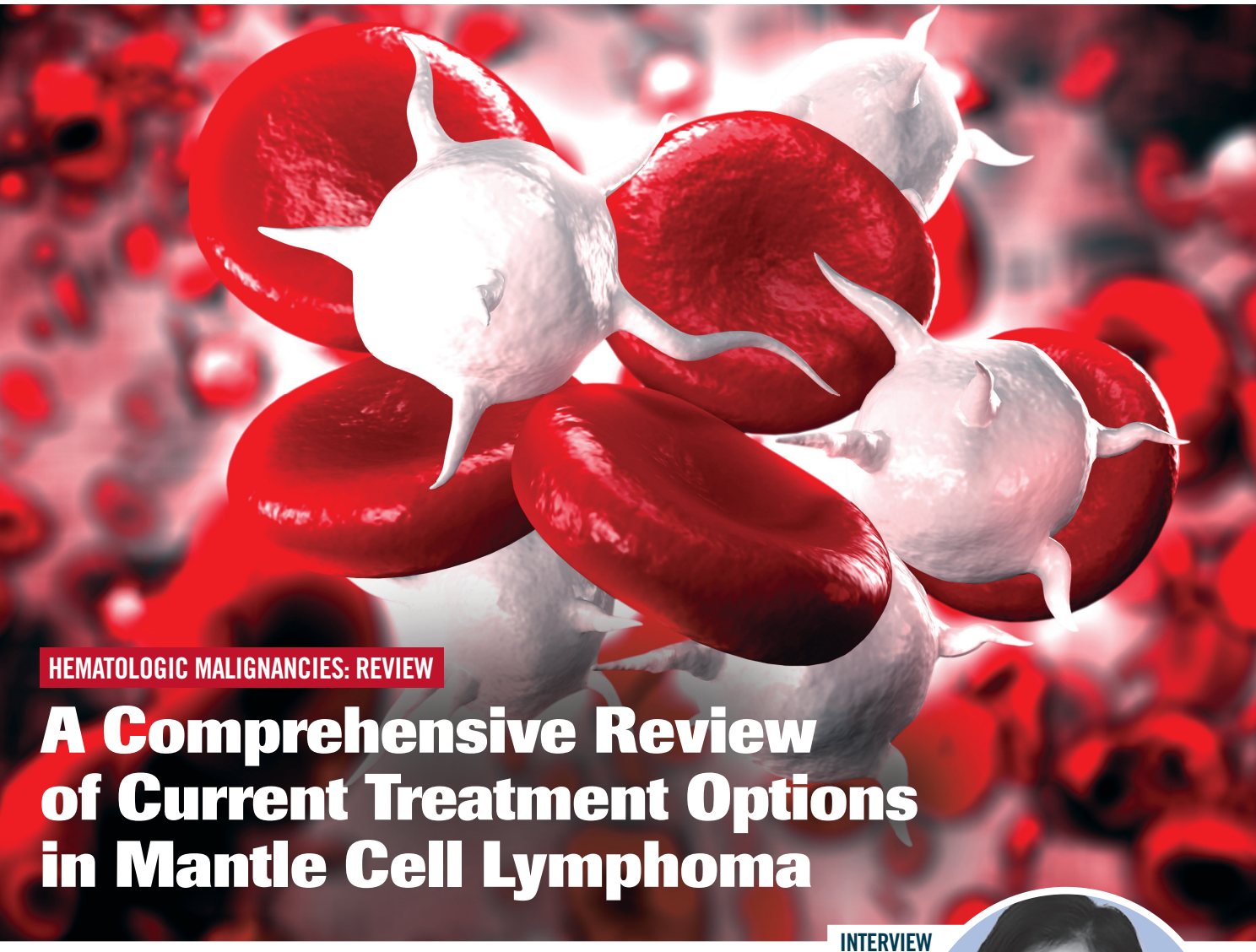

HEMATOLOGIC MALIGNANCIES: REVIEW

A Comprehensive Review of Current Treatment Options in Mantle Cell Lymphoma

INTERVIEW

Avyakta Kallam, MD, on Mantle Cell Lymphoma

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RYBREVANT®
(amivantamab-vmjw)
Injection for IV Use | 350 mg/7 mL (50 mg/mL)

ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of *EGFR*+ mNSCLC, few challenges have been tougher to navigate than *EGFR* exon 20 insertion mutations.[1-10]

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with ***EGFR* exon 20 insertion mutations,** as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[11]

INDICATION

RYBREVANT® (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions

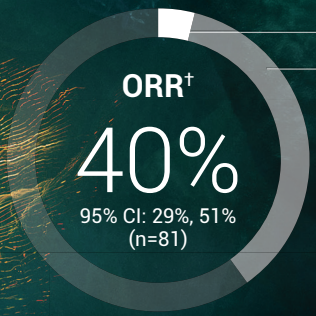
RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

In a multicenter, open-label, multicohort study[11]*

Results for tough-to-treat disease



- 3.7% of patients achieved a CR
- 36% of patients achieved a PR

- Efficacy was evaluated by ORR† and DOR[11]

MEDIAN DOR WAS 11.1 MONTHS[11]‡
(95% CI: 6.9, NE)[11]

*CHRYSALIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBREVANT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had *EGFR* exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBREVANT® was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.[11]

†According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).[11]

‡Based on Kaplan-Meier estimates.[11]

The safety of RYBREVANT® was evaluated in the CHRYSALIS* study (n=129)[11]:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity[11]
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%)[11]
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%)[11]
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion[11§]

§Based on the safety population, N=302.

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CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non-small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT®.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

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

References: 1. Clinical Test Report: Oncomine™ Dx Target Test US. Thermo Fisher Scientific. Accessed October 13, 2021. https://tools.thermofisher.com/content/sfs/brochures/oncomine-dx-target-test-sample-report.pdf **2.** Chiang AC. *BMC Cancer*. 2020;20(1):356. **3.** Robichaux JP. *Nat Med*. 2018;24(5):638-646. **4.** Riess JW. *J Thorac Oncol*. 2018;13(10):1560-1568. **5.** FoundationOne®CDx. Technical specifications. Foundation Medicine. Accessed October 13, 2021. https://assets.ctfassets.net/w98cd481qyp0YqqKHaqQmFeqc5ueQk48w/0a34fcdaa3a71dbe460cdcb01cebe8ad/F1CDx_Technical_Specifications_072020.pdf **6.** Arcila ME. *Mol Cancer Ther*. 2013;12(2):220-229. **7.** Oxnard GR. *J Thorac Oncol*. 2013;8(2):179-184. **8.** Naidoo J. *Cancer*. 2015;121(18):3212-3220. **9.** Chen D. *Onco Targets Ther*. 2016;9:4181-4186. **10.** Girard N. Presented at: IASLC 2020 World Conference on Lung Cancer; January 28-31, 2021; Singapore. **11.** RYBREVANT® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

janssen Oncology
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cp-213274v2

RYBREVANT (amivantamab-vmjw) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in Full Prescribing Information]*, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population *[see Adverse Reactions]*, IRR occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Interstitial Lung Disease/Pneumonitis

RYBREVANT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population *[see Adverse Reactions]*, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Dermatologic Adverse Reactions

RYBREVANT can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population *[see Adverse Reactions]*, rash occurred in 74% of patients treated with RYBREVANT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients *[see Adverse Reactions]*.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Ocular Toxicity

RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population *[see Adverse Reactions]*, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT. *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions]*
- Ocular Toxicity *[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.

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash and paronychia.

The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

Table 1 summarizes the adverse reactions in CHRYSALIS.

Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

Adverse Reactions	RYBREVANT (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue[b]	33	2.3
Edema[c]	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia[d]	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[f]	37	2.3
Cough[g]	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis[h]	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain[i]	11	0.8
Vascular disorders		
Hemorrhage[j]	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy[k]	13	0
Dizziness	12	0.8
Headache[l]	10	0.8

[a] Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis

[b] Fatigue: asthenia, fatigue

[c] Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling

[d] Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis

[e] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[f] Dyspnea: dyspnea, dyspnea exertional

[g] Cough: cough, productive cough, upper airway cough syndrome

[h] Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis

[i] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[j] Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage

[k] Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy

[l] Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

RYBREVANT™ (amivantamab-vmjw) injection

Table 2 summarizes the laboratory abnormalities in CHRYSALIS.

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT+ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

+ The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

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 amivantamab products may be misleading.

In CHRYSALIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in

multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivantamab-vmjw in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

Pediatric Use

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

Geriatric Use

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions *[see Warnings and Precautions]*.

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions]*.

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT *[see Warnings and Precautions]*. Advise patients to apply alcohol free emollient cream to dry skin.

Ocular Toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions]*.

Paronychia

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. *[see Warnings and Precautions, Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose *[see Use in Specific Populations]*.

Product of Ireland

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

cp-213278v1

PRACTICAL, PEER-REVIEWED PERSPECTIVES
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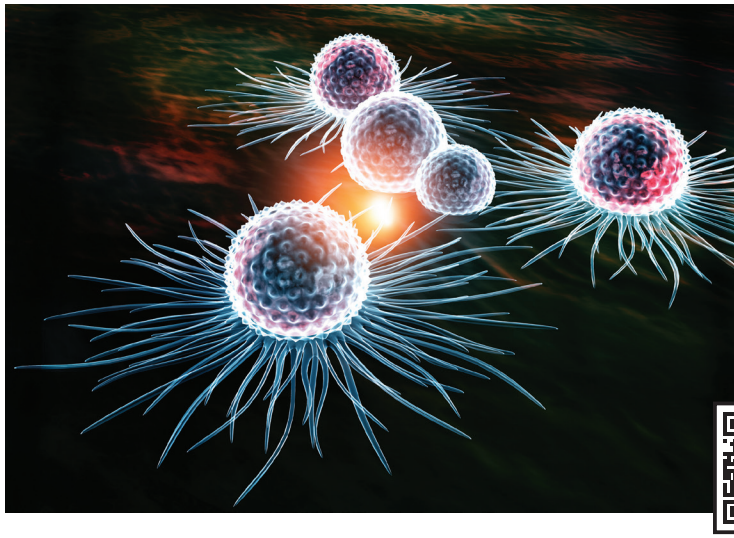

WEB FEATURE

Generic Drug Shortage Is Creating Treatment Barriers Across Cancer Space

In February 2023, the FDA announced a shortage of carboplatin and cisplatin, both of which are treatments that are often used in combination with other therapies for curative intent in patients with cancer. Notably, these shortages have had a negative impact across most disease states, including in the gynecologic and genitourinary cancer spaces.

Cancernetwork.com/DrugShortages_8.23

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PUBLISHER'S NOTE

OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

Edward S. Kim, MD, MBA, FACP, FASCO
Lung Cancer Editorial Board Member
Kim was recently featured on the *Today* show alongside his daughter for a viral TikTok they collaborated on. The father-daughter duo was seen showcasing their outfits for the opening night of Taylor Swift's Era's Tour. Currently, the video has over 980,000 views.

Scan to Watch our interview with Dr. Kim

Jun Gong, MD
Social Media Editorial Board Member
@jgong15
Gong, from Cedars-Sinai, has accepted a position as social media editorial board member for CancerNetwork and the journal *ONCOLOGY*. He will be hosting and facilitating different social events with his colleagues. Areas of focus are breaking research, recent FDA approvals, and conferences. Interested in this new initiative? Contact us today!

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Drug Shortages: What Can Be Done to Alleviate Them?

Oncology drug shortages have been a chronic issue for decades in the United States. In retrospect, the shortages seem to be cyclical, occurring about every 8 to 10 years. From 2001 to 2011, 58 drugs were classified as under a shortage. However, in 2011, there was a marked increase—with 267 agents on the shortage list. There seemed to be a decrease in the shortage issues from 2017 to 2021 and then a marked rise with 160 agents on shortage in 2022. So far in 2023, 301 agents are on the shortage list. The drug shortages increased by at least 30% from 2021 to 2022.[1]

Most recently, 15 commonly used oncology agents are on the FDA shortage list, including carboplatin, cisplatin, 5-fluorouracil, fludarabine, methotrexate, capecitabine, and azacitidine. We have all had issues with obtaining these agents for the care of our patients. And because many of these agents are used with curative intent or for treatments that prolong the time in remission, these shortages are overly concerning.

What are the issues causing these shortages? Although generic medications save money for the health care system, they are often not profitable for the manufacturers, leaving little incentive to invest in generic manufacturing. Also, the supply chain is fragile, so disruption of a single manufacturing facility can turn into a widespread shortage.

This is a widespread issue because, in some cases, generic medications are sometimes manufactured at only 1 or 2 sites worldwide. For example, Intas Pharmaceuticals Ltd, which is located in India, supplies a substantial portion of the generic cisplatin used in the United States.[2] If one plant goes offline due to quality issues or other reasons, this can produce a major downstream effect with oncology drug shortages. FDA guidance for quality control and supply chain modifications may be beneficial but is limited in scope.

Several organizations are trying to work on this issue. For example, the American Society of Clinical Oncology has published several recommendations including reprioritizing the nonessential use of chemotherapy in limited supply, increasing the dosing interval, minimizing waste by rounding down to optimize vial sizes, and prioritizing curative treatments.[3]

Civica Rx is a nonprofit organization with a mission to reduce and prevent drug shortages. Civica Rx signs 5-year, fixed-price, fixed-quantity contracts that include 6 months of inventory. Civica Rx members, consisting of several large health systems, identify which products are at elevated risk of shortage. Civica Rx also vets the manufacturers with whom it signs long-term agreements.

Although promising, these efforts have not been widely adopted because hospitals are reluctant to pay for resilience. The members of the Civica Rx cooperatives represent one-third of hospital beds, but fewer than 10% of the generic sales go through Civica Rx.[4] Standard contracts might include a review of reliability, but a higher contract price would drive hospitals to buy off contract.

Hopefully, these efforts will improve the ability to obtain the anticancer medications needed for the successful treatment of our patients in oncology. ■

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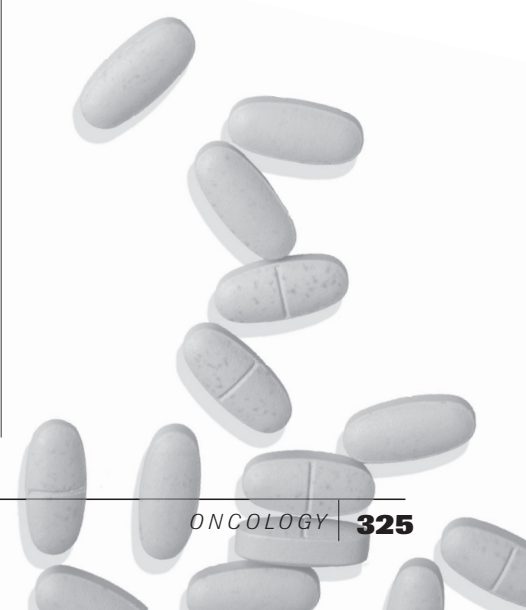


Current Treatments in Mantle Cell Lymphoma

Avyakta Kallam, MBBS[1]; and Julie Vose MD, MBA[1]

ABSTRACT

Mantle cell lymphoma (MCL) is characterized by heterogeneous biology and varied clinical presentations. Historically, it has been associated with a poor prognosis when compared with other non-Hodgkin lymphomas. With a better understanding of the disease biology, molecular pathogenesis, and new treatments, the outcomes have been gradually improving. Identification of high-risk mutations has resulted in better prognostication and paved the way for risk-adapted treatment approaches. Although chemoimmunotherapy remains the mainstay frontline treatment, combination therapies incorporating novel agents such as Bruton tyrosine kinase inhibitors, B-cell lymphoma inhibitors, and immunomodulatory agents are being studied, with promising results. Chimeric antigen receptor T-cell therapy and bispecific T-cell engagers have opened a new avenue for treatment. Also promising are antibody-drug conjugates such as ROR1 inhibitors and PI3K inhibitors, which are under clinical investigation. We provide an overview of the molecular mutations identified in MCL and the evolving treatment strategies for this disease.

INTERVIEW

Avyakta Kallam, MBBS, shares her thoughts on this research on page 330

Introduction

Mantle cell lymphoma (MCL) is a disease of older patients with a median age of 65 years. It accounts for 5% to 7% of all non-Hodgkin lymphoma (NHL) cases in North America.[1-5] Approximately 4000 cases are diagnosed every year, with disease prevalence estimated to be 20,000 cases. The initial studies among patients with MCL showed poor outcomes after standard chemotherapy, with a median survival of 3 years. Over the past 2 decades, significant progress has been made in the risk stratification and treatment of MCL.

MCL has varied presentations, and most patients present with palpable lymphadenopathy, with or without systemic presentations.[6-8] More than 80% of patients present with stage III/ IV disease at the time of diagnosis, with bone marrow involvement,[9] and approximately 30% of patients present with generalized symptoms, such as fever, night sweats, and weight loss. Central nervous system involvement at the time of diagnosis is unusual and associated with poor outcomes.

Patients sometimes present with peripheral lymphocytosis, without lymphadenopathy and systemic symptoms, often mimicking chronic lymphocytic leukemia. This presentation is often associated with an indolent course, with a good prognosis. Such patients are often managed by surveillance alone. Another unusual presentation of MCL is lymphomatous polyposis of the gastrointestinal (GI) tract, with the polyps involving any part of the GI tract and detected incidentally on a colonoscopy.

Current Standards of Diagnosis

A diagnosis of MCL requires a histopathological examination of a lymph node or lymph tissue. A peripheral flow cytometry test and a bone marrow biopsy can also be diagnostic in patients who present with peripheral lymphocytosis.

Historically, MCL was referred to as intermediate lymphocytic lymphoma or centrocytic lymphoma, based on the histologic observation that some of the cells had indented nuclei (as seen in small cleaved-cell lymphoma) and some cells had well-rounded nuclei (similar to small lymphocytic lymphoma). In the 1990s, with a better understanding of the molecular aberrations and the immunophenotype associated

with the disease, the term MCL was coined.[10] A typical histological appearance, with a distinct immunophenotype and molecular aberrations, is required to make a diagnosis of MCL.

Histologically, neoplastic cells in MCL are small-to medium-sized lymphocytes with scant cytoplasm, clumped chromatin, and inconspicuous nucleoli. The cytological subtypes include classical MCL, blastoid MCL, and pleomorphic MCL.[11-13] MCL can exhibit different growth patterns, including diffuse, in situ mantle cell neoplasia; MCL with expanded mantle zones; and nodular MCL. In nodular MCL, nodules consist of follicles with reactive germinal centers surrounded by mantles of neoplastic lymphocytes. This is also referred to as mantle zone pattern. As the disease progresses, there is an obliteration of the interfollicular/nodular pattern, resulting in a diffuse MCL growth pattern. In some cases, referred to as the blastic variant, the neoplastic cells are larger than the nodular variant, and the nuclei have finely dispersed chromatin, with a high mitotic rate. The pleomorphic variant has large cells with irregular nuclear contours and prominent nucleoli; its morphological appearance is like that of diffuse large B-cell lymphoma. The blastic and the pleomorphic variants are associated with a more aggressive clinical course and are frequently associated with more complex cytogenetic findings.

The immunophenotype of MCL is characterized by the expression of B-cell antigens: CD20 positive, CD19 positive, and CD22 positive, with monotypic immunoglobulins.[14] λ Light chains are more commonly seen than κ light chains. Cells are CD5 positive and have nuclear expression of cyclin D1. The cells are CD10 negative, BCL6 negative, and typically CD23 negative. Cytogenetic assessment for karyotype or fluorescence in situ hybridization showing t(11;14) (q13, q32) is a diagnostic feature and is seen in 90% to 95% of MCL cases. Ki-67 serves as a prognostic marker.

TABLE. **Molecular Mutations Detected in MCL, With Roles in Tumorigenesis and Clinical Significance[15-23]**

Molecular gene defects	Significance
Cyclin D1 gene expression[15]	• Increases cellular proliferation • Helpful in diagnosing MCL
Loss of CDKN2A[15]	• Impairs the ability to inhibit proliferation
TP53 mutation[16,20]	• Impaired apoptosis • Loss of cell cycle regulation • Resistance to chemotherapy
SOX11 overexpression[17]	• Improved cell survival
NOTCH1 mutations[15]	• Apoptosis resistance • Upregulation of MYC
BCL2/MCL1[18]	• Inhibits apoptosis • Confers chemotherapy resistance • Associated with high Ki-67
ATM[15]	• Inability to repair double-stranded DNA damage • Present in 20% to 40% of MCL cases
BCL6[18]	• Impaired differentiation and apoptosis • Less commonly seen • More common in germinal center lymphomas

MCL, mantle cell lymphoma.

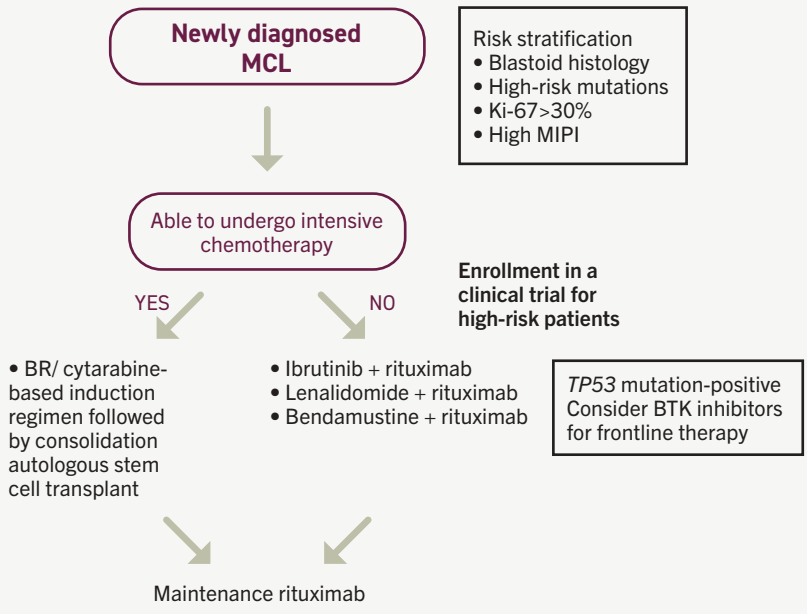
Molecular Mutations Of Significance

The **Table** shows common MCL molecular aberrations, all of which have been shown to play a role not only in prognostication, but also in predicting responses to conventional therapies.[19]

Common Molecular Aberrations in MCL

- **Cyclin D1 overexpression:** Chromosomal translocation t(11:14) (q13;q32) is detected in the majority of MCL cases. This translocation results in the transposition of the cyclin D1 gene, *CCND1*, on chromosome 11 (11q13) to a site downstream of the immunoglobulin heavy chain gene promoter on chromosome 14 (14q32).[20-22] The t(11;14) results in constitutive upregulation and increased cyclin D1 expression. Overexpression of cyclin D1 results in activation of CDK4/6, which in turn promotes the transition of a cell from G1 to the S phase.
- **CDKN2A deletions:** The CDKN2A gene encodes p16, a CDK inhibitor that inhibits CDK4/6. Deletion of CDKN2A results in uncontrolled cell proliferation. Seen in 25% of MCL cases, deletion is associated with aggressive histology.[15]
- ***TP53* mutations:** *TP53* is a tumor suppressor gene located at 17p13.1. *TP53* mutations or deletions can result in cell cycle upregulation, higher proliferation, and inhibition of apoptosis. *TP53* mutations predict an aggressive disease course and poor response to cytotoxic chemotherapy, and they are associated with inferior outcomes.[16,23] *TP53* mutations appear in approximately 11% of MCL cases, whereas 17p deletions are seen in up to 16% of all MCL cases.[22]
- **SOX11 overexpression:** SOX11 is a transcription factor encoded by the

FIGURE. **Current Approach to a Patient With Newly Diagnosed MCL**



MCL, mantle cell lymphoma.

SOX11 gene located on chromosome 2p25. SOX11 overexpression results in augmented B-cell antigen receptor signaling and activation of PAX-5. In turn, this results in inhibition of differentiation, promotion of angiogenesis, and upregulation of CXCR4, with the consequence of promoting invasiveness of the cells. Certain other mutations such as *BIRC3, CARD11, KMT2D, MAP2K 14*, and *MYC*, have also been reported.[17,24]

Stratification For Treatment Selection

As advances are made in molecular biology, MCL prognostic factors continue to evolve.[25] The Mantle Cell Lymphoma International Prognostic Index (MIPI) and a simplified MIPI are commonly used for predicting outcomes.[25,26] The simplified MIPI score takes into consideration age, lactate dehydrogenase levels, performance status, and white blood cell count, dividing patients into low-, intermediate-, and high-risk categories,[26] for which the 5-year overall survival (OS) rates are 81%, 63%, and 35%, respectively.[27] A Ki-67 index greater than 30% is associated with poor prognosis; this has been added to the MIPI risk score for a biologic MIPI score. A higher MIPI score is often an indication of a need for intensive therapy. Aggressive histology, such as blastoid and pleomorphic variants, are associated with poor prognoses.[28] Additionally, *TP53* mutations, 13q deletion, NOTCH1, CDKN2A deletion, and complex cytogenetics are associated with poor prognoses. Multivariate analysis showed that the patients harboring vs not harboring a *TP53* mutation had progression-free survival (PFS) of 1 year vs 12.7 years, respectively. Patients with *TP53* mutations do poorly with cytotoxic chemotherapy.[23] Absence of SOX11 expression is associated with a favorable prognosis.[25]

Therapy Selection

Treatment options for a patient with MCL should be tailored based on their functional age, clinical risk factors, and lymphoma biology (**Figure**).

Indolent MCL

Approximately 20% to 30% of patients with MCL have an asymptomatic presentation; they often present with leukocytosis, asymptomatic splenomegaly or low tumor volume, and without bulky lymphadenopathy. These patients often have a low biological MIPI score and can often be observed, without therapy.

Patients who require therapy for MCL are classified into 2 groups: those who can receive intensive chemotherapy and those who are considered unfit to receive intensive chemotherapy and autologous stem cell transplant (ASCT).

Rituximab (R)-based chemoimmunotherapies with or without consolidative ASCT, with maintenance rituximab, is the current standard of care in patients who are physically fit.[29] The choice of initial chemotherapy regimens varies widely among various institutions.[28] The Nordic regimen treated 160 patients with R-Maxi CHOP (cyclophosphamide 1200 mg/m^2, doxorubicin 75mg/m^2, vincristine 2 mg, prednisone) and high-dose cytarabine.[30] Patients who had a response to chemotherapy underwent ASCT. At a median follow-up of 11.4 years, the overall response rate (ORR) was 96%.

The phase 3 BRIGHT trial (NCT03180840) enrolled 447 patients with indolent lymphomas, including MCL, and compared outcomes between bendamustine and rituximab (BR) for 6 cycles vs R-CHOP (rituximab, cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, vincristine 1.4mg/m^2) for 6 cycles.[31] Among the 134 evaluable patients with MCL in this study, the

completed response rates were higher in the BR arm when compared with the R-CHOP arm (50% vs 27%, respectively). The median OS at 5 years was 82% with BR vs 85% with R-CHOP. This may reflect subsequent lines of chemotherapy, which included BR for patients in both the R-CHOP and rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP) arms.

The phase 3 StiL trial (NCT00991211) compared BR with R-CHOP among 514 patients with newly diagnosed indolent lymphomas.[32] In this study, 46 patients with MCL received BR and 48 patients with MCL received R-CHOP; BR gave rise to a superior PFS (69.5 months), compared with R-CHOP (PFS, 31 months).[32] There was no difference in median OS. BR was associated with lower rates of paresthesias and higher rates of secondary skin malignancies compared with R-CHOP.

The European Mantle Cell Lymphoma Network conducted a large phase 3 study evaluating 497 patients with MCL. Patients were randomly assigned to receive either 6 cycles of R-CHOP or 6 cycles of R-CHOP alternating with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP).[33] Patients in both arms received consolidative ASCT. Median PFS for patients who received R-CHOP/R-DHAP was 9.1 years vs 4.3 years in the R-CHOP arm, but the difference in OS did not reach statistical significance. There was a significant difference in the OS, favoring the R-CHOP/R-DHAP arm, when adjusted for the MIPI. However, the R-CHOP/R-DHAP arm was associated with higher rates of hematological and renal toxicity, so this regimen is not routinely used, given the toxicity concerns.

Another study combined (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone), alternating with high-dose methotrexate and cytarabine(R-HyperCVAD)[34] Ninety-seven patients with MCL received 6 cycles of R-HyperCVAD. Patients did not receive consolidation ASCT. The complete response (CR) rate was 87%. However, the toxicity rates with this regimen were high, with 29% of patients unable to complete therapy due to toxicities. The incidence of grade 3/4 hematological toxicities was 40% to 50%. The incidence of secondary hematological malignancies was 6.4%. Median OS in patients younger than 65 years was 13 years, but median OS among patients older than 65 years was much lower, at 5 years. This regimen, when used in clinical practice, has been associated with a high incidence of hematological toxicity and secondary infections.

At the University of Nebraska Medical Center, we prefer to use BR for induction, due to high response rates and good tolerability. We consider using a cytarabine-based regimen in young patients presenting with high Ki-67 and blastoid variants.

A 2021 study randomly assigned 122 patients with MCL who had achieved a CR or a partial response (PR) to a CHOP-based induction therapy to receive either consolidative ASCT or maintenance therapy with interferon.[35] Results showed that 3-year PFS was significantly longer in patients who received ASCT than those in the maintenance arm. Several retrospective studies showed a benefit in PFS and OS with ASCT.[36]

The 3-arm, randomized, phase 3 TRIANGLE trial (NCT02858258) assigned untreated patients with stage II or higher MCL to induction chemoimmunotherapy and ASCT (arm A); induction chemoimmunotherapy with ibrutinib and ASCT, followed by 2 years of ibrutinib maintenance (arm B); or induction chemoimmunotherapy with 2 years of ibrutinib maintenance alone (arm C). Patients in all 3 arms received maintenance rituximab. The addition of ibrutinib to ASCT showed a superior failure-free survival rate over ASCT alone. At a median follow-up of 31 months, the ibrutinib arm showed a 3-year failure-free survival rate of 88% vs 72% with ASCT alone. The 3-year OS was 86% in arm A, 91% in arm B, and 92% in arm C. The patients in arm A did not have a superior outcome when compared with patients in arm C, raising the question of whether ASCT can be replaced by Bruton tyrosine kinase (BTK) inhibitors. Although further data are necessary—including stratification of patients, as per *TP53* mutation status, and blastoid pleomorphic variants—the preliminary data do suggest that the addition of BTK inhibitors to ASCT does improve outcomes.

A phase 3 study, evaluating the role of maintenance rituximab in the post-ASCT setting, enrolled 299 patients younger than 65 years; they were randomly assigned 1:1 to receive rituximab given every other month for 3 years or observation following consolidative ASCT.[37] This study showed an improved 4-year PFS (83% vs 64%) and OS (89% vs 80%) with rituximab when compared with the observation arm, respectively. Based on these studies, induction chemotherapy followed by consolidation with ASCT and maintenance rituximab has become the current standard of care in patients who are physically fit.[38] For patients who are older and physically unfit, BR followed by maintenance rituximab is the preferred treatment approach. Certain non–chemotherapy-based approaches, such as lenalidomide/rituximab and ibrutinib/rituximab, have also been used with good response rates.

Novel Treatment Strategies of MCL

Improvement in understanding MCL's molecular pathogenesis has led to the development of several targeted agents that are currently being used in relapsed/refractory disease and are being studied

INTERVIEW

A Word from Study Author Avyakta Kallam, MD

"Given all the recent changes, we wanted to present a comprehensive overview of the new developments in MCL."

Avyakta Kallam, MBBS
Assistant Professor
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Duarte, CA

Q: What led you to want to give a comprehensive overview of current treatments in mantle cell lymphoma (MCL)?

KALLAM: In MCL, there have been several developments in recent years. Several targeted therapies have been developed in the past few years and there are many more on the way. In addition to the development of new targeted agents, there has been a better understanding of the tumor biology and of high-risk [disease]. Given all the recent changes, we wanted to present a comprehensive overview of the new developments in MCL.

Q: Which ongoing trials show the most promise?

KALLAM: The trial that has been very exciting in recent times has been the phase 3 TRIANGLE study [NCT02858258].[1] This was a large study designed to evaluate the benefit of ibrutinib [Imbruvica], a Bruton tyrosine kinase [BTK] inhibitor, with or without autologous stem cell transplantation in MCL. This study is exciting because even though it's too early to draw conclusions and we need longer follow-up, this study potentially suggests that we could eliminate stem cell transplant in certain subsets of patients.

Q: Pirtobrutinib was recently approved by the FDA. Have you adapted this treatment into your standard of care for the indicated patient population?

KALLAM: It's exciting to have a new agent we can use in patients who have experienced progression on a BTK inhibitor. Pirtobrutinib has been approved recently in patients who had progression beyond 2 lines of therapy, including a BTK inhibitor. I've personally not had the opportunity to use this agent, but I intend to [in the future].

Q: What is something your colleagues should know in this disease space?

KALLAM: Risk stratification in MCL—specifically, knowing a patient's *TP53* mutation status prior to diagnosis—is helpful in determining treatment approaches because we know that presence of a *TP53* mutation is associated with a poor response to standard chemoimmunotherapy. Clinical trial participation is strongly encouraged in these patients. Outside a clinical trial setting, I would recommend treating patients with targeted therapies, such as BTK inhibitors, over chemotherapy in certain subsets of patients.

Q: In your opinion, what is the main point of this review article?

KALLAM: Risk stratification is important. At the time of diagnosis, it's very important to include targeted genomic sequencing to assess for *TP53* mutations. The treatment paradigm in MCL is rapidly evolving. We could be using novel, biologically targeted therapies in the frontline setting. The outlook for patients with MCL who had progression on BTK inhibitors was initially very poor, but with recent advances—the advent of CAR T-cell therapy; bispecific antibodies; reversible, noncovalent BTK inhibitors such as pirtobrutinib—we have hope in this disease space. ■

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in the first-line setting. These include BTK inhibitors, BCL-2 inhibitors, immunomodulatory drugs (IMiDs), proteasome inhibitors, mTOR inhibitors, and PI3K inhibitors.

BTK Inhibitors

Ibrutinib, acalabrutinib, and zanubrutinib are currently approved in the United States for patients with relapsed MCL.

Ibrutinib, an irreversible BTK inhibitor, demonstrated a CR rate of 58% in patients with relapsed MCL when used in combination with rituximab.[39] At a 4-year follow-up, median PFS was 43 months and median OS was not reached. Grade 3 or higher adverse events (AEs) included neutropenia (16%), thrombocytopenia (11%), atrial fibrillation (6%), and bleeding (5%). Several studies have explored the use of ibrutinib in combination with other novel agents, with promising results. The phase 2 PHILEMON study (NCT02460276) evaluated the combination of ibrutinib, rituximab, and lenalidomide in 50 patients with relapsed/refractory MCL and reported an ORR of 76% at a median follow-up of 40 months.[40] Ibrutinib has also been used in combination with venetoclax in patients with relapsed disease, with promising results. In the phase 2 AIM study (NCT02471391), 23 patients with relapsed disease (less than 2 lines of therapy) received venetoclax plus ibrutinib, resulting in an ORR of 72% and a CR rate of 62%.[41] Notably, 50% of the patients had a *TP53* mutation and 75% had a high MIPI score, which are disease features that are usually associated with poor prognoses. Ibrutinib has also been combined with venetoclax and obinutuzumab, with a 2-year PFS of 69.5%.[42]

Acalabrutinib, a second-generation irreversible BTK inhibitor, has better selectivity and minimal off-target effects (due to fewer cardiovascular complications) when compared with ibrutinib. The phase 2 ACE-LY-004 study (NCT02213926) enrolled 124 patients with relapsed/refractory disease (more than 2 lines of therapy) and reported an ORR of 81% and a CR rate of 48% with acalabrutinib. The incidence of atrial fibrillation (2.4%) was significantly lower when compared with ibrutinib.[43] The responses were consistent in high-risk groups as well.

Zanubrutinib is also a selective, irreversible BTK inhibitor, with studies demonstrating an ORR of 84% and a CR rate of 68% in patients with relapsed/refractory MCL (more than 2 prior lines of therapy).[44] Incidence of atrial fibrillation (0.89%) with zanubrutinib was lower than with acalabrutinib and ibrutinib.

Pirtobrutinib, a reversible BTK inhibitor, has shown activity in patients who are refractory to irreversible BTK inhibitors. In the phase 1/2 BRUIN trial (NCT03740529), 134 patients with relapsed/refractory disease—90% of whom were exposed to a prior BTK inhibitor—received pirtobrutinib.[45] The ORR was 51% and the CR rate was 25% in patients who were previously exposed to a BTK inhibitor. In patients who were BTK naïve, the ORR was 82% and the CR rate was 18%. Incidence of atrial fibrillation and bleeding was less than 2%, making this a promising therapy in patients with MCL.[45]

BTK inhibitors are being increasingly explored as frontline therapy, with promising results. A phase 2 study evaluated ibrutinib plus rituximab as first-line therapy in older patients and reported an ORR of 96%. The phase 2 OASIS-II study (NCT04802590) evaluated ibrutinib, venetoclax, and obinutuzumab in relapsed and treatment-naïve patients.[42] In this study, 15 patients were treatment naïve and their ORR was 86%, with 73% attaining undetectable minimal residual disease (MRD).[42] The combination of acalabrutinib with venetoclax has also been studied, with early-phase trials showing good safety and efficacy. The phase 3 SHINE study (NCT01776840) randomly assigned 523 patients who were treatment naïve and older than 65 years to receive ibrutinib, bendamustine, and rituximab or BR.[46] Patients who responded to therapy were given maintenance rituximab for 2 years; ibrutinib was continued until disease progression. At a median follow-up of 7 years, PFS was superior in the ibrutinib arm compared with the chemotherapy-only arm (80 vs 5.2 months). However, there was no difference in OS. Although there was a lower incidence of death due to progressive disease in the ibrutinib arm compared with the chemotherapy arm (11% vs 21%, respectively), there was a higher incidence of death due to AEs (11% vs 6%). Subgroup analysis did not show a statistically significant improvement in outcomes in the patients with high-risk disease and *TP53* mutations with the ibrutinib-based regimen, suggesting that ibrutinib may not entirely overcome the poor prognostic significance of *TP53* mutations.

In a phase 1 study, 12 patients received acalabrutinib, rituximab, and bendamustine for 3 cycles, followed by acalabrutinib, rituximab, and cytarabine for 3 cycles.[47] Patients who responded to therapy underwent stem cell collection for ASCT. The ORR with this regimen was 85%. Based on these results, a larger phase 2 study, EA4181 (NCT04115631), is currently enrolling patients to evaluate MRD rates and ORRs.

BCL-2 Inhibitors

Venetoclax is a selective, oral BCL-2 inhibitor that has shown to be active in MCL. In a phase 1 study of 28 BTK inhibitor–naïve patients with relapsed/refractory MCL, single-agent

venetoclax resulted in an ORR of 75% and a median PFS of 14 months.[48] The ORR was 50% in patients who were BTK refractory. In clinical practice, venetoclax is being used as a single agent in BTK-refractory settings. Venetoclax has synergistic activity with BTK inhibitors; combination therapies show impressive response rates in high-risk disease, particularly in patients with *TP53* mutations.[49] Combination therapy is being actively investigated in combination in the frontline and relapsed settings.

Immunomodulatory Agents

Lenalidomide, a second-generation IMiD, has shown efficacy in MCL. In the single-arm phase 2 MCL-001 study (NCT00737529), single-agent lenalidomide showed an ORR of 28% and a duration of response of 16.6 months in patients with relapsed/refractory MCL.[49] A phase 1/2 study evaluating a rituximab/lenalidomide combination showed an ORR of 57%, with a PFS of 11 months and an OS of 24 months.[50] Retrospective studies showed poor outcomes with rituximab/lenalidomide in patients who are BTK refractory, so this combination is not preferred in post-BTK relapse settings. This regimen is reserved for patients who are unable to tolerate or have a contraindication to BTK inhibitors. Lenalidomide has been combined with BTK inhibitors and BCL-2 inhibitors, with ORRs ranging from 50% to 56%.

Risk-Adapted Approach

Given the heterogeneity in MCL's disease biology, several studies are being designed using a risk-stratified approach.[19] Given the poor outcomes of chemotherapy for patients with high-risk mutations, it is advisable to enroll such patients in clinical trials. In the phase 2 WINDOW II study (NCT03710772), patients were risk stratified as low-risk (Ki-67 less than 30%, low MIPI, lacking high-risk mutations, tumors smaller than 3 cm) and high-risk (Ki-67 of more than 30%, *TP53*, NSD2, *NOTCH* mutations, complex karyotype or 17p deletion, MYC positivity, blastoid/pleomorphic histology, partial response to induction).[51] All patients received ibrutinib, rituximab, and venetoclax as an induction regimen. Following induction, patients who were low risk were observed, and patients who were high risk received R-Hyper-CVAD alternating with methotrexate/cytarabine. The ORR with this regimen was 96%.

The phase 2 BOVEN study (NCT03824483) is evaluating zanubrutinib, obinutuzumab, and venetoclax in patients with *TP53* mutations.[52] This study incorporates MRD and response-guided treatment duration. Patients received zanubrutinib plus venetoclax for a minimum of 2 years and, based on MRD undetectable status and response, were placed on surveillance. The study is ongoing, but the initial results show an ORR of 86%.

CAR T-Cell Therapy

Brexucabtagene autoleucel (KTE-X19), an anti-CD19 autologous chimeric antigen receptor (CAR) T-cell product, is FDA approved for the treatment of relapsed/refractory MCL.[53] In the pivotal phase 2 ZUMA-2 study (NCT02601313), 68 patients with relapsed/refractory MCL were treated with lymphodepleting chemotherapy, followed by a single infusion of KTE-X19. All patients had disease progression on BTK inhibitors and had received 3 or more prior lines of therapy. At a median follow-up of 12 months, the ORR was 93%, with a CR rate of 67%. At 6 months, 79% were MRD negative.[53] What is notable is that although the ORR was more than 90% in patients with *TP53* mutations, it was less than 50% in those with Ki-67and 80% in patients with blastoid histology. The incidence of grade 3 or higher cytokine release syndrome (CRS) was 15% and neurotoxicity was 31%.

Lisocabtagene maraleucel, an anti-CD19 CAR T-cell product, is also being evaluated in MCL. The phase 1 MCL-TRANSCEND- NHL-001 study (NCT02631044) enrolled 32 patients with relapsed/refractory MCL (2 or more prior lines of therapy).[54] At a median follow-up of 6 months, the ORR was 84%, with a CR rate of 59%. As with KTE-X19, efficacy was noted in patients with high-risk features.

Promising Therapies

Bispecific Antibodies

Bispecific T-cell engagers (BiTEs) are agents that can engage CD3 and redirect T cells against B cells that express specific antigens, such as CD20 and CD19. Glofitamab is an intravenously administered CD20 × CD3 BiTE, engineered with a 2:1 configuration of CD20:CD3.[55] Updated subgroup analysis of this study showed that 29 patients with MCL had an ORR of 83%.[56] It was well tolerated, with grade 3 or higher CRS and infections occurring in 14% and 13% of the patients, respectively. No grade 3 or higher neurotoxicity was reported.

Epcoritamab is a subcutaneously administered CD20 × CD3 BiTE, with initial studies showing an ORR of 50% in patients with MCL.[57]

Antibody-Drug Conjugates

Zilovertamab vedotin is an antibody-drug conjugate that binds specifically to the ROR1, which is an oncoprotein that is expressed in MCL and other B-cell malignancies.[58] The preliminary data report promising safety and efficacy in heavily pretreated patients with MCL, with an ORR of 47%. The commonly observed AEs were peripheral neuropathy and neutropenia.

Conclusions

Advances made in MCL have improved patient outcomes significantly. The current standard of care

for transplant-eligible patients includes high-dose chemoimmunotherapy with a cytarabine-based regimen, followed by ASCT. Patients with high-risk molecular mutations, such as *TP53* mutations, continue to do poorly despite conventional treatment approaches, which puts the role of conventional chemotherapy in such patients into question. Studies incorporating BTK inhibitors have shown superior outcomes in patients with high-risk mutations when compared with conventional chemoimmunotherapy. With several novel agents being developed for this disease, there is a need to better risk stratify, identify high-risk mutations, and tailor treatments accordingly. Studies are ongoing, evaluating the role of MRD; it is also being used as a tool to guide therapies and is likely to be incorporated in clinical settings. BiTE antibodies, anti-ROR1 antibodies, and next-generation CAR T cells are promising. Many more potential new molecules that are in clinical trials could eventually be incorporated into the current treatment landscape. With the rapid advances being made in the field of MCL, the future looks promising. ■

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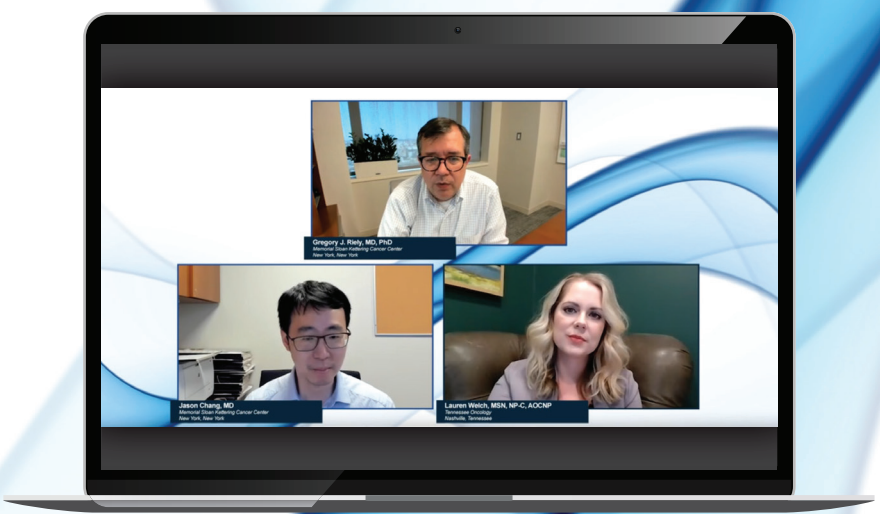

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Unusual Initial Presentation of Hepatocellular Carcinoma as a Clavicular Head Mass

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a common cancer worldwide. Extrahepatic spread is not unusual during HCC disease, but bone metastases at initial presentation are rare.

Case Description: We describe a case of HCC presenting with a clavicular head mass and spinal metastases with normal α-fetoprotein (AFP) level and hepatitis C virus infection without cirrhosis. After undergoing bone and liver biopsies, the patient started a 12-week course of sofosbuvir/velpatasvir and bevacizumab/atezolizumab for lifelong therapy with palliative intent. Since 2021, the patient has been receiving a combination of bevacizumab and atezolizumab every 21 days. On this regimen as of March 2023, his osseous metastases were stable and his liver lesions had not enlarged.

Conclusions: This case demonstrates a very unusual HCC presentation, the importance of a thorough workup of bone metastasis, and the limited value of AFP for HCC screening, even in disseminated disease.

Introduction

Hepatocellular carcinoma (HCC) is among the most common cancers worldwide, with incidence steadily increasing in the United States.[1] The vast majority of HCC cases develop in the setting of liver cirrhosis and are diagnosed based on clinical evaluation, risk factor assessment, and imaging.[1] Liver biopsy may be performed to confirm a diagnosis or evaluate suspicious lesions in atypical presentations.[1] Prognosis of HCC is generally poor, with a median survival of 9 months from diagnosis.[2] Extrahepatic spread frequently occurs, but it is present in only 5% to 15% of cases at diagnosis.[2] Although the lungs are the most common site, metastasis also occurs to the bone—most frequently the vertebra—although this is rare at diagnosis and associated with significant morbidity and mortality.[3] Here, we present a patient with a large clavicular head mass who was found to have HCC with spinal metastases in the setting of chronic hepatitis C virus (HCV) infection without clinical evidence of cirrhosis, an unusual presentation not previously described in literature.

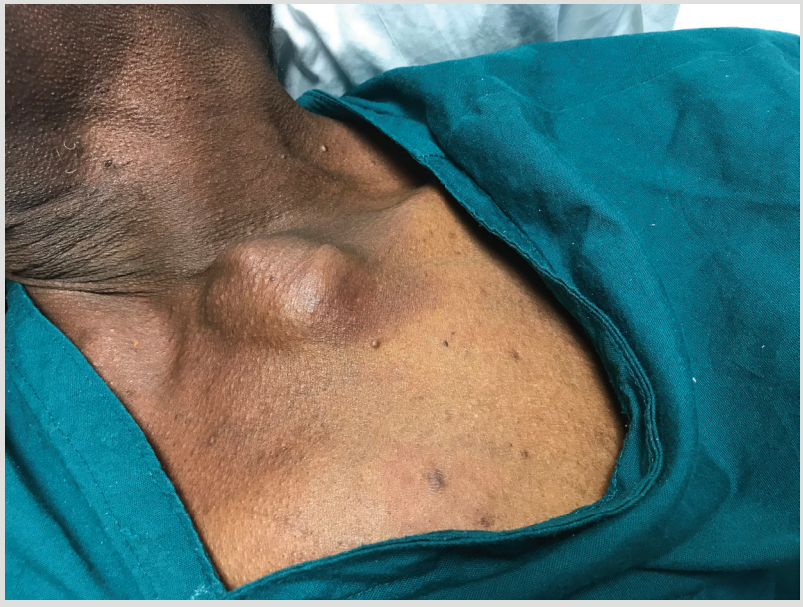
Initial Presentation

A man, aged 70 years, with untreated HCV infection, alcohol use disorder, and tobacco dependence, presented with a 5 x 4 - cm left clavicular head mass of unknown duration (**Figure 1**). He also endorsed 6 months of decreasing appetite and weight loss. He denied any pain from the mass, cough, hemoptysis, hematochezia, melena, hematuria, urinary hesitancy, abdominal or back pain, nausea/vomiting, or skin changes. Organomegaly and palpable masses apart from the clavicular head mass were absent.

Diagnosis

A thoracic CT scan revealed a soft tissue clavicular mass and multiple lytic vertebral lesions (**Figures 2A and 2B**). A CT scan of the abdomen/pelvis identified 2 poorly defined hepatic masses. Liver mass protocol MRI showed an ill-defined area of enhancement within the periphery of the right hepatic lobe that demonstrated partial washout on the portal venous phase, and the liver surface was not suggestive of cirrhosis and did not have evidence of portal hypertension (**Figure 2C**). Admission laboratory studies showed that aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total

FIGURE 1. **Left Clavicular Head Mass at Patient Presentation**



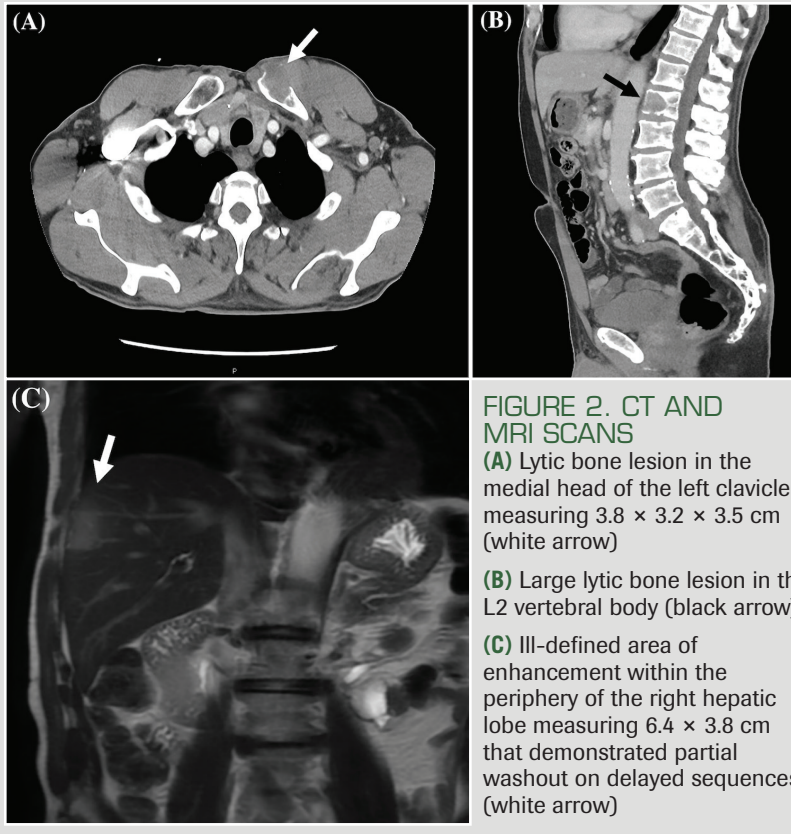


FIGURE 2. CT AND MRI SCANS

(A) Lytic bone lesion in the medial head of the left clavicle measuring 3.8 × 3.2 × 3.5 cm (white arrow)

(B) Large lytic bone lesion in the L2 vertebral body (black arrow)

(C) Ill-defined area of enhancement within the periphery of the right hepatic lobe measuring 6.4 × 3.8 cm that demonstrated partial washout on delayed sequences (white arrow)

bilirubin, serum albumin, prothrombin time, international normalized ratio, and platelets were within normal limits. HCV viral load was 10,400,000 IU/mL, and HIV and hepatitis B virus (HBV) core antibody/surface antigens were negative. α-fetoprotein (AFP), cancer antigen (CA)-19-9, CA-125, carcinoembryonic antigen, and prostate-specific antigen levels were within normal limits.

Assessment

To identify the primary site of the presumed metastatic disease, the clavicular mass was biopsied, and immunohistochemistry was strongly positive for arginase-1 and glypican-3 and negative for CDX2, CK7, CK20, and TTF-1. In conjunction with histology (**Figure 3A**), this was consistent with metastatic HCC. A liver mass biopsy confirmed the diagnosis, showing a similar lesion on histology (**Figure 3B**) and extensive sinusoidal vessel CD34 staining. Pathology review of the biopsy did not include surrounding liver tissue.

Patient and Disease Management

The patient was started on a 12-week course of sofosbuvir/velpatasvir and bevacizumab/atezolizumab for likely lifelong therapy for palliation. Since 2021, he has been receiving a combination of bevacizumab/atezolizumab every 21 days. As of March 2023, his liver lesions and osseous metastasis had remained stable and had not enlarged. The patient did later develop a left upper lobe abscess of the lung, which was aspirated by interventional radiology. Microbiology revealed *Proteus mirabilis*, and the patient was treated for 21 days with levofloxacin with symptomatic improvement.

Discussion

We describe a patient diagnosed with HCC in the setting of chronic untreated HCV infection without clinical evidence of cirrhosis and with metastases

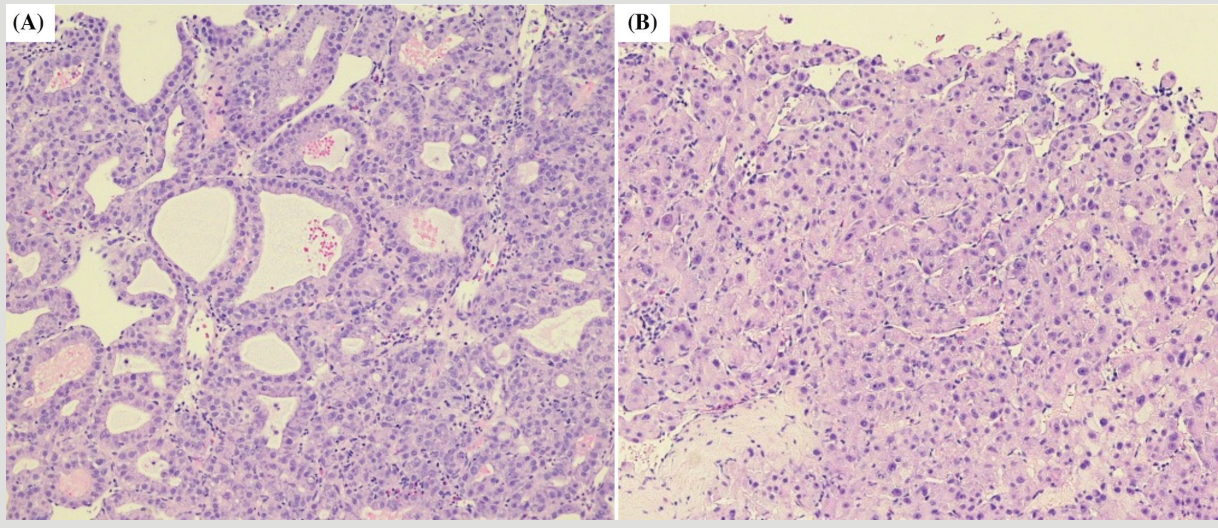


FIGURE 3.

(A) Hematoxylin and eosin staining (×100 magnification) of clavicular lesion showing tumor cells with eosinophilic cytoplasm in a trabecular and pseudoglandular pattern

(B) Hematoxylin and eosin staining (×100 magnification) of the liver mass showing tumor cells with eosinophilic cytoplasm in a trabecular pattern

All figures are published with the consent of the patient.

to the axial and appendicular skeletons. Despite the burden of metastasis at presentation, the patient was largely asymptomatic with normal tumor markers, including AFP.

Bone involvement is rare at the time of HCC diagnosis, and few cases exist in the literature.[4] The **Table** summarizes other patients from the literature with HCC who initially presented with bone involvement. In 395 patients with histopathologically verified HCC, patients with bone metastases at presentation (5%) were similar in clinical and demographic characteristics to those without; there was no significant difference in age, sex, AFP level, hepatitis B surface antigen seropositivity, or frequency of cirrhosis.[4] When bone metastases occur with HCC, they are most often accompanied by musculoskeletal symptoms, frequently causing severe pain and deterioration in the quality of life.[3] Metastatic spread to the bones has been described to occur in 13% to 16% of patients with HCC on average.[3] The VEGF pathway has been implicated in bone metastases, with cells spreading via the hepatic portal system. The most common sites of skeletal involvement are the spinal column, pelvis, ribs, and skull.[3,5] Multiple lytic bone lesions at the time of HCC diagnosis have been reported, but this is not as common as single-bone involvement.[6] The prognostic significance of presenting with disseminated HCC has not been well explored, but studies suggest that developing bone metastases at any point during the disease course carries a poorer prognosis. Bhatia et al examined 1017 patients with confirmed HCC, 20 (2%) of whom developed bone metastases at some point during the disease course. These patients had a median survival following diagnosis of bone metastases of only 86 days (range, 16-2449).[5] This is significantly shorter than the mean survival of HCC without metastases, which ranges from 6 to 20 months.[7]

Only 20% of HCC cases occur in a noncirrhotic liver.[8] This subgroup generally presents with advanced-stage disease, as routine liver surveillance for HCC in the absence of cirrhosis is not currently recommended.[1] Cases are often associated with nonalcoholic fatty liver disease or chronic HBV. HCC in patients with noncirrhotic HCV represents only 4.4% to 10.6% of all HCC diagnoses.[7] The risk of HCC in these patients increases with male sex, advanced age, diabetes, alcohol abuse, and coexisting hepatic steatosis.[8] Although AFP levels may play a role in disease prognosis, a normal AFP should not be used to rule out HCC, as normal levels can be seen in all stages of the disease, from localized to widely metastatic, as observed in this patient.[8] This is especially common in HCC without cirrhosis, where the sensitivity of AFP to detect disease is only 31% to 67%.[8]

The use of atezolizumab/bevacizumab in HCC has demonstrated markedly improved overall and

TABLE. **Cases Reported in the Literature of Hepatocellular Carcinoma Presenting Initially as Bone Metastases**

Publication (year, authors)	Patients (N)	Age (mean, years)	Sex	Bone metastasis site(s)	Median survival time
1989; Liaw et al[4]	20	50	80% male, 20% female	Spine, chest wall, skull	5-mo postdiagnosis
2008; Kim et al[11]	37	61.1	84% male, 16% female	Spine, pelvis, ribs, skull, scapula, long bone	9.7-mo postdiagnosis for treated group, 2.9 mo for untreated
2011; Rastogi et al[6]	1	65	Male	Spine, shoulder, skull	Alive at 2-mo follow-up
2014; Ruiz-Morales et al[3]	2	66	100% male	Spine, ribs, pelvis, shoulder	N/A
2015; Hwang et al[12]	1	61	Male	Spine	Alive at 8 mo postdiagnosis
2015; Subasinghe et al[13]	1	56	Male	Skull	N/A
2016; Alauddin et al[14]	1	55	Female	Chest wall	N/A
2017; Monteserin et al[15]	3	68	100% male	Spine, pelvis, femur	Two patients alive at 42 and 41 mo post diagnosis; 1 dead at 20 mo
2019; Belli et al[16]	1	77	Male	Shoulder	Alive at 9-mo follow-up
2023; Gupta et al (this case)	1	70	Male	Clavicle, spine	Alive at 24-mo postdiagnosis

N/A, not available.

progression-free survival for patients with advanced HCC, and treatment should begin as soon as the diagnosis is confirmed, including in cases with bone metastases.[9] Patients with concurrent HCV infection should be treated for HCV following viral genotype testing, as some evidence suggests that treatment with antivirals may improve survival.[10] However, concurrent HCV infection treatment should not delay HCC therapy initiation.

Our case demonstrates an atypical presentation of HCC with metastasis to skeletal and vertebral bone in a patient with chronic HCV uncomplicated by cirrhosis. We highlight the importance of a thorough workup to rule out usual bone metastasis causes. The case exemplifies how, because routine screening is not recommended in the absence of cirrhosis, HCC in a noncirrhotic liver generally presents with advanced-stage disease. The case also illustrates the limited value of AFP for HCC screening, even when the condition is widely metastatic. Despite an unusual presentation and multiple sites of metastasis at the time of diagnosis, our patient was still able to receive a timely diagnosis and initiation of appropriate treatment under the coordination of a multidisciplinary care team. ■

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AUTHOR ROLES: RG and AT contributed to conception of the work idea. All authors contributed to drafting the work, revising the work, and the final approval of the version to be submitted.

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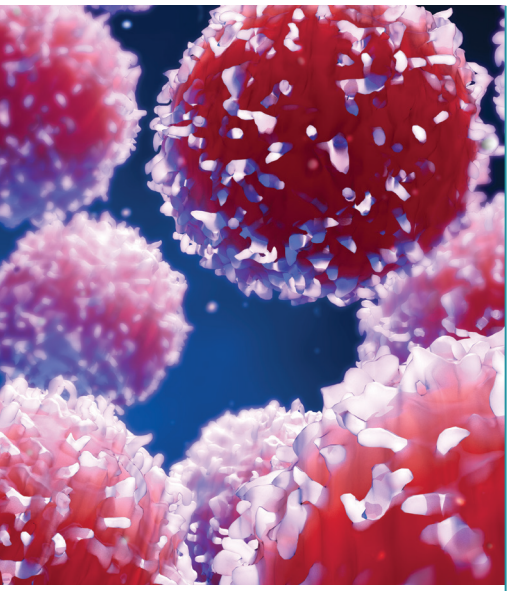
Amivantamab vs Mobocertinib in Exon 20 NSCLC



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An expert panel of lung cancer specialists convened for a Frontline Forum focused on testing, treatment options, and the management of patients with *EGFR* exon 20 non–small cell lung cancer (NSCLC). The panel also addressed a variety of other subjects, including the continuum of care and efficacy results from relevant trials.

Alexander I. Spira, MD, PhD, FACP, codirector of the Virginia Cancer Specialists Research Institute and director of the Thoracic and Phase I Program, led the discussion. He was joined by **Christine Bestvina, MD**, assistant professor of medicine, University of Chicago Medicine; **Joshua K. Sabari, MD**, assistant professor of medicine and director of high-reliability organization initiatives, Perlmutter Cancer Center; **Millie Das, MD**, clinical associate professor of medicine and oncology, Stanford Health; and **Misako Nagasaka, MD, PhD**, associate clinical professor, University of California, Irvine.

Testing for NSCLC Gene Mutations

The panel began with a review of genes and mutation types commonly associated with NSCLC. Sabari noted that about 1% of his patients have squamous disease compared with about 20% who present with adenocarcinoma; he treats both aggressively. Testing is required to determine if patients harbor specific mutations. Bestvina has recently changed her practice from testing only nonsmokers who present with squamous disease to testing everyone. Nagasaka tests all patients with squamous and nonsquamous disease alike and has started testing patients with early-stage disease.

Das said she works with pathology to test all patients who present in the clinic. "I've been trying to push our pathologists to perform reflexive testing on any lung cancer specimen, regardless of stage or histology. By the time these patients show up in our clinics, hopefully, we have the data that we need. As has been said before, we do sometimes see some driver alterations in patients with squamous cell carcinoma and I'm always glad that I tested that patient."

Whether to test a patient is often debated. While clinicians increasingly test every patient they see, some still prefer to wait and be more selective. Spira noted that those in the breast cancer community, who commonly see mutation in the disease they treat, never discuss whether to test; they test automatically.

The panel also spoke about the use of tumor tissue vs plasma and liquid biopsy. Spira wanted to know if, in practice, his colleagues obtained comparable results regardless of test type. Nagasaka recommends using both, especially for patients with stage IV disease.

Bestvina cited a poster she presented at the 2023 American Society of Clinical Oncology Annual Meeting comparing the use of next-generation sequencing (NGS) to PCR testing.[1]

NGS was more cost-effective based on the accuracy of the diagnosis and a fast return on the results. In terms of when to test, results are typically presented to a tumor board and a workflow has been established to include testing for *EGFR* mutations.

For Nagasaka, these tests are not done reflexively and need to be ordered. For Sabari, testing for *EGFR* and ALK mutations is done reflexively, but is based on patient's immunohistochemistry (IHC). "[Using IHC] misses a ton of the *EGFR* mutations. For *ALK* [testing it] gets a little bit more sensitive. Then for NGS, we tried to order tests reflexively, but there are reimbursement issues, particularly if someone's had testing done before, whereas if you're early stage, some insurance companies won't cover anything outside EGFR [testing] because that's where the therapies are approved," said Sabari.

Spira questioned the use of IHC results to determine the need for EGFR or ALK testing. Sabari said these results are returned within 24 to 48 hours and can help better inform decisions.

The big question revolves around why all institutions, from community to academic practices, don't reflexively test in the lung cancer space. Nagasaka said it comes back to reimbursement issues. Specifically, the pathologists conducting these studies do not have relationships with these patients and are typically not oncology-specific, but service the entire institution.

CHRYSALIS Trial

The panel looked to the results of the phase 2 CHRYSALIS trial (NCT02609776) which evaluated amivantamab (Rybrevant) in patients with *EGFR* exon 20 insertion–mutated NSCLC who have progressed on platinum therapy.[2] A total of 258 patients were given the recommended phase 2 dose of 1050 mg of amivantamab once weekly for the first 4 weeks and then once every 2 weeks beginning at week 5.

Patients had a median age of 62 years, 59% of patients were women, 49% were Asian, and all had received previous platinum-based chemotherapy. Patients had received a median of 2 prior lines of therapy, with 25% receiving previous EGFR tyrosine kinase inhibitors and 46% having received previous immune-oncology therapies.

The objective response rate (ORR) was 40% (95% CI, 29%-51%). The duration of response (DOR) was 11.1 months (95% CI, 6.9-not reached [NR]) and 75% of responses were observed at the first disease assessment. The clinical benefit rate was 74% (95% CI, 63%-83%), which included an additional 28 patients who had stable disease at 11 weeks or more.

All 81 patients in the efficacy population had circulating tumor DNA (ctDNA) or tumor samples submitted for testing, and 63 patients had detectable ctDNA. If patients harbored mutations, antitumor responses were observed. When NGS testing was conducted, 1 patient had *MET* amplification with a partial response.

Overall, 58% of patients died. The median progression-free survival (PFS) was 8.3 months (95% CI, 6.5-10.9). The median overall survival (OS) was 22.3 months (95% CI, 14.6-NR), and 23 deaths occurred, although results for this remain immature.

In terms of safety, the median duration of treatment was 3.7 months for this population. In patients who had EGFR inhibition, adverse effects (AEs) associated with it were rash (86%), paronychia (45%), stomatitis (21%), pruritus (17%), and diarrhea (12%). AEs associated with MET inhibition included hypoalbuminemia (27%) and peripheral edema (18%). Additionally, 4% of patients had interstitial lung disease.

In 35% of patients, grade 3 or higher AEs occurred. The most common was hypokalemia (5%), and 4% of patients each experienced rash, pulmonary embolism, diarrhea, and neutropenia. Grade 3 or higher treatment-related AEs occurred in 16% of patients, and 30% experienced serious AEs.

Dose reductions related to treatment occurred in 13% of patients, and 4% had treatment-related discontinuation. There were no grade 5 AEs.

After the results were discussed, the panelists were asked how they felt about these data and if it would begin to change their standard of practice. "I did feel that the data were strong enough for me to consider using this in the second-line [setting]. Now the field has to move on to figuring out how best to manage to treat these patients, including the management of AEs," said Nagasaka.

Das said she is excited to be able to use this treatment in the second line, as TKIs cannot be used up front in this patient population. Sabari said this trial was practice-changing for his clinic, but he wonders how best to implement this strategy in the first-line setting.

Clinical Study of Mobocertinib

A phase 1/2 dose expansion/escalation trial (NCT02716116) evaluated mobocertinib (Exkivity) at 160 mg daily in patients with *EGFR* exon 20 metastatic NSCLC, assigned to either the platinum-pretreated patients (PPP) cohort (n = 114) or the EXCLAIM cohort (n = 96).[3] Demographics between both cohorts were similar.

In the PPP and EXCLAIM cohorts, 35% and 34% of patients had brain metastases, respectively. In the PPP cohort, 23% of patients remained on treatment vs 26% in the EXCLAIM cohort, the median time on treatment was 7.4 months vs 6.8 months, and the median follow-up was 14.2 months and 13.0 months.

In the PPP cohort, the ORR was 28% (95% CI, 20%-37%) by independent-review committee (IRC) assessment and 35% (95% CI, 26%-45%) by investigator assessment. Per IRC, the confirmed disease rate was 78% (95% CI, 69%-85%). The

median time to IRC-assessed confirmed response was 1.9 months (95% CI, 1.8-3.6) and the median DOR was 17.5 months (95% CI, 7.4-20.3). The median PFS was 7.3 months (95% CI, 5.5-9.2) and the median investigator-assessed PFS was 7.3 months (95% CI, 5.6-8.8). The median OS was 24.0 months (95% CI, 14.6-28.8).

In the EXCLAIM cohort, the ORR by IRC was 25% (95% CI, 17%-35%) vs 32% (95% CI, 23%-43%) by investigators. The median time to IRC confirmed response was 1.9 months (95% CI, 1.8-3.6) and the median DOR was not estimable. Disease progression occurred in 55% of patients, the median PFS was 7.3 months (95% CI, 5.5-9.1), and the median OS was not reached. The brain was the first site of investigator-assessed progression in 38% of patients, and 68% had progressive disease.

The most common treatment-related AEs in both cohorts were diarrhea and rash. Diarrhea was reported as a grade 3 AE in 10% or more of patients.

When to Sequence Amivantamab vs Mobocertinib

Spira pondered what the treatment options would be for patients during or after second-line therapy and whether a biopsy was taken again. Nagasaka will typically conduct a biopsy, but after using amivantamab or even mobocertinib, there are not many options outside a clinical trial.

Das discussed the use of single-agent chemotherapy like gemcitabine or docetaxel as an interlude between the 2 drugs. She will begin with amivantamab, proceed with chemotherapy, and, if disease progression occurs, she proceeds with mobocertinib.

Nagasaka prefers to use amivantamab based on the ORR; however, she still has a conversation with her patients to discuss the treatment. "Amivantamab is a great drug, but it's inconvenient. You have to be in the clinic for the first 2 days consecutively, then every week for the first 5 weeks, and then every 2 weeks thereafter. Some of our patients don't have the luxury of back-and-forth transportation."

Mobocertinib, an oral agent, can be more convenient. Das, who practices in both an academic and a community setting, still prefers amivantamab over mobocertinib because of the toxicity profiles observed.

The conversation then turned to the toxicity profiles of the 2 drugs. In the CHRYSALIS study, patients typically experienced flushing 35 to 45 minutes into the infusion. When this occurs, Sabari stops the drug for the day and will continue the rest of the treatment the next day.

Regarding mobocertinib, diarrhea is a concerning AE. As this is an agent that is given to patients who cannot travel back and forth to the treatment centers, Sabari likes to set up a plan of action on how to best manage this AE if it occurs.

Grade 2 diarrhea has been defined as 7 bowel movements a day. In a trial where the median duration of treatment was 15 months, this AE can take a serious toll on patients and their quality of life.[4] Sabari noted that diarrhea can be managed but clinicians need to be "hyperaware" when it occurs. Another option is to dose-reduce or hold the drug, but that could impair the efficacy of the treatment.

"The real thing is having a patient understand that the pill is not easier than the intravenous [treatment]. It might be easier to [stay at home] and time [won't be spent] in the cancer center, but it's not easier from a tolerability standpoint. With the efficacy data we reported, amivantamab has a slightly higher edge. As we said, there's a lot of work to be done in this space. We're not where we want to be," said Sabari.

Bestvina pointed out that these patients have received prior chemotherapy, so it is often already part of their routine to come into the treatment facility.

The Next Steps

Spira noted how quickly new drugs can come onto the market: "Who would have thought 10 years ago that we were going to have 2 drugs being developed for *EGFR* exon 20 insertions? It is mind-boggling if you think about it."

One unmet need that Bestvina hopes these new drugs in the pipeline can help address is central nervous system (CNS) efficacy. Spira agreed, calling it a big concern in this space. When patients present with brain metastases, clinicians often want to avoid whole-brain radiation. When Das sees patients presented with brain metastases, she refers them to CyberKnife, a fully robotic radiotherapy device.

Sabari uses stereotactic radiotherapy and has experience with investigational drugs like CLN-081, which has a cleaner toxicity profile, and BLU-451, which addresses CNS efficacy.

A big concern with the development of these new drugs is toxicity: Will they be cleaner than amivantamab? Will they affect the gastrointestinal system more severely than mobocertinib? Sabari hypothesizes that the drugs in development could be combined with amivantamab to create better opportunities CNS-wise. ■

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RAPID REPORTER

ONCOLOGY Reviews key presentations in the breast and hematology space from the **2023 American Society of Clinical Oncology Annual Meeting**

HEMATOLOGIC MALIGNANCIES

Brexu-cel Demonstrates Real-World Efficacy in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

Treatment with brexucabtagene autoleucel (Tecartus; brexu-cel) resulted in notable complete remissions (CR) and minimal residual disease (MRD) negativity in a real-world population with relapsed or refractory B-cell acute lymphoblastic leukemia previously treated with the therapeutic following its approval by the FDA, according to findings from a retrospective study.

Of the 70 patients who underwent a 28-day-plus evaluation, 91% achieved a CR or a CR with incomplete count recovery. The majority of those who responded to brexu-cel experienced MRD-negative remissions (n = 54/64). Of 10 patients who had central nervous system disease and received the product, 80% achieved a CR; notably, 7 of the 8 patients who responded had CNS3 status.

Duration of remission was evaluated in 54 responders, and 83% of patients with an MRD-negative CR continued to be in remission at 6 months after infusion with brexu-cel. Only 35% of the 10 patients who were in CR and had MRD positivity remained in remission at that time point.

→ **To read the full article, visit:** cancernetwork.com/ASCO23_Brexu-cel

Luspatercept Meets Primary End Point of Transfusion Independence in Myelodysplastic Syndrome

Findings from the phase 3 COMMANDS trial (NCT03682536) indicated that treatment with luspatercept-aamt (Reblozyl) yielded a higher rate of sustained transfusion independence compared with erythropoiesis-stimulating agents (ESAs) for those with ESA-naïve, lower-risk myelodysplastic syndrome.

In the intention-to-treat population, 58.5% of patients who received luspatercept achieved transfusion independence for at least 12 weeks, with a hemoglobin increase of at least 1.5 g/dL compared with 31.2% of patients who received epoetin alfa, meeting the primary end point of the study ($P < .0001$).

Additional results demonstrated higher rates of transfusion independence with luspatercept regardless of stratification criteria. Moreover, patients experienced improved rates of transfusion independence with luspatercept regardless of *SF3B1* mutation status.

In all patients, the median duration of transfusion independence for at least 12 weeks was 126.6 weeks (95% CI, 108.3-not evaluable [NE]) with luspatercept vs 77.0 weeks (95% CI, 39.0-NE) with epoetin alfa (HR, 0.456; 95% CI, 0.260-0.798). In the ring sideroblast–positive patients, the median duration of transfusion independence was 120.9 weeks (95% CI, 76.4-NE) with luspatercept vs 47.0 weeks (95% CI, 36.6-NE) with epoetin alfa (HR, 0.626; 95% CI, 0.361-1.085). In ring sideroblast–negative patients, the median durations were NE (95% CI, 46.0-NE) and 95.1 weeks (95% CI, 35.3-NE), respectively (HR, 0.492; 95% CI, 0.148-1.638).

→ **To read the full article, visit:** cancernetwork.com/ASCO23_COMMANDS

Teclistamab/Talquetamab Appears Tolerable in R/R Multiple Myeloma

A novel combination of the CD3 and B-cell maturation antigen bispecific teclistamab-cqyv (Tecvayli) and the CD3- and GPRC5D-targeted bispecific talquetamab demonstrated promising signs of activity and manageable toxicity for patients with relapsed/refractory multiple myeloma, according to findings from the phase 1b RedirecTT-1 study (NCT04586426).

In the study, the objective response rate (ORR) with the dual bispecific combination was 86.6% across all doses and 96.3%

at the recommended phase 2 regimen (RP2R) dose level. The combined complete response (CR) or stringent CR (sCR) rate was 40.2% and 40.7% for those treated at all dose levels and the RP2R dose, respectively. The safety profile was consistent with the profiles of each agent as a monotherapy.

Across all doses administered in the study, 88.2% of patients experienced a grade 3/4 treatment-emergent adverse event, and 76.3% of patients experienced cytokine release syndrome.

The median progression-free survival (PFS) was not yet reached in the RP2R arm compared with 20.9 months in the full population (95% CI, 13.0-not evaluable [NE]). The 9-month PFS rate was 70.1% (95% CI, 58.0%-79.4%) across all doses and 77.1% in the RP2R group (95% CI, 50.8%-90.5%).

In those specifically with extramedullary disease (EMD), the ORR with the RP2R dose was 85.7%, which consisted of a CR rate of 28.6%, a very good partial response rate of 42.9%, and a partial response rate of 14.3%. Across all doses, the ORR in those with EMD was 71.4%, which included a sCR rate of 3.6%, CR rate of 17.9%, very good partial response rate of 28.6%, and a partial response rate of 21.4%. The median duration of response across all doses was 12.9 months (95% CI, 4.17-NE). It was not yet reached in the RP2R group. Median PFS for those with EMD was 6.1 months (95% CI, 2.5-9.9) across all doses and 9.9 months in the RP2R arm (95% CI, 2.4-NE).

→ **To read the full article, visit:** cancernetwork.com/ASCO23_RedirecTT-1

Axi-Cel Improves Survival vs SOC in Relapsed/Refractory Large B-Cell Lymphoma

Treatment with axicabtagene ciloleucel (Yescarta; axi-cel) improved survival outcomes among patients with early relapsed or refractory large B-cell lymphoma vs standard-of-care (SOC) treatment with high-dose therapy plus autologous stem cell transplant, according to findings from the phase 3 ZUMA-7 trial (NCT03391466).

Although the trial was not powered for subgroup analysis, the overall survival (OS) benefit was consistent across all key patient subgroups, even though 57% of patients in the SOC arm received subsequent cellular immunotherapy, off protocol, following disease progression with platinum-based chemoimmunotherapy.

At a median follow-up of 47.2 months, the median OS with axi-cel was not reached vs 31 months with SOC (HR, 0.726; 95% CI, 0.540-0.977; P = .0168). The 4-year OS rates were 54.6% vs 46.0%, respectively.

Of note, patients in the SOC arm achieved increased survival rates compared with historical studies—yet axi-cel was still associated with superior OS.

This OS analysis revealed that axi-cel also significantly improved progression-free survival (PFS). The 4-year PFS rates in the axi-cel vs SOC arm, respectively, were 41.8% vs 24.4%, and the median PFS was 14.7 months with axi-cel vs 3.7 months with SOC (HR, 0.506; 95% CI, 0.383-0.669; P < .0001).

→ **To read the full article, visit:** cancernetwork.com/ASCO23_ZUMA-7

BREAST CANCER

Sacituzumab Govitecan Yields Enduring Survival in HR+, HER2– Breast Cancer

Findings from the final overall survival (OS) analysis of the phase 3 TROPiCS-02 study (NCT03901339) highlighted the enduring benefit of sacituzumab govitecan-hziy (Trodelvy), further supporting the agent as a novel treatment option for those with pretreated, endocrine-resistant, hormone receptor–positive, HER2-negative metastatic breast cancer.

The median OS in the sacituzumab govitecan arm was 14.5 months (95% CI, 13.0-16.0) vs 11.2 months (95% CI, 10.2-12.6) in the physician's-choice-of-treatment arm (HR, 0.79; 95% CI, 0.65-0.95; P = .0133). Moreover the 12-, 18-, and 24-month OS rates in each respective arm were 60.9% (95% CI, 54.8%-66.4%) vs 47.1% (95% CI, 41.0%-53.0%), 39.2% (95% CI, 33.4%-45.0%) vs 31.7% (95% CI, 26.2%-37.4%), and 25.7% (95% CI, 20.5%-31.2%) vs 21.1% (95% CI, 16.3%-26.3%).

The continued OS benefit of sacituzumab govitecan vs physician's choice at a longer follow-up translated to a 21% reduction in risk of death, with more patients remaining alive in the experimental arm at each landmark.

When OS was assessed by Trop-2 expression, investigators reported that patients with an H-score of less than 100 and 100 or more continued to benefit from sacituzumab govitecan with longer follow-up. Among those with an H-score of less than 100, the median OS was 14.9 months (95% CI, 12.7-18.1) in the experimental cohort vs 11.3 months (95% CI, 10.0-13.3) in the physician's-choice-of-treatment cohort (HR, 0.78; 95% CI, 0.57-1.06). Additionally, those with an H-score of 100 or more had a median OS of 14.4 months (95% CI, 12.7-17.0) vs 11.2 months (95% CI, 9.9-12.7), respectively (HR, 0.82; 95% CI, 0.63-1.08).

→ **To read the full article, visit:** cancernetwork.com/ASCO23_TROPiCS-02

Abemaciclib Combo Maintains Efficacy in Older HER2– Breast Cancer Population

Abemaciclib (Verzenio) and endocrine therapy (ET) maintained a clinically meaningful absolute risk reduction in invasive disease–free survival (iDFS) and distant relapse–free survival (DRFS) in an older population with hormone receptor–positive, HER2-negative, high-risk early breast cancer, according to an age group analysis of the phase 3 monarchE trial (NCT03155997).

The 4-year iDFS rate for patients 65 years and older who received abemaciclib plus ET (n = 437) was 82.0% vs 76.8% for patients who received ET alone (n = 413) for an absolute magnitude of benefit of 5.2% (HR, 0.767; 95% CI, 0.556-1.059). For patients younger than 65 years, the 4-year iDFS rates were 86.5% with abemaciclib and ET (n = 2371) vs 79.8% with ET alone (n = 2416) for an absolute magnitude of benefit of 6.7% (HR, 0.646; 95% CI, 0.554-0.753).

In terms of DRFS, an absolute magnitude of benefit of 6.2% was observed in the younger patient population, and a 4.6% benefit was observed in the older population. Specifically, the 4-year iDFS rates in the younger patient population were 88.8% with abemaciclib plus ET vs 82.6% with ET alone (HR, 0.647; 95% CI, 0.548-0.764). In older patients, the 4-year DRFS rate was 86.1% with the addition of abemaciclib to ET vs 81.5% with ET alone (HR, 0.748; 95% CI, 0.520-1.077).

In the intention-to-treat population, the 4-year DRFS rate was 88.4% with adjuvant abemaciclib and ET vs 82.5% with ET alone for a 34% reduction in the risk of developing a DRFS event (HR, 0.659; 95% CI, 0.567-0.767).

→ **To read the full article, visit:** cancernetwork.com/ASCO23_monarchE

Ribociclib/Endocrine Therapy Improves iDFS in HR+/HER2– Breast Cancer

Adding ribociclib (Kisqali) to endocrine therapy yielded clinically and statistically significant improvement in invasive disease–free survival (iDFS) in patients with hormone receptor–positive or HER2-negative early breast cancer vs endocrine therapy alone, according to findings from the phase 3 NATALEE trial (NCT03701334).

At the January 11, 2023, data cutoff, patients who received the CDK4/6 inhibitor in combination with standard-of-care endocrine therapy (n = 2549) achieved a 3-year iDFS rate of 90.4% compared with 87.1% among patients treated with endocrine therapy alone (n = 2552; HR, 0.748; 95% CI, 0.618-0.906; *P* = .0014). The benefit was consistent across patient subgroups, regardless of disease stage, menopausal status, or nodal status. The median duration of follow-up for iDFS was 27.7 months for both arms at the time of this second interim efficacy analysis.

Additional findings from the study revealed that the iDFS benefit was present across all key prespecified subgroups. Notably, patients with N0 disease experienced a benefit (HR, 0.630; 95% CI, 0.341-1.165) as well as those with N1 through N3 disease (HR, 0.771; 95% CI, 0.630-0.944). Patients with stage II (HR, 0.761; 95% CI, 0.525-1.103) and stage III disease (HR, 0.740; 95% CI, 0.592-0.925) and those with prior exposure to neoadjuvant (HR, 0.785; 95% CI, 0.610-1.011) or adjuvant chemotherapy (HR, 0.671; 95% CI, 0.486-0.927) derived an iDFS benefit with the addition of ribociclib.

→ **To read the full article, visit:** cancernetwork.com/ASCO23_NATALEE

HER3-DXd Yields Positive Efficacy/Safety Profile in Breast Cancer

Treatment with patritumab deruxtecan (HER3-DXd) produced a tolerable safety profile and improved clinical activity among patients with heavily pretreated estrogen receptor (ER)–positive and triple-negative metastatic breast cancers, according to the results of a phase 2 study (NCT04699630).

The overall response rate (ORR) was 35.0%, and the clinical benefit rate (CBR) was 43.3%. In heavily pretreated patients, the all-comer ORR was 35%, the overall CBR was 43%, and the duration of response (DOR) was at least 6 months in approximately half of those who responded.

The results focused on cohort A, which included patients receiving 5.6 mg/kg of HER3-DXd intravenously on day 1 every 3 weeks. Trials for arms B and Z are still ongoing.

In patients who had HER3 expression of 75% or more and either ER-positive (n = 16) or triple-negative (n = 11) disease, the ORR was 37.5% (95% CI, 15.2%-64.6%) vs 18.2% (95% CI, 2.3%-51.8%), the CBR was 50.0% (95% CI, 24.7%-75.3%) vs 18.2% (95% CI, 2.3%-51.8%), and the proportion achieving a DOR of 6 months or more was 50.0% vs 50.0%, respectively.

In patients who had HER3 expression of 25% to 74% and either ER-positive (n = 5) or triple-negative (n = 5) disease, the ORR was 60.0% (95% CI, 14.7%-94.7%) vs 20.0% (95% CI, 0.5%-71.6%), the CBR was 60.0% (95% CI, 14.7%-94.7%) vs 40.0% (95% CI, 5.3%-85.3%), and the proportion achieving a DOR of 6 months or more was 33.3% vs 0%, respectively.

In patients who had ER-positive disease (n = 29) and triple-negative breast cancer, the ORR was 41.4% (95% CI, 23.5%-61.6%) vs 21.1% (95% CI, 6.1%-45.6%), respectively.

→ **To read the full article, visit:** cancernetwork.com/ASCO23_patritumab ■

CONTINUING MEDICAL EDUCATION (CME)

Improving Outcomes in Autoimmune Hemolytic Anemias: What the Oncologist Needs to Know

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LEARNING OBJECTIVES

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

- Construct diagnostic algorithms to identify patients with cold agglutinin disease (CAD)
- Interpret clinical trial data for current and emerging agents used to treat patients with CAD
- Outline individualized management plans for patients with CAD

RELEASE DATE: AUGUST 1, 2023
EXPIRATION DATE: AUGUST 1, 2024

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Cause of Cold Agglutinin Disease Involves Intra- and Extravascular Hemolysis

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia (AIHA) in which immunoglobulin M (IgM) autoantibodies target red blood cells (RBCs).[1] These IgM antibodies are produced clonally from B cells due to a pathologic lymphoproliferative disorder in the bone marrow. Pathologic IgM antibodies bind to RBCs and complement factors in peripheral blood, which is cooler than core body temperature. There, the antibody may dissociate from the RBC, leaving the complement to either form the membrane attack complex and cause intravascular hemolysis or opsonize the surface of the RBC and cause extravascular hemolysis, primarily in the liver. Regulation of terminal complement proteins by CD55 and CD59 on the surface of RBCs limits intravascular hemolysis, except in severe cases of CAD. IgM antibodies that remain bound to RBCs can agglutinate, resulting in clumps of RBCs incapable of passing through capillaries. Therefore, CAD is characterized by hemolysis due to immunoglobulin-antigen–complex activation of the classical complement pathway and is associated with agglutination- and complement-driven signs, symptoms, and complications.[1]

Importantly, CAD should be distinguished from secondary cold agglutinin syndrome (CAS), which is a similar, but heterogeneous, condition that occurs secondary to specific bacterial or viral infections or malignancies (most typically, B-cell lymphoma).[1]

Diagnosis of CAD Involves Markers of Hemolysis and In Vitro Agglutination Tests

Blockage of capillaries by IgM-agglutinized RBCs leads to the cold-induced agglutination–driven symptoms listed in **Figure 1**.[1] The complement-driven symptoms are caused by the intra- and extravascular lysis of the RBCs.

FIGURE 1. **Signs and Symptoms of Cold Agglutinin Disease[1]**

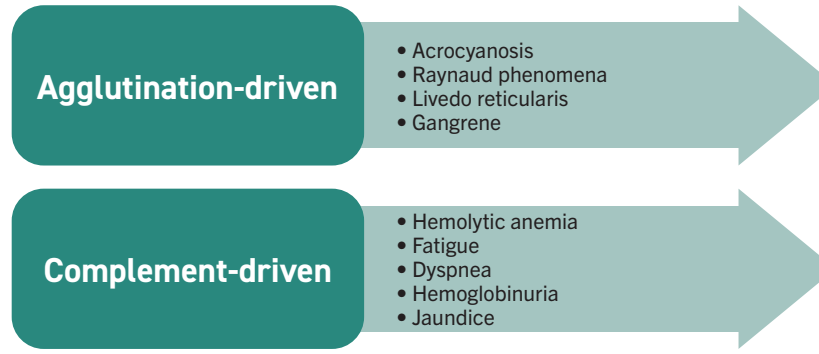
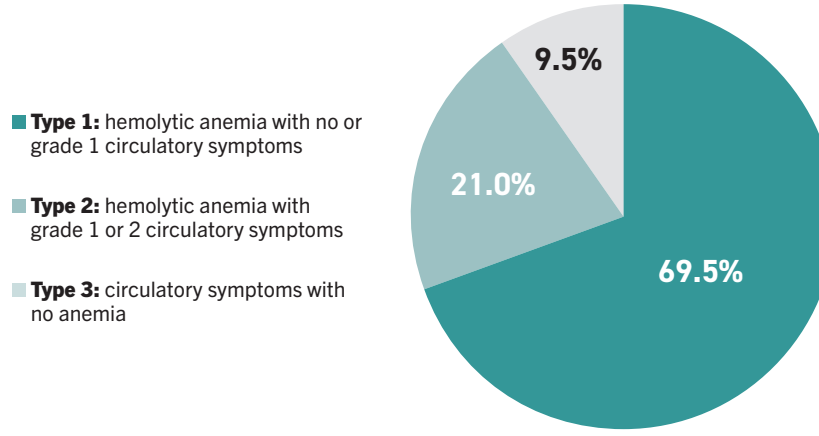


FIGURE 2. **Percentages of Patients With Type 1, 2, or 3 CAD[2]**



Clinically, CAD is divided into 3 types based on whether hemolysis has caused anemia or is compensated and the level of circulatory symptoms. Grade 1 circulatory symptoms consist of acrocyanosis; grade 2 symptoms are Raynaud-like, and they interfere with daily living. Grade 3 symptoms are gangrene or ulcerations. In a multinational, observational study, 232 cases of CAD were classified by type (**Figure 2**).[2]

When RBCs degrade, lactate dehydrogenase (LDH) is released. Hemoglobin (Hb) is also released, which degrades first into heme and subsequently into bilirubin. Laboratory tests for LDH, Hb, and bilirubin can determine the level of anemia resulting from hemolysis in patients with CAD. In the 232-patient observational study, levels of anemia ranged from compensated to severe, as outlined in the **Table**.[3]

Differential diagnosis of CAD as the cause of the hemolysis requires the use of the Coombs, or direct antiglobulin, test.[4] In this test, a patient's RBCs are exposed to antihuman antibodies. Agglutination of the sample demonstrates that the surfaces of the RBCs are coated with autoantibodies. Collection tubes for the blood draw must be prewarmed, and the test must be conducted above 30 °C to avoid agglutination.

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Current and Emerging Treatments for CAD Center on Inhibiting B-Cell and Complement Activity

A combination therapy of rituximab—a B-cell targeting, anti-CD20 monoclonal antibody—and the chemotherapeutic agent bendamustine produces a durable response in patients with CAD.[5] In a prospective, nonrandomized, multicenter trial (NCT02689986), the combination of rituximab and bendamustine was administered to 45 patients.[5] Responses were seen in 32 patients (71%), with 40% of patients having a complete response (CR) and 31% having a partial response (PR). The study included 14 patients who had been treated with rituximab monotherapy or a combination of rituximab and fludarabine. Half (50%) of these patients responded (CR, 3 patients; PR, 4 patients) to the combination of rituximab and bendamustine. Hb levels increased by an average of 3.7 g/dL. The most common grade 3 or 4 adverse event (AE) was neutropenia (33%), and 11% of all patients reported infection.

The median time to response was 1.9 months (range, 1 week to 12 months).[5] In a follow-up study of these 45 patients, another 3 patients had a delayed response, bringing the total number of responders to 35 (78%).[2] CR was achieved in 53%, and PR was noted in 24%. The estimated 5-year sustained response rate to rituximab plus bendamustine was 77%.[2] Furthermore, the 5-year estimated sustained response rate to rituximab plus fludarabine was 71%.[3]

Complement inhibitors have also been evaluated in patients with CAD. In the open-label, phase 2 DECADE trial (NCT01303952), 12 patients with chronic CAD and 1 patient with acute CAS were given the C5 inhibitor eculizumab for 26 weeks.[6] Median LDH level decreased from 572 U/L (IQR, 534-685 U/L) to 334 U/L (IQR, 243-567 U/L) (P = .0215). Hb level increased from 9.35 g/dL (IQR, 8.80-10.80 U/L) to 10.15 g/dL (IQR, 9.00-11.35 U/L) (P = .0391). Eight of 13 study participants became transfusion independent, and 3 maintained independence; 1 patient experienced a reduction in transfusion frequency, whereas 1 patient experienced an increased need for transfusions. Severe AEs of peritonitis and pneumonia were reported in 1 patient each; they were considered possibly and probably related to treatment, respectively. Moderate AEs of hemorrhoidal hemorrhage, fatigue, muscle cramps, arterial stenosis, hypertension, pruritus, and urinary tract infection were reported in 4 patients.

Pegcetacoplan inhibits C3 upstream of C5, and it has the potential to prevent opsonization and the formation of the membrane attack complex.[7] Pegcetacoplan was evaluated in 13 patients with CAD in a phase 2, open-label study (NCT03226678).[7] Mean Hb level increased from 8.9 g/dL (SE, 0.4) in 13 patients to 11.6 g/dL (SE, 0.5) in 7 patients. No treatment-emergent AEs were considered related to pegcetacoplan.

In the ongoing, phase 3 CASCADE trial (NCT05096403), investigators plan to randomly assign 57 patients 2:1 to receive either pegcetacoplan or placebo for 24 weeks, followed by both an open-label phase lasting an additional 24 weeks and a further maintenance period.[8] The primary endpoint is an increase in Hb level of at least 1.5 g/dL from baseline that is maintained for the last 8 weeks of the initial phase.

Sutimlimab is an IgG4 humanized monoclonal antibody that targets C1s in the classical complement cascade, upstream of both C3 and C5. In the open-label CARDINAL trial (NCT03347396), 24 patients with CAD who had received at least 1 transfusion in the preceding 6 months were given sutimlimab for 26 weeks.[9] The primary endpoint was normalization of Hb level, with an increase of Hb of at least 2 g/dL from baseline without transfusion from week 5 to the end of the study. The endpoint was met in 13 patients (54%; 95% CI, 33%-74%). An additional 6 patients had evidence of a treatment response that fell short of the prespecified endpoint. No treatment-emergent AEs were attributed to sutimlimab.

A 2-year extension phase of the CARDINAL trial included 22 of the 24 patients who completed the initial 26-week treatment with sutimlimab.[10] Mean Hb levels were maintained above 11 g/dL through week 53; 55% of patients had a normalized Hb level (> 12 g/dL) at week 53. Mean

TABLE. **Distribution of Anemia Among Patients With CAD[3]**

Level of anemia (patients, %)	Hemoglobin (g/dL)	LDH (U/L)	Bilirubin (µmol/L)	IgM (g/L)
Compensated (12%)	≥ LLN	291	31	5.8
Mild (24%)	10.0 to LLN	385	37	6.7
Moderate (37%)	8.0-10.0	450	43	4.2
Severe (27%)	< 8.0	534	47	5.5

CAD, cold agglutinin disease; IgM, immunoglobulin M; LDH, lactate dehydrogenase; LLN, lower limit of normal.

total bilirubin level was also normalized to less than 20.5 µmol/L, and it remained at that level through week 53 in 63.6% of patients. A total of 19 patients (86.4%) remained transfusion independent through week 53. No new safety signals were identified in the extension phase. Sutimlimab was approved by the FDA in 2022 for the treatment of CAD.[11]

In the phase 3 CADENZA trial (NCT03347422), 42 patients with CAD who had not received transfusions in the preceding 6 months were randomly assigned 1:1 to receive sutimlimab or placebo.[12] The primary endpoint—a composite of Hb increase of at least 1.5 g/dL with transfusion independence—was met in 16 patients (73%) receiving sutimlimab and 3 patients (15%) given placebo (odds ratio, 15.9; 95% CI, 2.9-88.0; $P < .001$). Treatment with sutimlimab increased the Hb level by more than 1 g/dL by the end of the first week, and the least-squares (LS) mean increase in Hb was 2.66 g/dL (95% CI, 2.0-3.2 g/dL) by week 26. In the placebo arm, the Hb level increased by only 0.09 g/dL (95% CI, –0.50 to 0.68 g/dL). The mean total bilirubin level was normalized within the first 3 weeks of sutimlimab administration and was maintained in 88.2% of patients receiving sutimlimab and in 22.2% of patients receiving placebo. Other markers of hemolysis, including LDH and haptoglobin levels and the reticulocyte count, improved in patients receiving sutimlimab but not in those in the placebo arm. Sutimlimab treatment led to an LS mean change in the Functional Assessment of Chronic Illness Therapy–Fatigue score of 10.8 points (95% CI, 7.45-14.22 points) in the sutimlimab arm and 1.9 points (95% CI, –1.65 to 5.46 points) in the placebo arm. Treatment-related AEs were reported in 36.4% of patients in the sutimlimab arm and 20.0% of patients in the placebo arm. ■

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