cancernetwork.com

gotoper.com

PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

FEBRUARY 2024 | Vol 38 • No 2

MANTLE CELL LYMPHOMA: ORIGINAL RESEARCH

Twenty Years of Advancing Discoveries and Treatment of Mantle Cell Lymphoma

A Lymphoma Research Foundation Report:

2023 Mantle Cell Lymphoma Scientific Consortium and Workshop

MANTLE CELL LYMPHOMA: INTERVIEW

Michael Wang, MD

A Look Into the Consortium and Upcoming Treatment Options in MCL

Frontline Forum
Inpatient vs Outpatient Use of Teclistamab in Multiple Myeloma

Rapid Reporter
***ONCOLOGY* Reviews 2023 SABCS and ASH**

Acute Lymphocytic Leukemia: CME
Pediatric-Inspired Asparaginase Regimens for Patients With Acute Lymphocytic Leukemia
Rachel Rau, MD

Find podcasts, webinars, and expert interviews at cancernetwork.com

TECVAYLI®
(teclistamab-cqyv) Injection for subcutaneous use
10 mg/mL and 90 mg/mL

POWER WITHIN REACH[1]

For the 61.8% of patients who achieved ORR in MajesTEC-1

61.8%ORR*
(n=68/110 [95% CI, 52.1%-70.9%])

28.2% ≥CR†
(n=31/110)

29.1% VGPR
(n=32/110)

4.5% PR
(n=5/110)

MajesTEC-1 study design:

The efficacy of TECVAYLI® was evaluated in patients with RRMM in a single-arm, open-label, multi-center, phase 1/2 study. The study included patients who had previously received at least 3 prior therapies, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

INDICATION AND USAGE
TECVAYLI® (teclistamab-cqyv) is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI®. Initiate treatment with TECVAYLI® step-up dosing schedule to reduce risk of CRS. Withhold TECVAYLI® until CRS resolves or permanently discontinue based on severity.

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and serious and life-threatening reactions, can occur in patients receiving TECVAYLI®. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold TECVAYLI® until neurologic toxicity resolves or permanently discontinue based on severity.

TECVAYLI® is available only through a restricted program called the TECVAYLI® and TALVEY™ Risk Evaluation and Mitigation Strategy (REMS).

WARNINGS AND PRECAUTIONS
Cytokine Release Syndrome - TECVAYLI® can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions. In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI® at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI®. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days. Clinical signs and symptoms of CRS included, but were not limited to, fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation).

Initiate therapy according to TECVAYLI® step-up dosing schedule to reduce risk of CRS. Administer pretreatment medications to reduce risk of CRS and monitor patients following administration of TECVAYLI® accordingly. At the first sign of CRS, immediately evaluate patient for hospitalization. Administer supportive care based on severity and consider further management per current practice guidelines. Withhold or permanently discontinue TECVAYLI® based on severity.

TECVAYLI® is available only through a restricted program under a REMS.

Neurologic Toxicity including ICANS - TECVAYLI® can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

In the clinical trial, neurologic toxicity occurred in 57% of patients who received TECVAYLI® at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most frequent neurologic toxicities were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%). With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI®.

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

You are now viewing a subsequent follow-up analysis of the MajesTEC-1 trial. This information is not included in the current full Prescribing Information.

Longer-term follow-up analysis at 23 months[2,3]

61.8%ORR*
(n=68/110 [95% CI, 52.1%-70.9%])

46.4% ≥CR†
(n=51/110)

11.8% VGPR
(n=13/110)

3.6% PR
(n=4/110)

Learn more at TecvayliHCP.com

*ORR: sCR+CR+VGPR+PR.
†≥CR: sCR+CR.

CD38, cluster of differentiation 38; CI, confidence interval; CR, complete response; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

In the clinical trial, ICANS was reported in 6% of patients who received TECVAYLI® at the recommended dose. Recurrent ICANS occurred in 1.8% of patients. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). Less than 3% of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI®. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose with a median duration of 3 (range: 1 to 20) days. The most frequent clinical manifestations of ICANS reported were confusional state and dysgraphia. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or permanently discontinue TECVAYLI® based on severity per recommendations and consider further management per current practice guidelines.

Due to the potential for neurologic toxicity, patients are at risk of depressed level of consciousness. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI® step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves.

TECVAYLI® is available only through a restricted program under a REMS.

TECVAYLI® and TALVEY™ REMS - TECVAYLI® is available only through a restricted program under a REMS called the TECVAYLI® and TALVEY™ REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Hepatotoxicity - TECVAYLI® can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI® at the recommended dose in the clinical trial, there was one fatal case of hepatic failure. Elevated aspartate aminotransferase (AST) occurred in 34% of patients, with Grade 3 or 4 elevations in 1.2%. Elevated alanine aminotransferase (ALT) occurred in 28% of patients, with Grade 3 or 4 elevations in 1.8%. Elevated total bilirubin occurred in 6% of patients with Grade 3 or 4 elevations in 0.6%. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI® or consider permanent discontinuation of TECVAYLI® based on severity.

Infections - TECVAYLI® can cause severe, life-threatening, or fatal infections. In patients who received TECVAYLI® at the recommended dose in the clinical trial, serious infections, including opportunistic infections, occurred in 30% of patients, with Grade 3 or 4 infections in 35%, and fatal infections in 4.2%. Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI® and treat appropriately. Administer prophylactic antimicrobials according to guidelines. Withhold TECVAYLI® or consider permanent discontinuation of TECVAYLI® based on severity.

Monitor immunoglobulin levels during treatment with TECVAYLI® and treat according to guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Neutropenia - TECVAYLI® can cause neutropenia and febrile neutropenia. In patients who received TECVAYLI® at the recommended dose in the clinical trial, decreased neutrophils occurred in 84% of patients, with Grade 3 or 4 decreased neutrophils in 56%. Febrile neutropenia occurred in 3% of patients.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines. Monitor patients with neutropenia for signs of infection. Withhold TECVAYLI® based on severity.

Hypersensitivity and Other Administration Reactions - TECVAYLI® can cause both systemic administration-related and local injection-site reactions. Systemic Reactions - In patients who received TECVAYLI® at the recommended dose in the clinical trial, 1.2% of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue. Local Reactions - In patients who received TECVAYLI® at the recommended dose in the clinical trial, injection-site reactions occurred in 35% of patients, with Grade 1 injection-site reactions in 30% and Grade 2 in 4.8%. Withhold TECVAYLI® or consider permanent discontinuation of TECVAYLI® based on severity.

Embryo-Fetal Toxicity - Based on its mechanism of action, TECVAYLI® may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECVAYLI® and for 5 months after the last dose.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, upper respiratory tract infection, nausea, headache, pneumonia, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥20%) were decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.

cp-322928v3

References: 1. TECVAYLI® (teclistamab-cqyv) Prescribing Information. Janssen Biotech, Inc., Horsham, PA 19044. **2.** Data on file. Janssen Biotech, Inc. **3.** van de Donk NWCJ, Moreau P, Garfall AL, et al. Long-term follow-up from MajesTEC-1 of teclistamab, a BCMA x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). Poster presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, IL.

11/23 cp-422791v1

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Brief Summary of Prescribing Information for TECVAYLI® (teclistamab-cqyv)

TECVAYLI® (teclistamab-cqyv) injection, for subcutaneous use

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI. Initiate treatment with TECVAYLI step-up dosing schedule to reduce risk of CRS. Withhold TECVAYLI until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and serious and life-threatening reactions, can occur with TECVAYLI. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold TECVAYLI until neurologic toxicity resolves or permanently discontinue based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Because of the risk of CRS and neurologic toxicity, including ICANS, TECVAYLI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TECVAYLI and TALVEY REMS *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

TECVAYLI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome

TECVAYLI can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions *[see Adverse Reactions]*.

In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days.

Clinical signs and symptoms of CRS included, but were not limited to, fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation).

Initiate therapy according to TECVAYLI step-up dosing schedule to reduce risk of CRS *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information]*. Administer pretreatment medications to reduce risk of CRS and monitor patients following administration of TECVAYLI accordingly *[see Dosage and Administration (2.2, 2.4) in Full Prescribing Information]*.

At the first sign of CRS, immediately evaluate patient for hospitalization. Administer supportive care based on severity and consider further management per current practice guidelines. Withhold or permanently discontinue TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

TECVAYLI is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Neurologic Toxicity including ICANS

TECVAYLI can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) *[see Adverse Reactions]*.

In the clinical trial, neurologic toxicity occurred in 57% of patients who received TECVAYLI at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most frequent neurologic toxicities were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%).

With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI.

In the clinical trial, ICANS was reported in 6% of patients who received TECVAYLI at the recommended dose *[see Adverse Reactions]*. Recurrent ICANS occurred in 1.8% of patients. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). Less than 3% of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose with a median duration of 3 (range: 1 to 20) days. The most frequent clinical manifestations of ICANS reported were confusional state and dysgraphia. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or permanently discontinue TECVAYLI based on severity per recommendations and consider further management per current practice guidelines *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Due to the potential for neurologic toxicity, patients receiving TECVAYLI are at risk of depressed level of consciousness *[see Adverse Reactions]*. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

TECVAYLI is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

TECVAYLI and TALVEY REMS

TECVAYLI is available only through a restricted program under a REMS called the TECVAYLI and TALVEY REMS because of the risks of CRS and neurologic toxicity, including ICANS *[see Warnings and Precautions]*.

Notable requirements of the TECVAYLI and TALVEY REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving TECVAYLI about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with Patient Wallet Card.
- Pharmacies and healthcare settings that dispense TECVAYLI must be certified with the TECVAYLI and TALVEY REMS program and must verify prescribers are certified through the TECVAYLI and TALVEY REMS program.
- Wholesalers and distributers must only distribute TECVAYLI to certified pharmacies or healthcare settings.

Further information about the TECVAYLI and TALVEY REMS program is available at www.TEC-TALREMS.com or by telephone at 1-855-810-8064.

Hepatotoxicity

TECVAYLI can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI at the recommended dose in the clinical trial, there was one fatal case of hepatic failure. Elevated aspartate aminotransferase (AST) occurred in 34% of patients, with Grade 3 or 4 elevations in 1.2%. Elevated alanine aminotransferase (ALT) occurred in 28% of patients, with Grade 3 or 4 elevations in 1.8%. Elevated total bilirubin occurred in 6% of patients with Grade 3 or 4 elevations in 0.6%. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Infections

TECVAYLI can cause severe, life-threatening, or fatal infections. In patients who received TECVAYLI at the recommended dose in the clinical trial, serious infections, including opportunistic infections, occurred in 30% of patients, with Grade 3 or 4 infections in 35%, and fatal infections in 4.2% *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI and treat appropriately. Administer prophylactic antimicrobials according to guidelines *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor immunoglobulin levels during treatment with TECVAYLI and treat according to guidelines, including infection precautions and antibiotic or antiviral prophylaxis *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Neutropenia

TECVAYLI can cause neutropenia and febrile neutropenia. In patients who received TECVAYLI at the recommended dose in the clinical trial, decreased neutrophils occurred in 84% of patients, with Grade 3 or 4 decreased neutrophils in 56%. Febrile neutropenia occurred in 3% of patients *[see Adverse Reactions]*.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines.

Monitor patients with neutropenia for signs of infection.

Withhold TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Hypersensitivity and Other Administration Reactions

TECVAYLI can cause both systemic administration-related reactions and local injection-site reactions.

Systemic Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, 1.2% of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue.

Local Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, injection-site reactions occurred in 35% of patients with Grade 1 injection-site reactions in 30% and Grade 2 in 4.8%.

Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action, TECVAYLI may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECVAYLI and for 5 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are also described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions]*
- Neurologic Toxicity including ICANS *[see Warnings and Precautions]*
- Hepatotoxicity *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Neutropenia *[see Warnings and Precautions]*
- Hypersensitivity and Other Administration Reactions *[see Warnings and Precautions]*

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

MajesTEC-1

The safety of TECVAYLI was evaluated in MajesTEC-1 *[see Clinical Studies (14) in Full Prescribing Information]* which included adult patients with relapsed or refractory multiple myeloma. Patients received step-up doses of 0.06 mg/kg and 0.3 mg/kg of TECVAYLI followed by TECVAYLI 1.5 mg/kg, subcutaneously once weekly (N=165). Among patients who received TECVAYLI, 47% were exposed for 6 months or longer and 7% were exposed for one year or longer.

The median age of patients who received TECVAYLI was 64 years (range: 33 to 84 years); 58% were male; 81% were White, 13% were Black or African American, and 2% were Asian.

Serious adverse reactions occurred in 54% of patients who received TECVAYLI. Serious adverse reactions in >2% of patients included pneumonia (15%), cytokine release syndrome (8%), sepsis (6%), general physical health deterioration (6%), COVID-19 (6%), acute kidney injury (4.8%), pyrexia (4.8%), musculoskeletal pain (2.4%), and encephalopathy (2.4%).

Fatal adverse reactions occurred in 5% of patients who received TECVAYLI, including COVID-19 (1.8%), pneumonia (1.8%), septic shock (0.6%), acute renal failure (0.6%), and hemoperitoneum (0.6%).

Permanent discontinuation of TECVAYLI due to adverse reactions occurred in 1.2% of patients. Adverse reactions resulting in permanent discontinuation of TECVAYLI included pneumonia (adenoviral and pneumocystis jirovecii pneumonia in the same patient) and hypercalcemia.

Dosage interruptions of TECVAYLI due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in >5% of patients included neutropenia, pneumonia, pyrexia, cytokine release syndrome, upper respiratory tract infection, and COVID-19.

The most common adverse reactions (≥20%) were pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, upper respiratory tract infection, nausea, headache, pneumonia, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥20%) were decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.

Table 1 summarizes the adverse reactions in MajesTEC-1.

Table 1: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1

Adverse Reactions	TECVAYLI (N=165)	
	Any Grade (%)	Grade 3 or 4 (%)
General disorders and administration site conditions		
Pyrexia	76	3#
Injection site reaction[1]	37	0.6#
Fatigue[2]	33	2.4#
Chills	16	0
Pain[3]	15	1.8#
Edema[4]	13	0
Immune system disorders		
Cytokine release syndrome	72	0.6#
Hypogammaglobulinemia[5]	11	1.2#
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[6]	44	4.2#
Bone pain	16	3#
Infections		
Upper respiratory tract infection[7]	26	2.4#
Pneumonia[8*]	24	15
Urinary tract infection[9]	11	5#

TECVAYLI® (teclistamab-cqyv) injection

Table 1: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1 (continued)

Adverse Reactions	TECVAYLI (N=165)	
	Any Grade (%)	Grade 3 or 4 (%)
Gastrointestinal disorders		
Nausea	25	0.6#
Diarrhea	21	2.4#
Constipation	18	0
Vomiting	12	0.6#
Nervous system disorders		
Headache	25	0.6#
Motor dysfunction[10]	16	0
Sensory neuropathy[11]	15	1.2#
Encephalopathy[12]	13	0
Vascular disorders		
Hypotension	18	1.2#
Hemorrhage[13*]	12	1.8
Hypertension[14]	12	4.8#
Respiratory, thoracic, and mediastinal disorders		
Hypoxia	18	1.8
Cough[15]	15	0
Cardiac disorders		
Cardiac arrhythmia[16]	16	1.8
Metabolism and nutrition disorders		
Decreased appetite	11	0.6#
Renal and urinary disorders		
Acute kidney injury[17]	11	3.6

Adverse reactions were graded based on CTCAE Version 4.03, with the exception of CRS, which was graded per ASTCT 2019 criteria.

[1] Injection site reaction includes application site erythema, injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site edema, injection site pruritus, injection site rash, injection site reaction and injection site swelling.

[2] Fatigue includes asthenia and fatigue.

[3] Pain includes ear pain, flank pain, groin pain, oropharyngeal pain, pain, pain in jaw, toothache and tumor pain.

[4] Edema includes face edema, fluid overload, fluid retention, edema peripheral and peripheral swelling.

[5] Hypogammaglobulinemia includes hypogammaglobulinemia and hypoglobulinemia.

[6] Musculoskeletal pain includes arthralgia, back pain, muscle discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain and pain in extremity.

[7] Upper respiratory tract infection includes bronchitis, influenza like illness, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tracheitis, upper respiratory tract infection and viral upper respiratory tract infection.

[8] Pneumonia includes COVID-19 pneumonia, enterobacter pneumonia, lower respiratory tract infection, metapneumovirus pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia klebsiella, pneumonia moraxella, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia staphylococcal and pneumonia viral.

[9] Urinary tract infection includes cystitis, cystitis escherichia, cystitis klebsiella, escherichia urinary tract infection, urinary tract infection and urinary tract infection bacterial.

[10] Motor dysfunction includes cogwheel rigidity, dysgraphia, dysphonia, gait disturbance, hypokinesia, muscle rigidity, muscle spasms, muscular weakness, peroneal nerve palsy, psychomotor hyperactivity, tremor and VIth nerve paralysis.

[11] Sensory neuropathy includes dysesthesia, hypoesthesia, hypoesthesia oral, neuralgia, paresthesia, paresthesia oral, peripheral sensory neuropathy, sciatica and vestibular neuronitis.

[12] Encephalopathy includes agitation, apathy, aphasia, confusional state, delirium, depressed level of consciousness, disorientation, dyscalculia, hallucination, lethargy, memory impairment, mental status changes and somnolence.

[13] Hemorrhage includes conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemoperitoneum, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage and subdural hematoma.

[14] Hypertension includes essential hypertension and hypertension.

[15] Cough includes allergic cough, cough, productive cough and upper-airway cough syndrome.

[16] Cardiac arrhythmia includes atrial flutter, cardiac arrest, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia and ventricular tachycardia.

[17] Acute kidney injury includes acute kidney injury and renal impairment.

Only grade 3 adverse reactions occurred.

* Includes the following fatal adverse reactions: hemorrhage (n=1), pneumonia (n=3).

Clinically relevant adverse reactions in <10% of patients who received TECVAYLI included febrile neutropenia, sepsis, ICANS, seizure, Guillain-Barré syndrome, hepatic failure, and new onset or reactivated viral infections (including adenovirus, hepatitis B virus (HBV), cytomegalovirus (CMV), varicella zoster virus (VZV), and herpes simplex virus (HSV)).

Table 2 summarizes laboratory abnormalities in MajesTEC-1.

Table 2: Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1

	TECVAYLI (N=165[1])	
Laboratory Abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology		
Lymphocyte count decreased	92	84
White blood cell decreased	86	41
Neutrophil count decreased	84	56
Platelet count decreased	71	22
Hemoglobin decreased	67	33
Chemistry		
Albumin decreased	68	6
Alkaline phosphatase increased	42	2.4
Phosphorus decreased	38	13
Gamma-glutamyl transferase increased	37	8
Sodium decreased	35	10
Aspartate aminotransferase increased	34	1.2
Calcium (corrected) decreased	31	1.2
Creatinine increased	30	3

[1] The denominator used to calculate the rate varied from 164 to 165 based on the number of patients with a baseline value and at least one post-treatment value.
Laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

DRUG INTERACTIONS

TECVAYLI causes release of cytokines *[see Clinical Pharmacology (12.2) in Full Prescribing Information]* that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of TECVAYLI step-up dosing schedule up to 7 days after the first treatment dose and during and after CRS *[see Warnings and Precautions]*. Monitor for toxicity or concentrations of drugs that are CYP substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant CYP substrate drug as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action, TECVAYLI may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on the use of TECVAYLI in pregnant women. No animal reproductive or developmental toxicity studies have been conducted with TECVAYLI. Teclistamab-cqyv causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, teclistamab-cqyv has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

TECVAYLI is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI should be considered.

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.

Lactation

Risk Summary

There are no data on the presence of teclistamab-cqyv in human milk, the effect on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to TECVAYLI are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with TECVAYLI and for 5 months after the last dose.

Females and Males of Reproductive Potential

TECVAYLI may 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 TECVAYLI.

TECVAYLI® (teclistamab-cqyv) injection

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 5 months after the last dose of TECVAYLI.

Pediatric Use

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

Geriatric Use

Of the 165 patients with relapsed or refractory multiple myeloma treated with TECVAYLI in MajesTEC-1 at the recommended dosage, 48% were 65 years of age or older, and 15% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients 65 to 74 years of age compared to younger patients. There is an insufficient number of patients 75 years of age or older to assess whether there are differences in safety or effectiveness.

PATIENT COUNSELING INFORMATION

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

Cytokine Release Syndrome (CRS)

Discuss the signs and symptoms associated with CRS, including fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of CRS. Advise patients that they will be hospitalized for 48 hours after administration of all doses within the TECVAYLI step-up dosing schedule *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neurologic Toxicity including ICANS

Discuss the signs and symptoms associated with neurologic toxicity, including ICANS, including headache, confusion, dysgraphia, motor dysfunction, neuropathy, or encephalopathy. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of neurologic toxicity. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

TECVAYLI and TALVEY REMS

TECVAYLI is available only through a restricted program called TECVAYLI and TALVEY REMS. Inform patients that they will be given a Patient Wallet Card that they should carry with them at all times and show to all of their healthcare providers. This card describes signs and symptoms of CRS and neurologic toxicity which, if experienced, should prompt the patient to immediately seek medical attention *[see Warnings and Precautions]*.

Hepatotoxicity

Advise patients that liver enzyme elevations may occur and that they should report symptoms that may indicate liver toxicity, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions]*.

Infections

Discuss the signs and symptoms of infection *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neutropenia

Discuss the signs and symptoms associated with neutropenia and febrile neutropenia *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Hypersensitivity and Other Administration Reactions

Advise patients to immediately seek medical attention for any signs and symptoms of systemic administration-related reactions. Advise patients that local injection-site reactions may occur and to report any severe reactions *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with TECVAYLI and for 5 months after the last dose *[see Warnings and Precautions and Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with TECVAYLI and for 5 months after the last dose *[see Use in Specific Populations]*.

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

For patent information: www.janssenpatents.com

cp-337020v2

51

Mantle Cell Lymphoma: Original Research

Twenty Years of Advancing Discoveries and Treatment of Mantle Cell Lymphoma

A Lymphoma Research Foundation Report:
2023 Mantle Cell Lymphoma Scientific Consortium and Workshop

Special QAs From the Consortium

Elias Campo, MD, PhD; Michael Wang, MD; Martin Dreyling, MD; Julie M. Vose, MD, MBA

44

PUBLISHER'S NOTE

KOL Shoutouts and a Call for Submissions

45

LETTER TO THE READERS

Key Takeaways From ASH 2023: Emerging Trends in Hematologic Oncology

Julie M. Vose, MD, MBA

cancernetwork.com

Visit CancerNetwork.com, home of the journal *ONCOLOGY®* and a web destination for oncologists seeking expert peer perspectives, podcasts, and other clinically practical features.

68

RAPID REPORTER

***ONCOLOGY* Reviews 2023 SABCS and ASH**

71

FRONTLINE FORUM

Inpatient vs Outpatient Use of Teclistamab in Multiple Myeloma

82

ACUTE LYMPHOCYTIC LEUKEMIA: CME

Pediatric-Inspired Asparaginase Regimens for Patients With Acute Lymphocytic Leukemia

Rachel Rau, MD

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

Sara A. Hurvitz, MD, FACP
Breast Tumor Chair

Hurvitz presented efficacy results from the phase 3 HERCLIMB-02 trial (NCT03975647) evaluating tucatinib (Tukysa) plus ado-trastuzumab emtansine (Kadcyla) at the 2023 San Antonio Breast Cancer Symposium. The median time to disease progression or death was 9.5 months (95% CI, 7.4-10.9) and 7.4 months (95% CI, 5.6-8.1) in the experimental arm and placebo arm, respectively (HR, 0.76; 95% CI, 0.61-0.95; $P = .0163$). For patients with brain metastases, the median time to disease progression or death was 7.8 months (95% CI, 6.7-10.0) and 5.7 months (95% CI, 4.6-7.5) in the experimental arm and placebo arm, respectively (HR, 0.64; 95% CI, 0.46-0.89).

Shubham Pant, MD, MBBS
Colorectal/Gastrointestinal Editorial Board Member

Pant is currently involved in the development of a vaccine to help prevent relapse in patients with *KRAS*-mutated pancreatic and colorectal cancers. Findings from the phase 1 study were recently published in *Nature Medicine*, titled, "Lymph-Node-Targeted, mKRAS-Specific Amphiphile Vaccine in Pancreatic and Colorectal Cancer: the Phase 1 AMPLIFY-201 Trial". In patients who received the ELI-002 vaccine, 84% had a T cell response, and 100% had responses if they were enrolled in the highest dose cohorts.

CALL FOR REVIEWERS AND PAPERS

ONCOLOGY is seeking to expand its list of ad hoc reviewers to provide constructive feedback on manuscripts that have received initial editorial approval. Comments and criticisms are a necessary and invaluable part of the journal's process, and our need for more willing experts grows in step with the journal.

We are also seeking to expand coverage of original peer-reviewed research articles and are now encouraging authors to submit high-quality original manuscripts about clinical trials and investigations.

Please visit CancerNetwork.com/guidelines for more information or contact us at **CancerNetwork@mjhlifesciences.com**

PRACTICAL, PEER-REVIEWED PERSPECTIVES
ONCOLOGY®

FEBRUARY 2024 ▪ VOL. 38 ▪ NO. 2

MJH Life Sciences, LLC | 2 Commerce Dr. Suite 100, Cranbury, NJ 08512 | (609) 716-7777

Julie M. Vose, MD, MBA
CHIEF, HEMATOLOGY/ONCOLOGY,
BUFFETT CANCER CENTER
UNIVERSITY OF NEBRASKA MEDICAL CENTER
OMAHA, NE 68198-9860

Key Takeaways From ASH 2023: Emerging Trends in Hematologic Oncology

There have been several breakthroughs in nonmalignant hematology care recently, including the 2023 FDA approvals of Casgevy and Lyfgenia for the treatment of patients with sickle cell disease.[1] During the 65th American Society of Hematology (ASH) Annual Meeting and Exposition, results from the phase 2/3 CLIMB SCD-121 trial (NCT03745287) using exagamglogene autotemcel (exa-cel) were presented, demonstrating the utility of editing ex vivo with CRISPR-Cas9 technology of the erythroid-specific enhancer region of *BCL11A*.[2] This resulted in increased hemoglobin F production, with 96.7% of patients with severe sickle cell disease being free from vaso-occlusive events and 100% being free from hospitalization.

Additional studies were presented for patients with severe β-thalassemia who received exa-cel; more than 90% of patients achieved transfusion independence, with an improvement in quality of life.[3] Another potentially major accomplishment for patients with severe hemophilia A or B was presented with the treatment of marstacimab, a novel monoclonal antibody that neutralizes tissue factor pathway inhibitor.[4] This antibody then increases thrombin through the extrinsic pathway. Taken together, these therapies represent major advancements in the treatment of these nonmalignant hematologic disorders.

Several updates on outcomes of clinical trials and real-world experiences for hematologic malignancies were also presented at ASH. A late-breaking abstract of the phase 3 SYMPATICO study (NCT03112174) of ibrutinib (Imbruvica) plus venetoclax (Venclexta) vs ibrutinib plus placebo for patients with relapsed mantle cell lymphoma was presented. The results demonstrated a statistically significant improvement in progression-free survival (PFS) for the combination of ibrutinib plus venetoclax vs ibrutinib plus placebo.[5]

In the phase 3 Perseus trial (NCT03710603), the results from the randomized trial of daratumumab (Darzalex) plus bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (D-VRd) vs VRd alone for patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplant were presented.[6] With a median follow-up of 47.5 months, the PFS was significantly improved in the D-VRd arm at 84.3% vs 67.7% in the VRd arm.

In the plenary session, the phase 2 AGAVE-201 study (NCT04710576) of axatilimab for the treatment of chronic graft-vs-host disease was presented. Over 75% of the patients, who had disease with which prior FDA-approved therapy had failed, demonstrated a response to axatilimab, with a median failure-free survival of 17 months.[7] Several of the malignant hematology studies also demonstrated the importance of minimal residual disease–negative status in multiple myeloma, non-Hodgkin lymphoma, and acute leukemias.[8]

With the continued progress in understanding the diagnosis, biology, and treatments for patients with malignant and nonmalignant hematologic disorders, the future remains bright for our patients. ■

REFERENCES

1. FDA approves first gene therapies to treat patients with sickle cell disease. News release. FDA. December 8, 2023. Accessed January 24, 2024. https://shorturl.at/axyJS

2. Frangoul, H, Locatelli F, Sharma A, et al. Exagamglogene autotemcel for severe sickle cell disease. *Blood*. 2023;142(suppl 1):1052. doi:10.1182/blood-2023-190139

3. Locatelli, F, Lang P, Corbacioglu S, et al. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. *Blood*. 2023;142(suppl 1):1053. doi:10.1182/blood-2023-190534

4. Matino D, Acharya S, Palladino A, et al. Efficacy and safety of the anti-tissue factor pathway inhibitor marstacimab in participants with severe hemophilia without inhibitors: results of the phase 3 Basis trial. *Blood*. 2023;142(suppl 1):285. doi:10.1182/blood-2023-181263

5. Wang M, Jurczak W, Trněný M, et al. Ibrutinib combined with venetoclax in patients with relapsed/refractory mantle cell lymphoma: primary analysis results from the randomized phase 3 Sympatico study. *Blood*. 2023;142(suppl 2):LBA-2. doi:10.1182/blood-2023-191921

6. Sonneveld P, Dimopoulos M, Boccadoro M, et al. Phase 3 randomized study of daratumumab (DARA) + bortezomib, lenalidomide, and dexamethasone (VRd) versus Vrd alone in patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation (ASCT): primary results of the Perseus trial. *Blood*. 2023;142(suppl 2):LBA-1. doi:10.1182/blood-2023-191911

7. Wolff D, Cutler C, Lee SJ, et al. Safety and efficacy of axatilimab at 3 different doses in patients with chronic graft-versus-host disease (AGAVE-201). *Blood*. 2023;142(suppl 1):1. doi:10.1182/blood-2023-186963

8. Roschewski M, Lindenberg L, Mena E, et al. End-of-treatment response assessment after frontline therapy for aggressive B-cell lymphoma: landmark comparison of singular PET/CT versus ultrasensitive circulating tumor DNA. *Blood*. 2023;142(suppl 1):192. doi:10.1182/blood-2023-180007

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.

The innovation you've been waiting for. | RYBREVANThcp.com

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
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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]*.

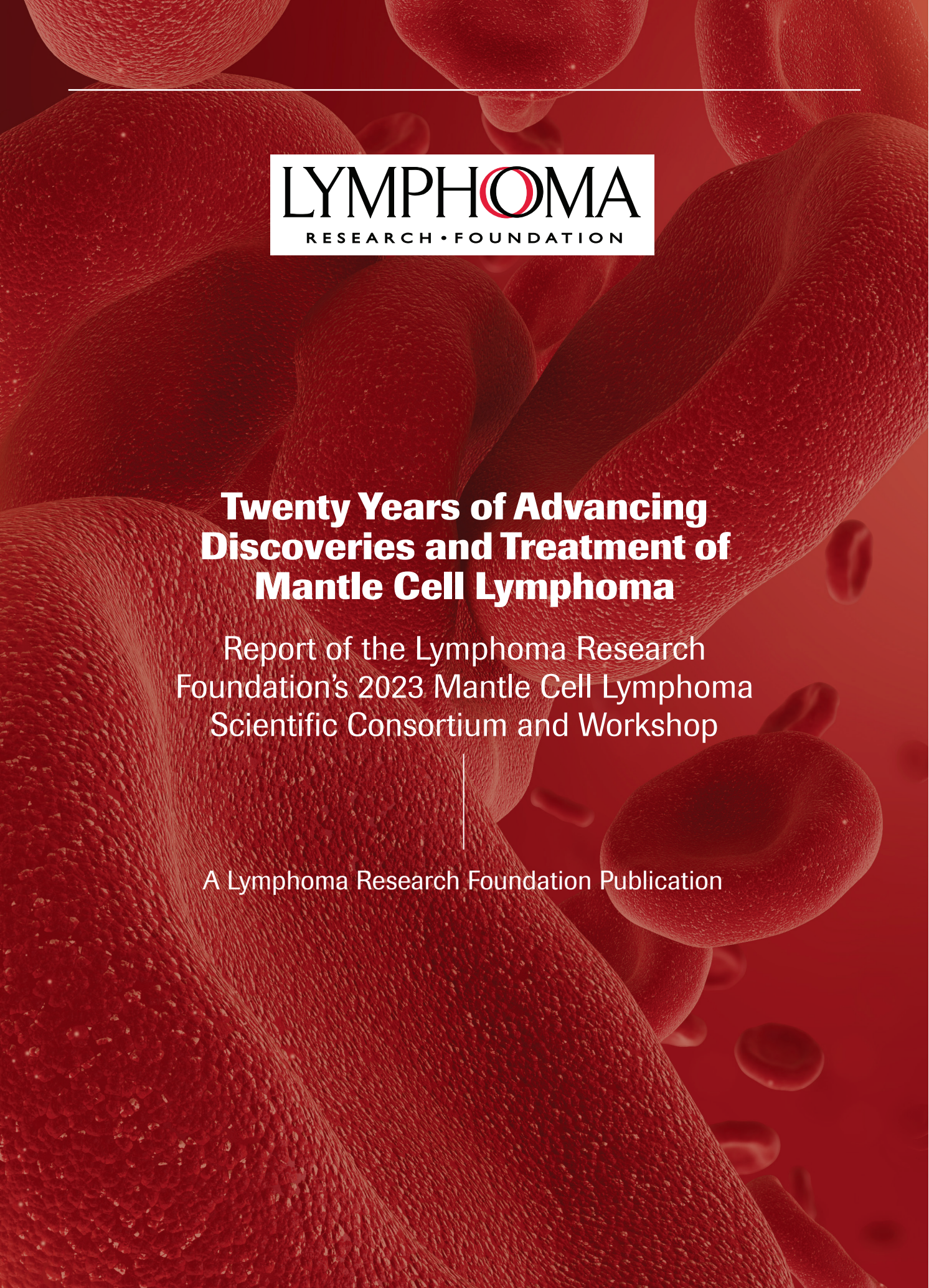
Lactation

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



LYMPHOMA RESEARCH • FOUNDATION

Twenty Years of Advancing Discoveries and Treatment of Mantle Cell Lymphoma

Report of the Lymphoma Research Foundation's 2023 Mantle Cell Lymphoma Scientific Consortium and Workshop

A Lymphoma Research Foundation Publication

Mantle Cell Lymphoma Consortium Executive Committee

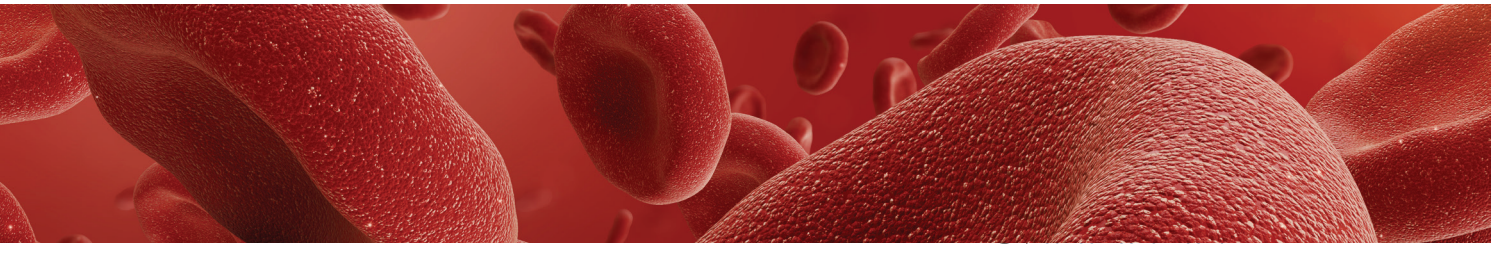
Eduardo M. Sotomayor, MD
Director of the Cancer Institute
Cancer Center of South Florida
Tampa General Hospital
Executive Committee Chair

Michael Wang, MD
Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center

Leticia Quintanilla de Fend, MD
Head of Immunohistochemistry and Core Facility Mouse Pathology, Reference Center Hematopathology
Institute of Pathology
Tübingen University Hospital
Eberhard Karls University of Tübingen

Julie M. Vose, MD, MBA
Neumann M. and Mildred E. Harris Professor
Division Chief, Division of Hematology and Oncology
University of Nebraska Medical Center
Coeditor in chief of *ONCOLOGY*

Peter Martin, MD
Professor of Medicine
Chief of Lymphoma Program
Weill Cornell Medicine



ABSTRACT

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma characterized by the t(11;14) chromosomal translocation, which leads to the dysregulation of the cell cycle through overexpression of cyclin D1. Although advances in treatment have improved outcomes, in particular the introduction of Bruton tyrosine kinase inhibitors to the treatment armamentarium and more recently chimeric antigen receptor T-cell therapy, MCL often rapidly develops resistance and has a high rate of relapse. In addition, MCL is clinically heterogeneous. Response to treatment can vary, making it difficult to establish a standard treatment approach. Thus, there remains a significant need for more research on MCL biology, including those molecular mechanisms underpinning treatment response or lack thereof, so that novel agents may be identified and/or the use of existing agents may be optimized. At the Lymphoma Research Foundation's 20th MCL Scientific Consortium and Workshop, researchers gathered to discuss recent developments in both basic scientific and clinical research to continue to develop an understanding of MCL and improve outcomes for patients. This report, which includes a summary of each presentation, reviews the findings presented at the workshop and highlights opportunities, open questions, and areas for future study that would pave the way for a cure for this disease in the coming decades.

INTRODUCTION

Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma most often associated with the t(11;14) translocation, leading to overexpression of cyclin D1. MCL is clinically heterogeneous, and as a result, there is no single therapeutic approach or standard of care. Furthermore, the determinants of these varying clinical phenotypes (eg, indolent disease vs more aggressive disease) are unclear and, thus far, there is no way to predict treatment response. Importantly, research results have revealed that it is not just the genetic or epigenetic profiles of individual tumor cells that affect treatment response, but also the tumor microenvironment (TME). In recent years, research has not only taken advantage of an improved ability to monitor genetic/epigenetic changes and gene expression on the single-cell level to evaluate MCL tumor biology but has expanded to include analysis of the cross talk between the tumor cells and the cells of the TME and analysis of the resultant impact on treatment response. In addition, the introduction of several new agents to treat patients with MCL has amplified the need to clearly define molecular response and clinical outcomes so that patient response may be rapidly and accurately assessed and the use of existing agents optimized. As clinical trials continue to be developed, it will be important to include biomarkers to better stratify patients and assess response in clinical trials so that these markers may eventually be used to guide clinical care.

The workshop included sessions on MCL genetics, mechanisms of resistance or response to treatment, personalization of therapy and prognostics using biomarkers, the TME, and an international overview of clinical trials, and an open forum to establish a road map toward the cure of MCL in the next 20 years.

Recognizing the need for accelerated MCL research and collaboration between clinical and scientific researchers, the Lymphoma Research Foundation has provided MCL-specific research grants and developed the Mantle Cell Lymphoma Consortium (MCLC), a working group that includes both basic scientists and translational/clinical researchers from North America and Europe. Since 2003, the MCLC has met regularly to allow researchers to share their work. It offers a unique opportunity for collaboration between investigators across a wide range of MCL areas of interest. Through this exchange, thoughts on the current and future direction of MCL research are shared and researchers are provided with a unique opportunity to develop collaborations needed to continue to drive MCL research forward. The 20th MCL Scientific Consortium and Workshop, from May 2-3, 2023, in Chicago, Illinois, included sessions on MCL genetics, mechanisms of resistance or response to treatment, personalization of therapy and prognostics using biomarkers, the TME, an international overview of clinical trials, and an open forum to establish a road map toward the cure of MCL in the next 20 years.

Elías Campo, MD, PhD

ARE THERE ANY RESEARCH FINDINGS THAT HAVE SIGNIFICANTLY IMPACTED THE UNDERSTANDING OF MANTLE CELL LYMPHOMA (MCL) BIOLOGY?

CAMPO: The initial observations were clinical observations when we started to study MCL years ago. It was considered to be a homogeneous and aggressive disease, but then there were clinical observations in which the tumor was not so aggressive, as was the general agreement for this type of reflux. What we asked ourselves was: Are those tumors that are behaving more indolently just the beginning of the disease and will [they] become aggressive [later], or is it a tumor with a different biology and different molecular characteristics? Through trying to answer this question, we set up a series of experiments, and that's what we have been substantiating. Recently, from different perspectives, the summary of these results was to propose that MCL was not a homogeneous disease; it was a disease in which we could identify 2 major biological subtypes of the disease with different biological features, different cell of origin, and different clinical evolution. [We found] that eventually, both will end up as aggressive disease, but regarding the beginning of the disease, one was useful in terms of growing and progressing and the other was faster. In spite of these different biological characteristics, we identified that both subtypes had the same genetic hallmark of the disease, the t(11;14) translocation. We thought that it was the same disease with 2 different pathways of evolution. It's important in all the clinical sites of the patients to know which of the [subtypes of this disease the patient has] because patients with different biological subtypes might respond to different treatments and different paces of evolutions of the disease.

WHAT TOPIC DO YOU THINK WAS MOST PREVALENT THAT WAS DISCUSSED DURING THE CONSORTIUM?

CAMPO: In the last few years, we've seen a substantial advancement in the treatment of patients with new drugs, new strategies that come in different families of treatments, new inhibitors, receptors, antiapoptotic tracks targeting the apoptotic pathways, and ongoing therapeutic strategies together with classical treatments. This results in substantial advancements in the improvement of the outcome of patients with longer survival rates. These new treatments also [come] with new challenges because we see how the biology of the tumor advances with these new treatments. Some of them are resistant to these new therapies. Some of these tumors are resistant from the beginning. We started to see, on one side, how good novel therapies were and our strategies [to incorporate them into treatment]. On the other hand, [we looked at] how these tumors are resistant to treatment. If we understand the mechanism of being refractory and resistant, we might be able to design new therapies that take into consideration these methods.

Until now, we have been concentrating on the biology of the tumor cells, and that has been important to understand how the cells evolved. There were several presentations that reflect the interests of the community. In addition to the tumor cells, [other topics discussed included] the host cells, the immune system, the tumor microenvironment, where each one of these cells is growing, and how the cells that are surrounding the tumor cells are interacting with the tumor. These are new perspectives that may help us to understand biology, but also there are a lot of mechanisms of resistance to the tumor cells.

The third point is that we started to see evidence that not all patients with MCL need the same therapeutic approach. Based on the biology of the tumor, we have patients who need intravenous control for long periods with nonchemotherapy protocols. For patients with not very aggressive disease, we can control the disease without introducing very harmful or infectious regimens. New treatments and new mechanisms of resistance and being refractory emphasize the tumor microenvironment and different strategies for different types of patients based on the biology of tumors.

LOOKING AHEAD, WHERE DO YOU THINK FUTURE RESEARCH EFFORTS SHOULD BE FOCUSED IN THE MCL FIELD?

CAMPO: Many of these tumors are complex in terms of biology. We need to accomplish different aspects, so it's difficult to [name] just one focus. All of them are interactive. The tumor is biologically heterogeneous, so we don't completely understand what the drivers of these different biologies are, why we are seeing some patients have stable disease for so many years, and why some patients develop the disease quickly and others slowly. We still need to understand that better. [In addition, another focus should be on] the opposite side of the disease. Why do some patients have very difficult-to-treat, aggressive disease up front? Understanding this biology better will lead us to key aspects to target it more aggressively. That biology is important to try to design drugs and therapies that might control or even cure the

disease without harming the patient. Lastly, understanding how the tumor cells and the host interact is also an area of increasing interest.

ARE YOU CURRENTLY INVOLVED IN ANY RESEARCH YOU WOULD LIKE TO HIGHLIGHT?

CAMPO: We are starting to treat tumor cells with high-resolution approaches. We are also trying to understand the economic implications and epigenetic alterations in cells. There is still much to discover in how the genes are regulated in the different biology of the tumors. Epigenetic modification of the tumor cells is important. Also important is how the tumor cells influence each host to facilitate the progression of those two. How the tumor evolves with different treatments and how they overcome these treatments are the main goals of our science.

Keynote Speaker

MCL From the Microscope to the Genome and Beyond: A Shared Journey

The keynote speaker was Elías Campo, MD, PhD, research director and professor of anatomic pathology at the Hospital Clinic of the University of Barcelona in Spain (Institut d' Investigacions Biomèdiques August Pi i Sunyer).

Campo discussed the history of MCL classification and reviewed the key research findings that over the years have built the current understanding of MCL molecular biology. In addition, how specific MCL features or molecular signatures have been found to affect disease clinical behavior, in particular progression and resistance, was discussed.

MCL is characterized by the t(11;14) translocation, leading to overexpression of cyclin D1 and dysregulation of the cell cycle. However, cyclin D1 has both canonical and noncanonical functions, each of which is affected by cyclin D1 overexpression. For example, cyclin D1 is a transcription factor and its overexpression in MCL induces global transcriptional downregulation, which gives rise to vulnerability against CDK9 and transcriptional inhibitors.[1] Thus, transcriptional inhibitors are a potential avenue for therapeutic development. Exploration of basic MCL biology and characterization of response to therapy are critical for identifying additional therapeutic targets.

Because MCL is heterogeneous, identification of molecular differentiators to be used in disease stratification is of central importance. *TP53* and *CDKN2A* alterations in MCL strongly affect prognosis across a range of studies but have yet to be systematically incorporated into clinical care or clinical trial planning.[2,3] Using next-generation sequencing (NGS), conventional and non-nodal MCL (cMCL and nnMCL) were identified as distinct molecular subtypes, which can be differentiated based on their expression of SOX11 and other features[4]; however, even within cMCL and nnMCL, clinical and molecular heterogeneity persists, with indolent and aggressive subtypes that remain challenging to identify. However, researchers have discovered through mutational analysis that a higher number of genomic alterations is associated with adverse outcomes in both cMCL and nnMCL.[5] Importantly, genetic mutations are not the only type of alteration that may contribute to the outcome: Epigenetic differences are also present within MCL. For nnMCL and cMCL, regions of chromatin activation differ, suggesting another possible source of differing clinical behavior.

The heterogeneity of MCL is perhaps most evident when considering the contrasting behavior of indolent MCL, which can fail to progress for years, and aggressive MCL, which progresses rapidly. Campo discussed recent research that has sought to determine the molecular drivers of disease phenotype, as well as the best clinical approach for those with indolent disease. Overall, a combination of clinical and biological factors may be used to determine treatment approach. Although there is evidence that monitoring MCL prior to initiating treatment is not associated with a worse outcome, researchers have also found that ibrutinib in combination with rituximab is associated with a high rate of complete response (CR) and minimal residual disease (MRD).[6] Campo also presented several recent findings that describe the differentiation of clinical response based on MCL genetic profile, highlighting recent work from Yi et al that used both genomic and transcriptomic profiling to identify distinct molecular subsets associated with differing outcomes.[7]

MCL Genetics, Epigenetics, and Genomics

In MCL, ongoing research is critical not only to identify novel therapeutics but also to better understand MCL disease biology and how it relates to clinical behavior so that treatment approaches may be tailored and outcomes optimized. In the workshop proceedings described here, the very latest research and advances within these areas are shared.

To open this session, Preetesh Jain, MBBS, MD, DM, PhD, assistant professor in the Department of Lymphoma/Myeloma in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston, discussed the impact of mutation profiling on MCL prognosis and outcomes. To date, there are no established biomarkers that are routinely used clinically to predict outcomes or to plan

treatment; however, there are findings from numerous studies that have identified associations between the mutational status of individual genes and patient outcomes. A 162-gene panel was used as part of routine care for 227 patients with MCL. Within the cohort, genomic DNA was isolated from a range of sources: bone marrow aspirate; formalin-fixed, paraffin-embedded blocks; fine-needle aspirate; and peripheral blood. Patients were either treatment naive (n = 130) or pretreated (n = 97). Of the pretreated patients, 47 had received a Bruton tyrosine kinase (BTK) inhibitor and had refractory disease, and 23 had been treated with chimeric antigen receptor (CAR) T-cell therapy. The mutations present in patient samples included *ATM* (51.1%), *TP53* (29.5%), *KMT2D* (21.1%), *CCND1* (19.3%), *BIRC3* (16.2%), *NSD2* (11.4%), *SMARCA4* (10.1%), *UBR5* (9%), *NOTCH1* (8.3%), *CARD11* (7%), *SAMHD1* (7%), *NFKB1E* (6.6%), *SP140* (6.6%), *S1PR1* (6.6%), *DNMT3A* (6%), *NOTCH2* (6%), *IGLL5* (6%), *TRAF2* (5%), and *TET2* (5%). For these patients, there was no single constellation of mutations predictive of outcome; however, patients with more than 3 mutations had significantly worse survival rate ($P < .0001$).

Brian Li, from Washington University School of Medicine, then presented a survey of the genomic landscape of MCL. Whole-exome sequencing (WES) on 27 tumor-normal tissue pairs (lymph node and skin, respectively) was carried out, and single-nucleotide variants, insertions/deletions, structural variants, and copy-number variants were compared. For a subset of samples, a combined analysis of whole-genome sequencing (WGS), structural analysis, and RNA fusion detection was carried out. The use of WES findings confirmed the presence of recurrent variants canonical to MCL, including t(11;14) translocation (8 of 10 WGS samples), as well as *TP53* (6 of 27), *CCND1* (4 of 27), *NSD2* (3 of 27), and *NOTCH1* (3 of 27). *CCND1* and *TP53* mutations were found to be co-occurring in the patient cohort ($P < .05$) and were associated with shorter progression-free survival (PFS; $P < .05$). Several novel mutations were also uncovered, including *ATM* (7 of 27; missense variants, frameshift variants, deletions, and duplications), *ZNF804B* (3 of 27), *DAZAP1* (3 of 27), and *ASXL1* (2 of 27). Of note, the mutational profile observed in patients following CAR T-cell therapy was unique, highlighting the need to continue research on mechanisms of relapse in this setting. Importantly, the use of multiple methods for assessment of molecular changes within this cohort of patients with MCL permitted an integrated analysis across variant types and provided some insights into the differing mechanisms by which genes are mutated. As our understanding of biomarkers expands, it will be important to include them in clinical trials for validation and to support their incorporation into clinical care.

In the next talk, Sunandini Sharma, MS, Department of Pathology and Microbiology at the University of Nebraska Medical Center, presented research results on the impact of tumor mutations on interactions with the TME, and how a combination of MCL genetics and TME composition may be used to identify prognostic subtypes in MCL. Initial research findings revealed that MCL tumors with high proliferative indices not only have different constellations of mutations but also are associated with differing populations of immune cells within the TME when compared with MCL tumors with low proliferative indices. To better understand this dynamic and how individual tumors regulate their immune landscapes, samples from 153 patients used imaging mass cytometry, a time-of-flight analysis that circumvents the need for complexing inherent in other single-cell analysis methods. The study identified at least 2 prognostic MCL subtypes dependent on *ATM* or *TP53* mutational status. *TP53*-positive tumor cells (which were also found to express high levels of p-STAT3, p-NFKB, and HLA) were associated with a diminished T-cell population (CD8+ and CD4+) compared with *ATM*-positive tumor cells, suggesting that the clinical outcomes for these subtypes may also hinge upon TME dynamics. By including information on the TME in stratification, accuracy may be improved beyond that achievable with tumor mutational analysis alone. Future research will include assessment of expression in nearest neighbors as well as expansion of analysis to include established tumor genetic markers of disease severity and their association with effects within the TME.

MCL Mechanisms of Resistance and Response

To open the session on mechanisms of MCL therapeutic resistance and response, Jianguo Tao, MD, PhD, professor in the Department of Pathology at the University of Virginia in Charlottesville, discussed the genetic heterogeneity and plasticity of MCL and how these features give rise to therapeutic resistance and clinical progression. In MCL, plasticity manifests as adaptive remodeling of the kinome, which limits the efficacy of even combination approaches with targeted kinase inhibitors. To overcome MCL resistance to BTK inhibitor (BTKi) therapeutics, an adaptation of the global kinome must be blocked. To understand the keystone activities that permit plasticity in MCL, a molecular assessment of venetoclax-tolerant MCL persister and expander cells was carried out. This analysis suggests that chromosomal 18q21 deletion and concomitant super-enhancer remodeling drive venetoclax resistance. Although expression levels of more than 100 genes were shown to either increase or decrease, all downregulation observed is 18q21 related, indicating pressure and selection for this mutation following BTKi exposure. Importantly, persister cells from both MCL cell lines and primary patient samples are sensitive to transcription inhibition (CDK7). Thus, cotargeting CDK7 transcription reprogramming and BCL-2 may prevent and/or overcome drug resistance achieved through adaptive remodeling. In the case of CAR T-cell

resistance, which eventually occurs in MCL,[8] in vitro targeting of CDK7/9 transcription also overcomes TME-mediated CAR T-cell therapy resistance and enhances CAR T-cell therapy efficacy against lymphoma growth through reshaping of TME evasion, thereby enhancing CAR T-cell trafficking and efficacy. Because residual disease is the eventual cause of relapse, this research provides important insight into how MCL cells may be managed to reduce the likelihood of persistence and expansion and highlights possible therapeutic strategies to improve the efficiency of or prevent resistance to existing therapies.

Next, Tycel Phillips, MD, associate professor in the Division of Lymphoma, Department of Hematology and Hematopoietic Cell Transplantation at City of Hope in Duarte, California, provided an update on bispecific antibodies in MCL. For non-Hodgkin lymphoma, the first data on bispecific agents using a T-cell engaging strategy were generated with blinatumomab. In the original phase 1 MT103-104 dose-escalation study (NCT00274742), blinatumomab was administered as a continuous infusion with mandated hospitalization (due to the short drug half-life), using doses as high as 90 µg/m^2/day.[9] The study was halted due to high rates of neurological toxicity, and step-up dosing with a reduced target dose of 60 µg/m^2/day was implemented to reduce complications.

TABLE 1. **Blinatumomab Dosing[9]**

Dose	n (%)
90 µg/m^2 per day	3 (8)
60 µg/m^2 per day	22 (58)
Below the target dose of 60 µg/m^2 per day	13 (34)

Although blinatumomab was shown to be effective, the need for inpatient infusion has limited its use for acute lymphoblastic leukemia (**Tables 1 and 2**).[9]

Thus, newer bispecifics have been modified to improve half-life and reduce the need for intensive infusion. In MCL, several CD20/CD3 bispecific studies have attempted to enroll patients with relapsed/refractory (R/R) MCL. To date, significant results have been reported with only 2 agents. The first was the phase 1/2 study of mosunetuzumab-axgb (NCT02500407), which enrolled 13 patients and had an objective response rate of 30.8% with a CR rate of 23.1%.[10] Another agent, glofitamab-gxbm, has shown promising results in a phase 1/2 study (NCT03075696) in patients with R/R MCL with prior BTKi exposure.[11] Thus far, glofitamab response has been positive, with most responses to therapy achieved early. Responses have also been durable, with a median duration of CR of 10.0 months (95% CI, 4.9-not eligible), and at the time of data cutoff, 74.1% of patients remained in remission. The most common glofitamab-related adverse effect was cytokine release syndrome (CRS; 73.0%). Of note, MCL has been a more difficult space for bispecific antibodies than other lymphomas, likely due to the presence of circulating tumor cells, which increases the risk of CRS/immune effector cell–associated neurotoxicity syndrome (ICANS). Beyond the efficacy of these agents in MCL, open questions include whether bispecifics can cross the blood-brain barrier as well as how these agents will be used within a landscape where CAR T-cell therapy is a treatment option.

TABLE 2. **Efficacy Outcomes for Blinatumomab[9]**

Efficacy	Outcome
Median treatment duration	51 days
CR	36%
PR	28%

CR, complete response; PR, partial response.

Next, Selina Chen-Kiang, PhD, professor of pathology and laboratory medicine, and microbiology and immunology at Weill Cornell Medicine in New York, New York, discussed how CDK4/6 inhibitors' control of T-cell surveillance may deepen or prolong the clinical response to BTKi. In MCL, overcoming drug resistance remains a significant hurdle. Due to the suspected role of transcriptional control in ibrutinib resistance, a phase 1 clinical trial (NCT02159755) exploring the effect of CD1/CDK4 inhibition, using palbociclib, on ibrutinib response in recurrent MCL was conducted in 27 patients. A CR rate of 42% was observed, and 5 patients (2 CRs and 3 partial responses) have maintained their treatment regimen for nearly 9 years.[12] To understand the molecular underpinnings of these clinical results, a comprehensive longitudinal analysis was performed using single-cell RNA sequencing (RNA-seq) on sequential tissue and blood samples collected from patients before, during, and upon progression. This exploration led to the identification of 4 transcriptomically distinct clusters (Cs) within MCL cells: C1, mirroring quiescent normal B cells; C2, exhibiting characteristics of hyperactivated B cells with enhanced B-cell receptor (BCR) and cytokine signaling; C3, representing nondividing, long-lived MCL cells; and C4, comprising highly proliferative cells. Primary resistance or progression on treatment for MCL was found to correlate with a significant expansion of either C3 or C2 cell populations. The latter fuels the proliferating C4 cells. This shift was accompanied by a substantial decrease in the expression of both MHC I and MHC II on MCL cells. As disease progressed, a sharp reduction in both CD8+ and CD4+ T cells was observed, which apparently arose from 2 independent mechanisms. This suggests that T-cell surveillance is required for maintaining a prolonged response to ibrutinib. In 1 patient, progression on palbociclib plus ibrutinib in the clinical trial was specifically associated with expansion of long-lived C3 MCL cells. Treatment of venetoclax with ibrutinib restored ibrutinib sensitivity, leading to recovery of CD4+ and CD8+ T cells and a complete

response for 3 years and continuing. These findings highlight the importance of T-cell mediated immunity in treatment response in MCL as well as the potential for leveraging these pathways and shifts in MCL cell cluster dynamics to improve outcomes for patients.

Marcus Messmer, MD, assistant professor in the Department of Hematology/Oncology at Fox Chase Cancer Center in Philadelphia, Pennsylvania, then presented a case study lending insight into the mechanism of acquired resistance to zanubrutinib. An 81-year-old man, given zanubrutinib following prior treatment with rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP); bendamustine and rituximab (BR); and acalabrutinib, was assessed using NGS on peripheral blood samples. The patient achieved a near-complete response on zanubrutinib but within 2 years developed a rising lymphocyte count with flow cytometry consistent with MCL. At this time in the treatment course, newly emerged mutations, *BTK* C481S and *TP53* F134L, were uncovered. Of note, *BTK* C481S is rare in ibrutinib-managed MCL and so may be unique to zanubrutinib resistance. At the time of relapse, the patient was initiated on venetoclax, with normalization of lymphocyte count within 3 weeks. Circulating primary lymphoma cells were later evaluated using a novel ex vivo model incorporating the tumor microenvironment (TME), which was able to accurately predict that the MCL cells were resistant to ibrutinib, zanubrutinib, and pirtobrutinib and sensitive to venetoclax. This is of particular interest because it lends further support to the use of this ex vivo model to assess drug sensitivity, which could reduce patient exposure to therapies against which their MCL is resistant. Additionally, further studies are needed to determine whether there is a relationship between BTKi use and efficacy of pirtobrutinib at relapse.

Hilka Rauert-Wunderlich, PhD, a pathologist at the University of Würzburg in Germany, discussed research on the role of CD52 and OXPHOS in MCL. The adaptations of the transcriptome in response to ibrutinib may be assessed via time-resolved small conditional RNA-seq to reveal key features of ibrutinib-surviving cells and was used in the presented study to identify pathways that may be targeted by therapeutics.[13] Following exposure to ibrutinib-sensitive MCL cells, cells that survive undergo metabolic reprogramming to reliance on oxidative phosphorylation (OXPHOS) and undergo a decrease in glycolysis and NF-B signaling, with a concomitant increase in CD52 and CD37 expression and decrease in CD40 expression.[14] By combining ibrutinib with the OXPHOS inhibitor IACS-010759, MCL toxicity was significantly increased, compared with ibrutinib monotherapy. Targeting CD52 using a CD52 monoclonal antibody following ibrutinib pretreatment was also effective, leading to complement-dependent cytotoxicity in an ibrutinib-sensitive cell line. Thus, the use of anti-CD52 therapy may be considered for consolidation therapy to achieve MRD negativity and prolong PFS in patients after ibrutinib treatment as the primary BTK. In addition, targeting OXPHOS using ibrutinib plus IACS-010759 as a coadministered combination therapy is of interest for future development.

Next, Mariusz Wasik, MD, the Donald E. and Shirley C. Morel, Stanley and Stella Bayster Chair in Molecular Diagnostics; professor and chair of pathology; and associate director of the Cancer Center at Fox Chase Cancer Center, continued the discussion of MCL mechanisms of resistance to BTKi. Although *BTK* or *PLCG1* mutations are drivers of resistance in chronic lymphocytic leukemia (CLL), these mutations are rare in MCL, suggesting a different mechanism of resistance. Additionally, patients with MCL can exhibit varying degrees of resistance, indicating a wide range of tumor biologies underpinning resistance. In MCL, *ROR1*, which is absent in normal hematopoietic cells, is frequently seen, both in MCL primary cells and cell lines, where it is associated with the CD19 receptor. Clustered regularly interspaced short palindromic repeats (CRISPR)–mediated disruption of ROR1 revealed that ROR1 dependence leads to resistance to BTKi ibrutinib through BCR- and BTK-independent but CD19-dependent activation of intracellular signaling pathways PI3K-AKT and MEK-ERK. ROR1 also sustains activity of MCL cell metabolic pathways, with both glycolysis and glutaminolysis remaining unaffected by BTK inhibition in ROR1-expressing MCL cells but not BCR/BTK-dependent MCL cells. Thus, ROR1 expression can promote MCL cell growth in a BCR/BTK-independent fashion, rendering cells insensitive to ibrutinib. Together, these findings raise the question of whether ROR1 monitoring in clinical practice would be of value and suggest a novel approach to MCL therapies that may be effective in managing BTKi-resistant MCL or even preventing the development of ROR1-dependent BTKi resistance.

Fangfang Yan, PhD, a postdoctoral fellow at MD Anderson Cancer Center, continued the discussion of resistance by presenting findings from a single-cell RNA sequencing analysis of 66 samples from 25 patients treated with BTKi and/or CAR T-cell therapy. Although CAR T-cell therapy is effective for overcoming ibrutinib resistance in MCL, many patients experienced relapse following this treatment. The analysis aimed to understand how tumor cell–intrinsic features shape resistance to BTKi therapy and CAR T-cell therapy after BTKi. Single-cell RNA was collected before and post BTKi treatment and before and post CAR T-cell treatment following ibrutinib failure. Analysis revealed that increasing MYC activity correlates with increasing, sequential resistance, relative to normal controls and BTKi-resistant samples. To permit the identification of early drivers of resistance, trajectory analysis was used to order cells based on transcriptome similarity and evaluate continuous transitions. Both HSP90AB1 and CDK9 expression, each

of which is correlated with MYC activity levels, were identified as early drivers distinct from those active in ibrutinib resistance. Further, HSP90AB1 also appears to be an early driver of CAR T-cell resistance, and CDK9 was significantly upregulated in CAR T-cell and ibrutinib dual-resistant samples. Importantly, cotargeting of HSP90 and CDK9 synergistically diminished MYC activity, decreasing MCL cell viability and inducing apoptosis. Collectively, findings from the study revealed that the HSP90-MYC-CDK9 network is the primary driving force of therapeutic resistance and uncovers a possible avenue for reducing the impact of dual ibrutinib and CAR T-cell resistance.

Pradeep Kumar Gupta, PhD, a research associate in the Department of Radiology at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, discussed methods for the detection of metabolic biomarkers indicative of ibrutinib response in MCL. The primary means by which ibrutinib can successfully treat patients with MCL is through inhibition of key cell proliferation pathways; however, these same pathways also affect cell metabolism. Thus, ibrutinib-induced metabolic changes may be a valuable tool for the assessment of MCL sensitivity and response. To investigate the predictive value of these changes, MCL metabolism analysis and high-resolution hydrogen 1 magnetic resonance spectroscopy (1H MRS), performed on a 9.4T vertical bore spectrometer, were carried out on patient-derived cell lines of varying sensitivity to ibrutinib in in vitro cell growth assays (MCL-RL; high responder), REC-1 (moderate), JeKo-1 (poor), and MCL-SL (nonresponder). 1H MRS is a noninvasive modality capable of dynamic assessment that evaluates tumor response using this approach of interest to support adaptive and personalized treatment approaches. Imaging studies revealed that ibrutinib affects glycolysis (lactate), amino acid metabolism (alanine), and membrane metabolism (choline) most strongly in ibrutinib-responsive MCL-RL, followed by REC-1, and borderline in IBR poorly responsive JeKo-1. In addition, ibrutinib markedly inhibited lactate accumulation in MCL-RL and REC-1 cell lines, much less so in JeKo-1, and essentially not at all in MCL-SL cells, an effect that directly correlates to ibrutinib impact on cell growth of these MCL cell lines. These findings indicate the potential of lactate, alanine, and choline to serve as early and sensitive signatures of effective BTK inhibition.

Tumor Microenvironment in MCL

To open this session, Jain discussed findings that describe TME subtypes and their impact on BTKi response and subsequent clinical outcomes. The study, for which research is still ongoing, used multiomic profiling of the TME in tissues from patients with MCL treated with a BTKi such as ibrutinib, acalabrutinib, or zanubrutinib. Sequencing methods include WES (n = 42) and RNA-seq (n = 42) in combination with a previously published analysis of a 122-patient MCL cohort. Based on the transcriptomic profiles obtained from patient samples, 4 distinct groups based on TME were identified: normal lymph node (n = 27), immune cell enriched (n = 46), mesenchymal (n = 44), and immune cell depleted D (n = 51). In patients with primary BTKi resistance, the D subtype was most common compared with responders and those with acquired resistance. Within the D subtype, a high tumor proliferation gene signature was observed, and Ki-67 of more than 50% of tissue biopsy results had a linear correlation with group proliferation rate signature. Somatic mutations previously reported in ibrutinib-resistant MCL and/or in patients with refractory high-risk MCL (mutations in *TP53, SMARCA4, NOTCH1, NSD2*) were also predominant in group D. Clinically, the D group had significantly shorter survival compared with other TME groups ($P < .001$). These findings may have prognostic/predictive value and suggest that the MCL TME may have a dominant role in the pathogenesis of MCL immune suppression and BTKi resistance.

Virginia Amador, PhD, group leader of the Functional Characterization of Oncogenic Mechanisms in Lymphomagenesis at the Institut d'Investigacions Biomèdiques August Pi i Sunyer in Barcelona, Spain, presented research that uncovered CD70 as a possible novel target for immunotherapy in MCL.[15] SOX11 transcription factor has an established role in MCL oncogenesis.[16] In cMCL, SOX11 is overexpressed, whereas in nnMCL, SOX11 is either not present or minimally expressed.[17] In this study, NanoString immune cell panel-based transcriptome analysis, along with immune-cell phenotyping by immunohistochemistry of both SOX11+ and SOX11– nodal MCL, was carried out to better understand the interactions between SOX11 expression in MCL cells and the surrounding TME. These analyses showed downregulation of most of the specific immune cell subtype markers, suggesting an immunosuppressive microenvironment in SOX11+ nodal MCL. Differential expression profile analyses resulted in the identification of CD70 as a target gene of SOX11 and revealed that in SOX11+ nodal MCL, CD70 expression is activated. CD70 upregulation in MCL cells was associated with worse patient prognosis and was accompanied by TME changes, including significantly higher infiltration of effective regulatory T (eTreg) cells and lower granzyme B+ and CD8+ T cells in nodal MCL. Furthermore, CD70 upregulation in MCL and higher infiltration of eTreg cells in nodal MCLs are associated with worse survival of patients. Additionally, in a preclinical 2D coculture model of MCL and allogeneic CD3+ activated T cells, CD70-blocking antibodies increased interferon secretion and MCL cell death. Thus, expression of CD70 promotes immune evasion through inhibition of T-cell antitumor toxicity and supports increased viability and proliferation. Taken together, these findings suggest that CD70 and CD19 dual

CAR T-cell therapy may be a promising therapeutic approach for MCL.

Next, Mamta Gupta, PhD, associate professor of biochemistry and molecular medicine and associate professor of dermatology at George Washington University in Washington, DC, continued the discussion of the MCL TME by sharing research on the role of macrophages in the cross talk between malignant MCL cells and intratumoral immune cells. In preclinical models, evaluation of lymphoma-associated macrophages (LAMs) showed polarization of F4/80+ LAMs into CD206+ M2 and CD80+ M1 phenotypes. Similarly, in an analysis using human MCL cell lines, coculturing monocyte-derived macrophages with MCL cells induced an M2-like phenotype by elevated CD163+ and IL-10 expression, whereas M1 markers CD80 and IL-12 were not altered. In the presented research, these findings were expanded by demonstrating that CCR1, which has established proinflammatory effects, is highly expressed in monocytes (Mo) and macrophages (M), and that pharmacologic inhibition or genetic deletion of CCR1 can block chemotactic Mo/M migration and reprogramming of M toward an MHC-II+/TNF+ immunogenic phenotype. Interestingly, MCL tumors raised in CCR1-null (CCR1 KO) mice showed significantly smaller tumors with decreased infiltration of peritoneal-M, compared with wild-type CCR1. In addition, CCR1 KO mice exhibited increased T-cell infiltration in MCL-TME and an antitumor CD8+ T-cell response. Collectively, these data highlight the importance of LAMs reprogramming in MCL progression and CCR1 antagonists as a potential therapeutic strategy against MCL.

To continue the discussion of the MCL TME, Dylan McNally, a graduate student at Weill Cornell Medicine, discussed findings from a study on TME structural and compositional patterns. First, multiparameter imaging of 44 proteins in 155 treatment-naive tumor samples from the prospective Lymphoma Epidemiology of Outcomes cohort study was carried out. A total of 5.5 million single cells were analyzed for established B-cell, NK, stromal, myeloid, T-cell, and mitotic markers. This analysis identified 46 cell types in MCL TME, including 5 malignant MCL states, 12 T-cell populations, 8 monocyte/macrophage populations, and 6 stromal populations. Next, composition-based clustering of protein expression revealed distinct TMEs, or structural patterns. "Cold" TMEs were largely depleted of infiltrating immune and stromal cells; "follicular" TMEs presented extensive follicular dendritic cell networks intermixed with malignant cells; "T-cell regulated" TMEs were highly enriched for CD4+ T cells, including FOXP3+ Tregs and only residual myeloid cell infiltration; "inflammatory" TMEs were enriched with plasma cells, neutrophils, cytotoxic lymphocytes, and CD163+/S100A9+ macrophages; and "atypical myeloid" TMEs were enriched with CD16+ monocytes and CD16+/CD206+ macrophages. These 5 MCL TME subtypes were subjected to a survival analysis, which revealed that follicular TME was significantly associated with superior outcome (OS; log rank $P < .01$). Importantly, the imaging technology used in this study allows for the assessment of spatial interactions and community analysis, which are important next steps.

Michael Wang, MD

CAN YOU DISCUSS THE RATIONALE BEHIND CREATING THIS CONSORTIUM?

WANG: MCL [mantle cell lymphoma] is a rare disease. [It's important] to have the combined wisdom, exchange ideas of how to cure this disease, exchange clinical practice knowledge, share and promote the progress of clinical research, and further promote basic research and the connection between clinical research and basic research. The overall goal is to cure MCL. We have been united under the MCL consortium for many decades, and the consortium will continue to grow. In 2023, we reached a new peak of activity [in the field]; therefore, we summarized this activity in terms of basic research, or translation research, and clinical research for this article. We are very happy to share this in a publication so everybody in the world can read it.

EXPERTS ACROSS THE FIELD CAME TOGETHER TO DISCUSS A RANGE OF TOPICS. WHICH DO YOU THINK WAS THE MOST PREVALENT?

WANG: I'm mainly a clinician and clinical researcher, and I do some translational research as well. The most important is our advances in therapeutics because this directly [benefits] our patients. One of the major advances in 2023 is that the consortium and the many investigators in the consortium participated in this international clinical trial with pirtobrutinib [Jaypirca] in relapsed/refractory [MCL] because the result [from the phase 1/2 BRUIN trial (NCT03740529)] is so good. The response rate was 50%, and the complete response rate was 13%. Because of the performed efficacy [and the tolerability] of pirtobrutinib, the FDA approved this drug for relapsed/refractory MCL in the United States in January 2023. Therefore, we have added another oral treatment for our patients…because this is a very well-tolerated pill and is highly effective.[1]

IN THE CONCLUSION OF THE ARTICLE, SURROGATE END POINTS WERE DISCUSSED. CAN YOU EXPAND ON WHAT THEY ARE AND WHY THEY'RE IMPORTANT?

WANG: We have many surrogate end points, with the best being overall survival [OS]. If you use OS, you will wait for too many years [for results, which] will slow down the clinical research. We use the surrogate marker called progression-free survival [PFS]. This is the internationally recognized surrogate end point, instead of OS. PFS is a good summary of efficacy plus durability. That's why it is in many clinical trials, especially the international phase 3 trials. It will continue to be a great surrogate marker for the clinical trials. The issue is that the end point for PFS is significantly different, in favor of the treatment arm. However, the OS may not be different. If you have OS [that is] not statistically different but still in favor of the treatment arm…the PFS difference will be very significant. That's the surrogate marker.

WHERE SHOULD FUTURE RESEARCH EFFORTS BE FOCUSED IN MCL?

WANG: The No. 1 thing is to continue to develop new therapies against different targets—not only our current different targets but also different therapies. We also need to continue to generate chimeric antigen receptor [CAR] T cells, not only against CD19 but [also] against other targets. We will focus on targeted therapies, developed with CAR T-cell therapies and we need to pay attention to other immunotherapies, such as the bispecific antibody glofitamab-gxbm [Columvi], another antibody called epcoritamab-bysp [Epkinly], and more to come. We're also combining polatuzumab vedotin-piiq [Polivy], which is the antibody immunoconjugate, plus mosunetuzumab-axgb [Lunsumio], which is a bispecific antibody; this combination is also very effective. We continue to focus on the development of therapeutics, but we [must also] understand the mechanisms of resistance because, after a while, every therapy becomes resistant. We hope we can understand the mechanism of this so we can bypass and use the combination to overcome the resistance. Those are the main areas, in my opinion.

REFERENCE

1. FDA grants accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma. FDA. January 27, 2023. Accessed January 5, 2024. https://bit.ly/47qhzyQ

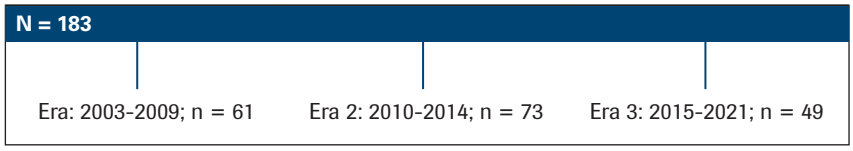
Michael Wang, MD, and His Treatment Approach to MCL

To open the second day of the workshop, Michael Wang, MD, professor in the Department of Lymphoma and Myeloma at MD Anderson Cancer Center, presented clinical pearls for treating patients with MCL along with several case studies illustrating preferred approaches to disease management. Wang began by discussing considerations for approaching the newly diagnosed patient with MCL, including features of both typical and atypical patient presentation, approaches to risk stratification, and important clinical and nonclinical factors for treatment selection. He then discussed his treatment approach for patients older than 65 years and younger than 65 years, including his approach to incorporating trial therapies and novel off-trial therapies and the rationale for considering or selecting each option. The presentation included a discussion of ibrutinib withdrawal and a review of open questions in MCL with regard to treatment selection and clinical management. Wang also provided a review of recent scientific findings that suggest alternative pathways in MCL for which novel therapeutics may be developed, including those that have been recently demonstrated to be critical for metabolic reprogramming and ibrutinib resistance. For example, the 17q gain and BIRC5 may cause clonal evolution and disease progression in ibrutinib-venetoclax nonresponders. Additionally, TIGIT overexpression has been recently shown to be a critical part of T-cell exhaustion and CAR T-cell resistance in MCL.

Advances in MCL Epidemiology: Prognostications, Predictive Biomarkers, and Precision Medicine

To begin the session, Max J. Gordon, MD, from the Department of Lymphoma/Myeloma of MD Anderson Cancer Center, presented a validated comorbidity score associated with survival in patients with MCL. First, to efficiently and accurately assess patient risk in CLL, the Three-Factor Risk Estimate Scale (TRES) comorbidity score was developed in CLL from the Cumulative Illness Rating Scale (CIRS).[18] In the presented study, the utility of the TRES was investigated for MCL. A multicenter retrospective cohort of patients with MCL from 4 US sites (n= 413), with a median age of 63 years (range, 37-86), was used. Of these patients, 361 were previously untreated; most treated patients received bendamustine-rituximab (n=120) and 173 received autologous stem cell transplants. Findings were then validated using a 1565-patient cohort from SEER-Medicare. The TRES score grades risk based on 3 categories to generate a measure of risk: low (0), intermediate (1), and high (2-3). A single point is given based on the presence of (1) vascular comorbidities (any CIRS grade; venous insufficiency/lymphedema, aortic stenosis,

FIGURE 1. **Timeline of Second-Line Therapy in the MER Model**



MER, Molecular Epidemiology Resource.

deep vein thrombosis or pulmonary embolism, symptomatic atherosclerosis, etc), (2) upper gastrointestinal comorbidities (documented opioid use disorder, acute or chronic pancreatitis, melena, history of perforated ulcer, or gastric cancer), and (3) moderate to severe endocrine disorders (eg, diabetes with oral agents or insulin, hyperthyroidism, obesity, adrenal insufficiency, etc). In this study's primary cohort, the TRES comorbidity risk score was low in 51% of patients, intermediate in 31%, and high in 18%. The median event-free survival (EFS) was 77, 56, and 42 months (P = .019) and 5-year OS was 81%, 78%, and 61% in patients with low, intermediate, and high TRES scores, respectively. TRES was also associated with EFS (P = .004) and OS (P = .002) in frontline MCL. Following a similar pattern, in the validation cohort, from time of diagnosis, 5-year OS was 52%, 41%, and 31% (P <.001) in low, intermediate, and high TRES, respectively. Because TRES is an easy-to-use comorbidity score independently associated with survival in older patients with MCL, it may be used in addition to age to stratify patients for clinical trials or in clinical practice to identify patients who are at high risk. Importantly, some of the identified comorbidities are treatable and/or modifiable, highlighting the importance of proactive management of non-MCL comorbidities as part of clinical care.

Yucai Wang, MD, PhD, a hematologist/oncologist at Mayo Clinic in Rochester, Minnesota, then presented findings from a prospective cohort study on treatment patterns and associated outcomes in patients with R/R MCL in the Mayo/Iowa Molecular Epidemiology Resource in a prospective cohort treated with second-line therapy. Patients in the study were diagnosed with MCL between 2002 and 2015.[19] During this time, the landscape of frontline therapy evolved, and several new agents for both first- and second-line therapy became available. To understand if these changes have given rise to changes in second-line treatment choice, response, and/or associated survival, 183 patients with R/R MCL who received second-line therapy were analyzed (**Figure 1**). Sixty-one patients from Era 1 (2003-2009), 73 from Era 2 (2010-2014), and 49 from Era 3 (2015-2021) were included in the analysis. There were no statistical differences in age, sex, stage, or simplified MCL International Prognostic Index (MIPI) between eras. Second-line treatment was clearly different between eras, indicating that second-line MCL therapy use has evolved. For example, second-line BTKi use was largely limited to Era 3 (44%), due to availability. Second-line bendamustine-rituximab use was minimal in Era 1 (3%) and less common in Era 3 (17%) than in Era 2 (37%). Second-line stem cell transplant use was similar across eras, ranging from 9% to 14%. Observed treatment advances appear to be associated with improved outcomes. The 2-year EFS rate was 21% in Era 1, 39% in Era 2, and 58% in Era 3. The 5-year OS rate was 31%, 38%, and 69%, respectively. The overall response rate (ORR) to second-line therapy was 56%, 80%, and 88%, respectively (CR, 31%, 54%, and 53%, respectively).

Kavindra Nath, PhD, research assistant professor of radiology at the University of Pennsylvania, continued the discussion by reviewing data on in vivo detection of BTK inhibition using MCL xenograft models. Currently, MCL and other lymphomas are staged by 18F fludeoxyglucose FDG PET/CT imaging, and therapeutic response is measured primarily by changes in tumor volume. However, BTKi activity is more cytostatic than cytotoxic, and changes in tumor burden are delayed. In contrast, metabolic changes indicative of BTKi response may occur within hours. Thus, to rapidly distinguish between responders and nonresponders, alternative methods are needed. In the presented study, MCL-derived cell lines REC-1 (ibrutinib responsive in in vitro studies), JeKo-1 (poorly responsive), and SL (resistant) were xenotransplanted into mice and examined for metabolic changes induced by treatment with ibrutinib using 1H MRS on days 0, 2, and 7 following initiation of BTKi therapy. In this model, ibrutinib produced an early and profound reduction in REC-1 tumor concentrations of lactate (biomarker of glycolysis), alanine (biomarker of amino acid metabolism), and, to a lesser degree, choline (biomarker of membrane metabolism) tumors. In JeKo-1 tumors, this reduction was less profound. Conversely, ibrutinib-resistant tumor cells showed no significant reduction of the above-listed metabolomic biomarkers. Thus, inhibition of metabolic pathways and resultant reduction of intratumoral concentrations of lactate, alanine, and possibly choline measured by 1H MRS hold potential as early biomarkers of BTK inhibition in MCL.

MCL Clinical Trials to Know

To begin a discussion of MCL clinical trials, Timothy Fenske, MD, MS, a professor at Froedtert & the Medical College of Wisconsin in Milwaukee, discussed MRD. MRD has been used in MCL to assess prognoses and guide the direction of therapy, as a clinical trial end point and sensitive measure for response to treatment, and for MCL surveillance. There is a range of methods for assessing MRD, including multicolor flow cytometry, quantitative polymerase chain reaction (PCR), immunoglobulin gene high throughput sequencing (Ig-HTS), and other NGS approaches (CAPP seq, PhasED seq). To date, most first-line and second-line clinical studies that have

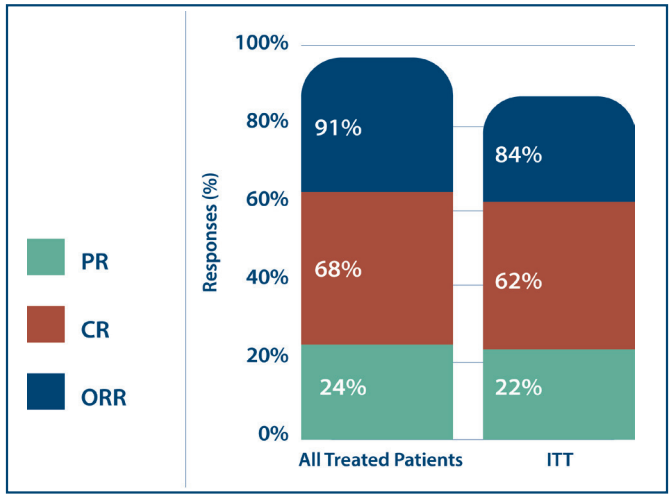
included MRD have used PCR-based measures and most often the end point used is the rate of MRD. In these studies, as well as in studies using Ig-HTS (clonoSEQ), MRD is consistently shown to be predictive of PFS. Despite its potential to accelerate clinical trial readout, there have been no MRD-driven trials. To meet this need, the phase 3 ECOG-ACRIN EA4151 trial (NCT03267433) was designed to assess the benefit from autologous hematopoietic cell transplantation in patients achieving MRD-negative CR in the first line, with a primary outcome of OS.[20] At the time of this presentation, 573 patients had been enrolled, with a target of 689 patients, across 4 arms; results are pending. Fenske also presented data on MRD as a surveillance tool that may be considered to identify patients who are at high risk for early interventions.

In the next presentation, Jia Ruan, MD, PhD, professor of clinical medicine in the Division of Hematology and Medical Oncology at Weill Cornell Medicine, presented the results of a phase 2 trial (NCT03863184) assessing acalabrutinib, lenalidomide, and rituximab with real-time monitoring of MRD in 24 patients with treatment-naive MCL.[21] Given the past success of lenalidomide plus rituximab in first-line MCL, as well as the positive effect of acalabrutinib, this study of the combination was not only designed to assess the viability of this triplet therapy but also to explore the feasibility of MRD response-adapted strategy during maintenance.[22,23] Patients received 12 cycles of the combination, followed by maintenance with real-time MRD using adaptive clonoSEQ of peripheral blood. At the end of induction, 83.3% of patients had a CR and there was a 100% ORR. After 24 cycles, therapy was de-escalated in those who achieved MRD negativity, and at the time of the consortium presentation, 10 patients with MRD-negative CR had discontinued acalabrutinib and lenalidomide. At a median follow-up of 26 months, all 22 patients had completed induction and remained in remission, and 2 patients had progressed during maintenance. The 2-year OS rate was 100%, and the 2-year PFS rate was 90%. Peripheral blood MRD was undetectable (less than 10^{-6}) in 50% of patients after 6 cycles, 67% after 12 cycles, and 80% after 24 cycles. Overall, preliminary data demonstrated that this combination is well tolerated and highly effective, and it produces high rates of MRD-negative CR as initial treatment, even in patients with *TP53* mutations. In addition, these findings suggest that real-time MRD has the potential to guide response-adapted treatment de-escalation, especially during maintenance where it is critical to minimize toxicity.

Nikesh Shah, MD, a hematologist/oncologist at Tampa General Hospital in Florida, discussed recent data on frontline treatment approaches in *TP53*-aberrant MCL. Patients with MCL who had *TP53* alterations (present in approximately 15% of cases) have poor outcomes, even when they receive intensive frontline chemotherapy.[23] Lenalidomide plus rituximab has been shown to have activity in MCL; however there are limited data available on activity specifically in *TP53*-mutated MCL.[24] Shah presented findings from a retrospective review of 89 patients with MCL with *TP53* mutations, deletions, or both who were diagnosed between 2005 and 2019 at 2 academic cancer centers in Florida. In the study cohort, *TP53* aberration was detected either at diagnosis (n = 54) or at relapse/progression (n = 35). Compared with MCL that did not have *TP53* mutations, *TP53*-altered MCL was associated with more aggressive disease at presentation and worse OS. Of the patients who had *TP53* alterations, 83.1% had 1 or more high-risk features and 58.3% had a high MIPI score. Frontline therapies received by these patients included bendamustine plus rituximab (BR) or R-CHOP (n = 28), a high-intensity regimen (cytarabine-based or autologous stem cell transplant consolidation; n = 23), lenalidomide plus rituximab (n = 14), BTKi plus rituximab (n = 2), palliation (n = 14), or observation (n = 8). There was no significant difference in EFS among patients with *TP53* mutation, deletion, or both ($P = .86$). For patients with *TP53* alterations detected at diagnosis, median EFS was higher for those receiving lenalidomide plus rituximab vs R-CHOP/BR or high-intensity regimens (85 vs 7.5 vs 19 months; $P < .001$), respectively. Median OS was not significantly different among regimens (lenalidomide plus rituximab [74 months], R-CHOP/BR [27.5 months], and high-intensity [28.5 months]; $P = .24$). Performance status was associated with better survival across treatment lines. Together, these data support consideration of lenalidomide plus rituximab as a chemotherapy-free first-line option for patients with *TP53*-mutated MCL, in particular in patients unfit for transplant and/or cytotoxic chemotherapy. There remains a substantial need for prospective trials to further explore immunomodulatory therapies for *TP53*-mutated MCL as well as CAR T-cell and bispecific antibodies.

Wang shared the US Lymphoma CAR T Consortium experience of brexucabtagene autoleucel (brexu-cel) for R/R MCL as standard of care. Brexu-cel was approved by the FDA for R/R MCL based on the pivotal phase 2 ZUMA-2 trial (NCT02601313), which showed a 91% ORR and 68% CR rate (**Figure 2**) and durable responses, with a median PFS of 25.8 months and a median OS of 46.6 months at 3-year follow-up.[24] After FDA approval, there is a need to continue to evaluate outcomes in real-world patients and to compare this experience with trial data. In the presented retrospective study, 189 patients who underwent leukapheresis between August 2020 and December 2021 at 16 US institutions that had an intent to manufacture commercial brexu-cel were included, and data were analyzed for treatment response, outcome, and toxicities.[25] Of the 189 enrolled patients, 168 (89%) received brexu-cel infusion. Of the 189 patients who received leukapheresis, 86% were BTKi refractory, and 68% received bridging therapy. Of note, 79% would not have met ZUMA-2 eligibility

FIGURE 2. **Response Rates in the ZUMA-2 Trial**



CR, complete response; ITT, intention to treat; ORR, objective response rate; PR, partial response.

criteria (61% would have been ineligible due to disease status). After a median postinfusion follow-up of 14.3 months, the 6-month PFS was 69% and the 12-month PFS was 59%. The 6-month OS was 86% and the 12-month OS was 75%. CRS occurred in 90% of patients, with 8% having grade 3 or higher and 61% of patients had neurotoxicity, with 32% having grade 3 or higher. CRS and ICANS incidences were similar to the clinical trial experience. In a univariable analysis, high-risk simplified MIPI, high Ki-67, *TP53* aberration, complex karyotype, and blastoid/pleomorphic variant were associated with shorter PFS after brexu-cel infusion. Patients with bendamustine exposure within 24 months before leukapheresis had shorter PFS and OS in the intention-to-treat univariable analysis. Taken together, these data show that the efficacy and toxicity of brexu-cel in SOC practice are consistent with that reported in the ZUMA-2 trial. Importantly, the study results highlight that tumor-intrinsic features of MCL, and possibly recent bendamustine exposure, may be associated with inferior efficacy outcomes.

To close the session on MCL clinical trials, Brad Kahl, MD, a professor in the Division of Oncology at the Washington University School of Medicine in St Louis, Missouri, and Martin Dreyling, MD, PhD, professor of medicine in the Department of Medicine and head of the Medical Clinic III at the University of Munich-Grosshadern in Germany, shared an update of US and European clinical trials, respectively. In the US, the National Clinical Trials Network continues to make significant contributions to MCL treatment, supporting multiple intergroup studies involving SWOG, ECOG-ACRIN, ALLIANCE, and BMT CTN. These trials are aimed at optimizing treatment approaches specifically for older or less fit patients, younger or fit patients, and those with relapsed/refractory disease, or treatment approaches that include novel drug combinations. Kahl first presented information on the phase 2 EA4181 trial (NCT04115631), which is comparing 3 chemotherapy regimens consisting of bendamustine, rituximab, high-dose cytarabine, and acalabrutinib in newly diagnosed MCL. Trial parameters were shared, and Kahl provided the update that the trial is now fully enrolled and primary end point analysis was expected by the end of 2023. Next, developments in EA4151, a phase 3 trial of rituximab after stem cell transplant comparing rituximab alone in MRD-negative MCL in first complete remission, were also presented. Although more than the 412 patients needed to be randomly assigned and have been enrolled, almost 10% of patients have refused treatment assignment and the study has enrolled additional patients to compensate. For the phase 2 E1411 trial (NCT01415752), data confirm BR as effective induction in patients who are older and show that rituximab, bendamustine hydrochloride, and bortezomib plus rituximab-based consolidation yield a median PFS of more than 5 years. Another phase 2 study, PrE0405 (NCT03834688), which is looking at bendamustine and rituximab plus venetoclax in patients with untreated MCL who are older than 60 years, has been fully enrolled since March 2022, and data were presented at the 2023 American Society of Hematology Annual Meeting & Exposition.[25] Finally, A052101 (NCT05976763), a randomized phase 3 trial comparing continuous vs intermittent maintenance therapy with zanubrutinib as up-front treatment in patients older than 70 years or those 60 years or older with comorbidities, is expected to enroll in 2024.

Dreyling then discussed updates to European MCL Network studies, starting with the SHINE trial (NCT01776840), a phase 3 study of ibrutinib in combination with BR and rituximab maintenance as first-line treatment for patients with MCL who are 65 years or older.[26] Findings from this study demonstrated that ibrutinib plus BR with rituximab

TABLE 3. **Efficacy Outcomes From the SHINE Trial[26]**

Outcome	Ibrutinib	Placebo
PFS (95% CI)	80.6 months (61.9-NE)	52.9 months (43.1-71.0)
ORR	89.7%	88.5%
CR	65.5%	57.6%
OS at 7 years	55.0%	56.8%

CR, complete response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Martin Dreyling, MD

HOW DO YOU THINK THE STANDARD OF CARE WILL BE IMPACTED BASED ON THE DISCUSSIONS FROM THE CONSORTIUM?

DREYLING: In mantle cell lymphoma [MCL], the standard first-line treatment was based on chemotherapy only. Now on the other hand, we do know that in relapsed disease, this has switched to targeted treatment, essentially Bruton tyrosine kinase inhibitors [BTKis], as they are the cornerstone [of treatment], at least in the early relapses of MCL. Therefore, for the next 5 years or so, the field will be moving to implement this application also in the first-line treatment of MCL.

WHAT TOPIC PRESENTED DO YOU THINK WAS THE MOST PREVALENT?

DREYLING: It depends on what your priorities are. There are very interesting data on the molecular makeup of MCL. When it comes to clinical application or therapeutic application, I think it's mainstream to consider BTKi plus [an additional treatment]. The other strong impact is the future role of immunotherapy. Now we know that chimeric antigen receptor [CAR] T cells are registered for relapsed MCL, essentially for BTKi failures, but the field is moving on. There are already some studies completed with patients who are BTKi naive. It might well be that at a certain point, we think that some patients may be treated with immunotherapy and others may be treated only with targeted treatment.

CAN YOU EXPLAIN SOME PRACTICE DIFFERENCES BETWEEN THE UNITED STATES AND EUROPE?

DREYLING: When it comes to, let's say, the strategies, they're quite similar; however, we do have a different registration status. Specifically, when referring to BTKis. Because in Europe, ibrutinib [Imbruvica] is the only registered BTKi, whereas in the US, it was withdrawn from the market at least for the indication of relapsed MCL.[1] But [in the US] you have acalabrutinib [Calquence] and zanubrutinib [Brukinsa], both of them second-generation BTKis. What we assume is that the second-generation BTKis are better tolerated, so their [adverse] effects are less. However, [when looking at] efficacy, there is no major difference.

LOOKING AT THE YEAR AHEAD, ARE THERE ANY TRIALS YOU'RE EXCITED TO SEE READ OUT?

DREYLING: The major theme is to challenge chemotherapy overall in the first line, so we have established a combination chemotherapy plus BTKi. Namely, the phase 3 TRIANGLE trial [NCT02858258], where we have established the significant benefit of ibrutinib as the first-generation BTKi, and my understanding is that this was also implemented in the US guidelines, and then mentioned that you could also apply second-generation BTKis.[2] Although we don't have the data [yet], I think it's obvious that with a similar efficacy, and with a better tolerability that makes sense. On the other hand, the next wave, I would say, of studies is moving a noncytostatic approach into first-line [therapy]. Some of these data are already available. We do have data from MD Anderson [Cancer Center], and we do have data from Barcelona, in patients with low-risk [disease], using a clear-cut randomized comparison of chemotherapy vs a nonchemotherapy approach.

There are at least 2 studies that have completed recruitment: one is the phase 2/3 ENRICH trial [NCT01880567], [comparing ibrutinib plus rituximab (Rituxan) followed by rituximab maintenance vs rituximab plus chemotherapy].[3] We are already working on the next study generation, which is investigating not only BTKi monotherapy but also combinations of BTKi plus [another treatment].

WHAT SHOULD BE A TAKE-HOME MESSAGE FOR YOUR COLLEAGUES?

DREYLING: The most important point when it comes to clinical application is that there is not 1 [type of] MCL, but there are essentially 2 types. The classical MCL can achieve long-term remissions over a couple of years, maybe even decades with our current standard of care. On the other hand, we have these aggressive subtypes, and they're identified by 3 major factors: P53, high cell proliferation, and blastoid cytology. These patients do much worse. In these patients, we have to work on that, and I believe that [these patients] will be the first ones who will benefit from the new treatment approaches.

REFERENCES

1. Update on IMBRUVICA (ibrutinib) U.S. accelerated approvals for mantle cell lymphoma and marginal zone lymphoma indications. News release. Johnson & Johnson and Pharmacyclics. April 6, 2023. Accessed January 22, 2024. bit.ly/3ZUpDnJ

2. Dreyling M, Doorduijn JK, Gine E, et al. Efficacy and safety of ibrutinib combined with standard first-line treatment or as substitute for autologous stem cell transplantation in younger patients with mantle cell lymphoma: results from the randomized Triangle trial by the European MCL Network. *Blood.* 2022;140 (suppl 1):1-3. doi:10.1182/blood-2022-163018

3. Jain P, Zhao S, Lee HJ, et al. Ibrutinib with rituximab in first-line treatment of older patients with mantle cell lymphoma. *J Clin Oncol.* 2022;40(2):202-212. doi:10.1200/JCO.21.01797

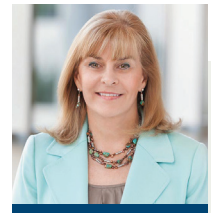
maintenance significantly improved PFS compared with standard chemoimmunotherapy, with a median PFS of 6.7 years (**Table 3**). TRIANGLE, a phase 3 trial (NCT02858258) of ibrutinib with SOC without autologous transplantation in first-line MCL, was also reviewed.[27] Adding ibrutinib improved PFS and OS, begging the question of whether autologous transplant is needed first line in MCL. The final analysis is currently underway, and questions remain about how these findings will impact SOC. Finally, building on results of the phase 2 AIM study (NCT02471391) of venetoclax plus ibrutinib in MCL, the phase 2 OAsIs trial (NCT02558816) investigated if adding venetoclax to ibrutinib plus obinutuzumab will result in improved outcomes in patients with relapsed MCL.[28,29]

Together, these studies not only evaluate a range of new therapeutic approaches in MCL but also contribute to the development of biomarkers and disease stratification. They present an opportunity to better understand the molecular, cellular, and tumor microenvironment changes that occur during treatment response and/or development of resistance.

Road Map to the Cure for MCL in the Next 20 Years: Panel Discussion

In the final session of the workshop, a panel of MCL expert academic researchers and industry representatives from various pharmaceutical companies discussed opportunities and challenges in MCL clinical trials. As our understanding of molecular drivers of disease continues to evolve, collaboration between regulatory and industry stakeholders will be critical for rapidly incorporating biomarkers and other molecular measures of response into clinical trials as end points or stratification tools. It is important to be aware that the adoption of surrogate end points can drastically reduce the costs of clinical trials, accelerate readout, and lead to improved patient care. Especially in an era of incremental progress, surrogate measures are needed because effect sizes are smaller, and therefore trials must include more patients. Furthermore, as more MCL subgroups are recognized, trials specific to disease subsets will be increasingly more difficult to enroll. In addition to innovation in the execution of clinical trials so that trials are smaller and smarter, the use of biomarkers to further reduce the time to readout and the number of patients needed will be critical.

Other challenges facing research in MCL are low enrollment and a lack of diversity in clinical trial populations. Although this represents a complex and multifaceted issue, one preliminary step could be to adjust exclusion criteria so that real-world patients may be more easily enrolled. Physicians emphasized that ongoing partnership and communication



Julie M. Vose, MD, MBA

CAN YOU DISCUSS THE RATIONALE FOR PUTTING THIS CONSORTIUM TOGETHER?

VOSE: This consortium has been going on for a number of years, now sponsored by the Lymphoma Research Foundation, and brings together researchers specifically in mantle cell lymphoma [MCL], which is a rare type of lymphoma and we don't have a lot of great treatments. [This consortium] brings scientists as well as physicians together to try to brainstorm new ideas and new clinical trials, to collaborate and work together on research for MCL to improve the outcome for patients, and to develop new therapies. Over the years, this has been helpful because there's researchers from around the world [who] have attended and collaborated, there have been publications out of each of the consortiums, and [it] has been helpful to the field...to work together to improve the outcomes for patients with MCL. We want to continue to do that and to improve our treatments for patients with this rare lymphoma.

WHAT TOPIC DO YOU THINK WAS MOST PREVALENT?

VOSE: There's a number of topics discussed; the first day is more focused on basic research, and the second day is more on clinical research. The things that are an important part of this consortium [are] to bring the basic and clinical scientists together, to try to come up with new therapies and translate that from basic research into clinical trials into treatments for patients eventually. That's how a lot of the new treatments that we have for MCL and other types of lymphomas have come about in this collaboration. This is a type of symposium that... we should [have] for other types of diseases as well as to bring researchers and clinical scientists together to collaborate and improve outcomes for patients and to develop new therapies. That's the [goal] of this consortium: to try to improve outcomes for these specific types of patients.

DURING THE MEETING'S CONCLUSION, THERE WAS A DISCUSSION ABOUT LACK OF DIVERSITY IN CLINICAL TRIAL POPULATIONS. CAN YOU EXPAND ON WHY THIS IS IMPORTANT TO TALK ABOUT?

VOSE: A lot of our therapies and clinical trials are tested on patients [who] are perhaps able to come to the large academic centers. They have insurance, they have the means to be able to participate in these types of

trials, whereas the patient population that has a disease is not always [represented] in the clinical trials. That's why it's important to be able to have a diversity of patients in clinical trials: to test these new therapies because [patients] may have other medical conditions that would change the outcome of trials and not be necessarily representative of the entire patient population with that disease. It's important to try to advance the treatment of a very diverse patient population through these clinical trial mechanisms.

WHERE SHOULD FUTURE RESEARCH EFFORTS LIE IN THE MCL FIELD?

VOSE: We have had several new therapies for MCL over the last several years. That's exciting. A lot of the patients with MCL are older patients with a lot of other comorbidities and other medical issues. Some of these more aggressive treatments don't necessarily apply to those patients. We need to focus on therapies for patients with MCL that are able to be administered across a lot of different patient populations. This way we don't have to be so concerned about some of their other medical illnesses. A lot of these patients have, for example, cardiac disease, pulmonary disease, or other medical issues that make some of our treatments not as applicable to them. Trying to discover new therapies that have decreased [adverse] effects and are completely applicable among a lot of different patient populations is important.

ARE YOU EXCITED TO SEE ANY TRIALS READ OUT IN 2024?

VOSE: For MCL, there are new trials where we're looking at some of these new therapies, particularly in combinations. We're always looking at new therapies to try to improve the outcomes for these patients. A lot of the big trials have recently been read out, and that's why we have a lot of these new therapies available. Combining these therapies that are FDA approved for MCL or adding additional new therapies is something that we're looking forward to in the future.

between industry and physicians throughout clinical trial planning can improve feasibility (especially around enrollment criteria and end point selection). As trials are designed, it is critical to involve clinicians who care for patients because they are better able to identify designs that are unnecessarily burdensome to patients (eg, frequent follow-ups for long periods). In addition, adequate support for sites (eg, study coordination) and industry support for rapid enrollment are critical. Clinicians agreed that enrollment is bolstered by including a comparative arm that includes a regimen appealing to patients. Patients with MCL tend to be well educated and savvy and largely uninterested in enrolling in trials where the comparator is clearly going to underperform, compared with the experimental arm.

In addition to traditional safety measures, there is a need to use efficient patient-reported outcome tools to assess quality of life as well as short- and long-term outcomes. Measures should also be age adjusted so that outcomes are relevant for the given age group.

Panelists agreed that the poor outcomes of patients with *TP53* mutations, even with immunotherapy, highlights that there is some aspect of disease pathology that remains to be uncovered and targeted. Incorporating exploratory measures that facilitate investigation into these mechanisms is needed.

Finally, the impact of out-of-pocket costs for patients continues to grow. These increasing costs are problematic for all patients, but also worsen access and increase health care disparity. The cost of care is especially burdensome for patients who may not be able to take time off work, live some distance from the center, or are underinsured or uninsured.

Summary

The 2023 MCL Scientific Consortium and Workshop covered recent advances in our understanding of MCL biology and how these advances have uncovered several potential avenues for drug development. Continuing efforts are needed to better understand the basic biology of MCL so that novel therapeutics can be developed to target MCL, especially BTKi-resistant MCL. As our ability to evaluate disease metabolism, molecular changes, and the TME continues to improve, it will be critical to incorporate these findings into clinical studies and treatment paradigms so that adjustments to therapy may be made in real time. As clinical trials continue to be developed, it is important that biomarkers of disease risk are applied for stratification and novel measures of response are incorporated as end points to increase the efficiency of clinical trials and to decrease the time to readout.

Acknowledgments

This meeting, in addition to several projects presented, was supported by grants from the Lymphoma Research Foundation Mantle Cell Lymphoma Initiative and the MCL Consortium. Each presenter whose work is included herein reviewed and approved the summary of that work. ■

For references visit
cancernetwork.com/2.24_MCL

RAPID REPORTER

ONCOLOGY Reviews Key Presentations From the
2023 San Antonio Breast Cancer Symposium

Dato-DXd Improves PFS vs Chemo in HR+/HER2– Metastatic Breast Cancer

Patients with previously treated hormone receptor–positive or HER2-negative inoperable or metastatic breast cancer experienced a significant improvement in progression-free survival (PFS) with datopotamab deruxtecan (Dato-DXd) compared with chemotherapy, according to results from the phase 3 TROPION-Breast01 trial (NCT05104866).

Results showed that the study met its dual primary PFS end point; at the July 17, 2023, data cutoff, the median PFS by blinded independent central review was 6.9 months in the Dato-DXd arm (n = 365) compared with 4.9 months in the chemotherapy arm (n = 367; HR, 0.63; 95% CI, 0.52-0.76; $P < .0001$). Additionally, the median PFS per investigator assessment was 6.9 months (95% CI, 5.9-7.1) vs 4.5 months (95% CI, 4.2-5.5), respectively (HR, 0.64; 95% CI, 0.53-0.76).

By investigator assessment, the 6-, 9-, and 12-month PFS rates in the Dato-DXd arm were 55.2%, 34.7%, and 21.7%, respectively. In the chemotherapy arm, these rates were 36.9%, 20.9%, and 9.9%, respectively.

Additional findings from the study demonstrated that treatment with Dato-DXd offered a PFS benefit over chemotherapy in patients with and without brain metastases. The median PFS among patients with brain metastases at study entry in the investigational (n = 35) and chemotherapy (n = 23) arms was 5.6 months (95% CI, 3.0-8.1) vs 4.4 months (95% CI, 1.4-5.7), respectively (HR, 0.73; 95% CI, 0.39-1.42). Patients without brain metastases experienced a median PFS of 7.0 months (95% CI, 5.7-8.1) vs 4.9 months (95% CI, 4.2-5.5) in the investigational (n = 330) and chemotherapy (n = 344) arms, respectively (HR, 0.62; 95% CI, 0.51-0.75). Similarly, patients achieved a PFS benefit with Dato-DXd vs chemotherapy regardless of prior duration of treatment with a CDK4/6 inhibitor. Patients in the Dato-DXd (n = 151) and chemotherapy (n = 136) arms who received a prior CDK4/6 inhibitor for a maximum of 12 months achieved a median PFS of 6.9 months (95% CI, 5.5-8.1) vs 4.2 months (95% CI, 4.0-5.5), respectively (HR, 0.61; 95% CI, 0.45-0.81). Patients who received treatment with a prior CDK4/6 inhibitor for more than 12 months achieved a median PFS of 7.1 months (95% CI, 5.6-8.5) in the investigational arm (n = 153) vs 5.0 months (95% CI, 4.1-5.7) in the control arm (n = 164; HR, 0.61; 95% CI, 0.45-0.82).

→ **For the full article, visit:** cancernetwork.com/SABCS_TROPION-Breast01

T-DM1/Tucatinib Improves PFS vs Placebo in HER2+ Metastatic Breast Cancer

Patients with previously treated HER2-positive metastatic breast cancer, including those with brain metastases, experienced a significant improvement in progression-free survival (PFS) with tucatinib (Tukysa) plus ado-trastuzumab emtansine (T-DM1; Kadcyla) compared with placebo plus T-DM1, according to primary analysis data from the phase 3 HER2CLIMB-02 trial (NCT03975647).

Data showed that tucatinib plus T-DM1 generated 151 PFS events and a median PFS of 9.5 months (95% CI, 7.4-10.9) vs 182 PFS events and a median PFS of 7.4 months (95% CI, 5.6-8.1) in patients who received T-DM1 plus placebo (HR, 0.76; 95% CI, 0.61-0.95; $P = .0163$). Patients with brain metastases who received tucatinib in combination with T-DM1 (n=99) experienced 70 PFS events and achieved a median PFS of 7.8 months (95% CI, 6.7-10.1). Conversely, those with brain metastases in the placebo arm (n=105) experienced 85 PFS events and achieved a median PFS of 5.7 months (95% CI,

4.6-7.5 [HR, 0.64; 95% CI, 0.46-0.89]). Across prespecified subgroups, the PFS HRs were consistent with that of the overall population.

At a median follow-up of 24.4 months and a data cutoff of June 29, 2023, 53% of the prespecified overall survival (OS) events had been observed. The interim OS data did not meet the prespecified crossing boundary of *P* less than or equal to .0041. There were 71 and 63 OS events that occurred in the tucatinib and placebo arms, respectively. The median OS was not reached (NR; 95% CI, NR-NR) in the tucatinib arm vs 38.0 months (95% CI, 31.5-NR) in the placebo arm (HR, 1.23; 95% CI, 0.87-1.74). Patients in both arms received comparable subsequent systemic therapies. Approximately 50% and 30% of patients received subsequent trastuzumab deruxtecan (Enhertu) or tucatinib (Tukysa), respectively.

→ **For the full article, visit:** cancernetwork.com/SABCS_HER2CLIMB-02

ONCOLOGY Reviews Key Presentations From the **65th American Society of Hematology Annual Meeting & Exposition**

Reduced-Dose Talquetamab Yields Responses, Safety in R/R Multiple Myeloma

Treatment with talquetamab (Talvey) at a reduced dose led to high response rates and improvements with respect to adverse effects in those with relapsed/refractory (R/R) multiple myeloma, according to data from the phase 1/2 MonumenTAL-1 studies (NCT03399799, NCT04634552).

After a dose reduction, the median duration of response (DOR) was 19.8 months for those in the weekly group, not evaluable for the biweekly arm, and 24.2 months for those receiving a prior T-cell receptor (TCR). The 12-month DOR rate was 78.3% in the weekly group, 84.6% in the biweekly group, and 100% in the TCR group.

A prospective cohort was subsequently enrolled to explore dose reduction following a response. For this analysis, 9 patients received a starting dose of talquetamab at 0.8 mg/kg every 2 weeks, which was reduced to 0.4 mg/kg every 2 weeks following a partial response (PR) or better. Another arm enrolled 10 participants and looked at 0.8 mg/kg every 2 weeks, which was reduced to 0.8 mg/kg every 4 weeks following a PR or better.

In this prospective cohort, dose reductions occurred at a median of 3.1 months following the initiation of therapy (range, 2.3-4.2). At a median follow-up of 13.2 months, the overall response rate (ORR) was 79.2% in this cohort, which consisted of a very good PR rate of 75.0%. Median progression-free survival (PFS) was 13.2 months (95% CI, 8.8-not estimable), and the 12-month PFS rate in this cohort was 50.1% (95% CI, 27.9%-68.7%). The median DOR was not yet reached.

To view the full article and references, visit:
cancernetwork.com/ASH_MonumenTAL-1

Tafasitamab Quadruplet Appears Safe, Feasible in Newly Diagnosed DLBCL

Treatment with a targeted combination regimen of LTRA (lenalidomide [Revlimid], tafasitamab-cxix [Monjuvi], rituximab [Rituxan], acalabrutinib) appeared safe and effective as a first-line treatment for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL), with the addition of CHOP (cyclophosphamide, doxorubicin hydrochloride [hydroxydaunomycin], vincristine sulfate [Oncovin], prednisolone) being effective in LTRA responders, according to data from the phase 2 Smart Stop study (NCT04978584).

The investigators of the study highlighted that after 4 cycles of treatment with LTRA, the overall response rate (ORR) was 100%; the complete response (CR) rate in the overall population (n = 30) was 63.3% (95% CI, 50.0%-75.2%), and 36.7% of patients achieved a partial response (PR). Among those with germinal center B-cell disease (n = 5), the CR rate was 80% and the PR rate was 20%. Additionally, in patients who were then treated with 6 cycles of LTRA followed by 2 cycles of CHOP, the ORR was 100%, with a CR rate of 93.3% and a PR rate of 6.7%.

Additionally, 7 in 10 patients treated with CHOP maintained

ongoing remission at over 9 months. To date, no patients have progressed, although progression-free survival and overall survival data were still immature at the time of presentation.

Moreover, the depth of response was assessed via circulating tumor DNA analysis in a population of 15 patients. Patients with a PET response had a CR rate of 80%, and 20% had a PR.

To view the full article and references, visit:
cancernetwork.com/ASH_SmartStop

Ibrutinib/Venetoclax Combo Shows PFS, OS Benefit as MRD-Guided Regimen in Frontline CLL

When used as a minimal residual disease (MRD)–guided treatment approach, ibrutinib (Imbruvica) combined with venetoclax (Venclexta) improved progression-free survival (PFS) and overall survival (OS) compared with FCR (fludarabine, cyclophosphamide, rituximab [Rituxan]) in patients with treatment-naive chronic lymphocytic leukemia (CLL), as observed in the phase 3 FLAIR trial (ISRCTN01844152). Data showed that 97.2% (95% CI, 94.1%-98.6%) of patients remained progression free with the investigational regimen vs 76.8% (95% CI, 70.8%-81.7%) with FCR (HR, 0.13; 95% CI, 0.07-0.24; $P < .0001$) at a median follow-up of 43.7 months. At a median follow-up of 43.0 months, 2.0% of patients died with ibrutinib/venetoclax vs 7.0% of patients who received FCR (HR, 0.31; 95% CI, 0.15-0.67; $P < .005$).

Improved PFS also was seen across biological subgroups, including those with unmutated *IGHV* (3-year PFS rate, 98.3% vs 70.9% with ibrutinib/venetoclax vs FCR, respectively; HR, 0.07; 95% CI, 0.02-0.19; $P < .001$), *ATM* (11q) deletion (100% vs 68.3%; $P < .001$), trisomy 12 (94.5% vs 74.1%; HR, 0.20; 95% CI, 0.06-0.67; $P = .002$), and 13q deletion (95.3% vs 74.5%; HR, 0.20; 95% CI, 0.08-0.48; $P < .001$).Patients with mutated *IGHV* experienced similar outcomes with ibrutinib/venetoclax and FCR, with 3-year PFS rates of 94.3% and 88.8%, respectively (HR, 0.54; 95% CI, 0.21-1.38; $P = .199$).

To view the full article and references, visit:
cancernetwork.com/ASH_FLAIR

Navitoclax Combo Significantly Reduces Spleen Volume in Myelofibrosis

Combining navitoclax with ruxolitinib produced significant reductions in spleen volume by at least 35% at week 24 (SVR35W24) compared with ruxolitinib plus placebo but did not lead to significant changes in total symptom score (TSS) in those with myelofibrosis, according to data from the phase 3 TRANSFORM-1 study (NCT04472598).

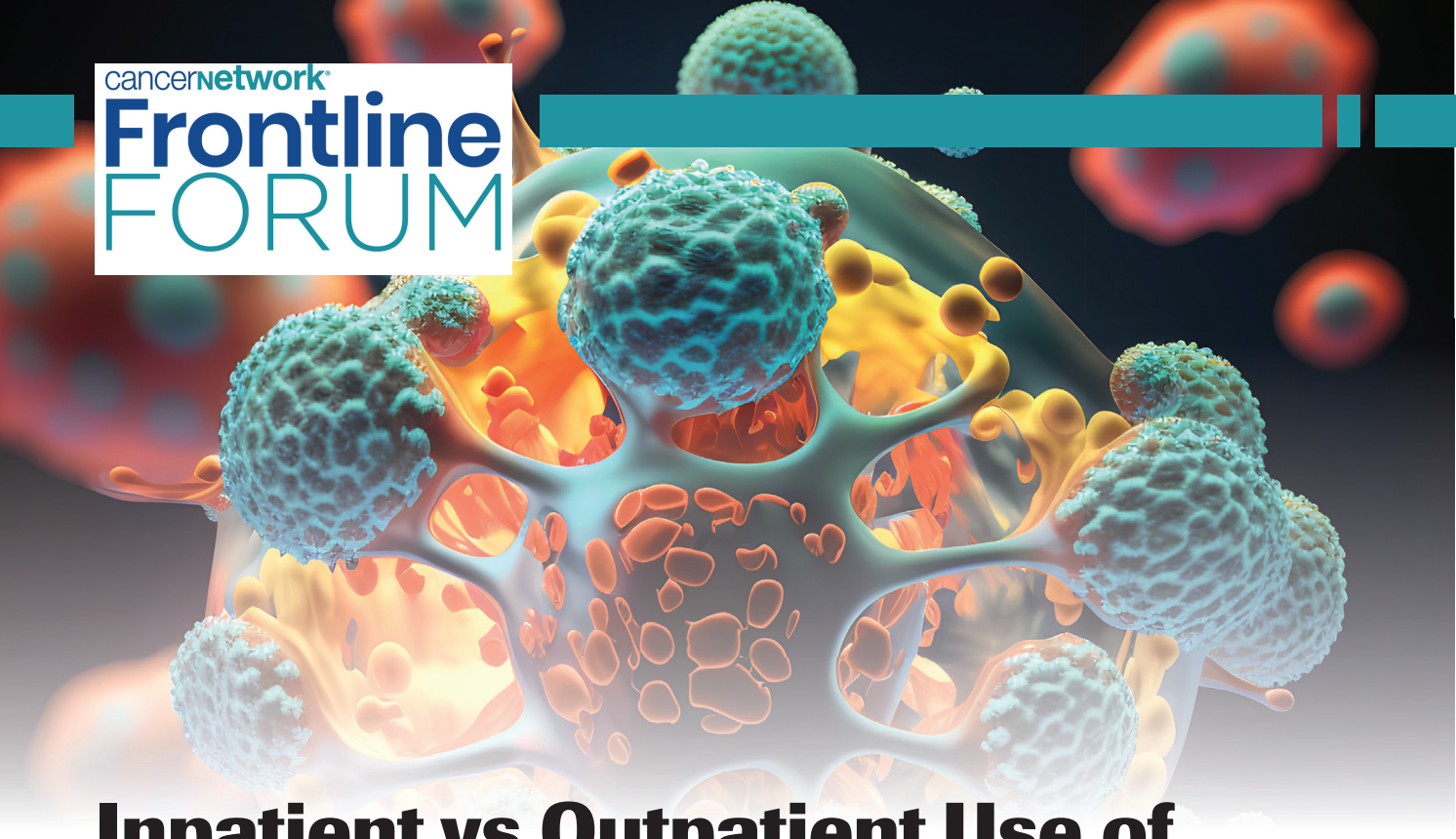
After a median follow-up of 14.9 months (range, 0.0-29.5), navitoclax and ruxolitinib elicited an SVR35W24 for 63.2% of patients compared with 31.5% with placebo plus ruxolitinib, marking a significant overall difference of 31.0% (95% CI, 19.5%-42.5%; $P<.0001$). At week 24, there was a mean –9.7 change in TSS with navitoclax/ruxolitinib from baseline (95% CI, –11.8 to –7.6) compared with a change of –11.1 for placebo plus ruxolitinib (95% CI, –13.2 to –9.1), which was not statistically significant ($P=.2852$).

The median TSS in the combination arm was 21 (range, 0.1-60.6) compared with 24 (range, 6.7-61.6) in the control group. A minority of patients were transfusion dependent at baseline, at 4% in the combination group and 3% in the control arm. The most common risk score was intermediate negative-2, at 83% in the combination group and 87% in the control. *JAK2* V617F was the most common driver mutation, with approximately two-thirds having this mutation in each group. Nearly half of patients had mutations associated with high molecular risk.

There was a significantly higher rate of SVR35 with the combination at all time points throughout the study. Across the full time scale of the study, 76.8% of those in the combination arm experienced an SVR35 compared with 41.7% with ruxolitinib plus placebo, which was a meaningful 34.6% reduction (95% CI, 23.6%-45.6%; $P<.0001$). The median time to first SVR35 response was similar between groups, at 12.3 (range, 10.1-48.3) vs 12.4 (range, 11.3-72.3) weeks, for the combination and control arms, respectively. Fewer patients lost SVR35 in the combination group (18.8%) compared with the control arm (26.4%). More than three-fourths of patients had a 12-month duration of SVR35 in each arm (76.7% vs 76.9%, combination and control, respectively).

To view the full article and references, visit:
cancernetwork.com/ASH_TRANSFORM-1

cancernetwork®
Frontline FORUM



Inpatient vs Outpatient Use of Teclistamab in Multiple Myeloma

Ajai Chari, MD
University of California, San Francisco

Natalie Callander, MD
University of Wisconsin School of Medicine and Public Health

Matthew James Pianko, MD
University of Michigan Health

Timothy Schmidt, MD
University of Wisconsin School of Medicine and Public Health

C. Ola Landgren, MD, PhD
University of Miami Miller School of Medicine

Caitlin Costello, MD
University of California, San Diego Health

During a Frontline Forum focused on multiple myeloma, experts in the field met to discuss the use of bispecific antibody therapies, treatment sequencing, and current trial updates. The panel discussed teclistamab-cqyv (Tecvayli) and how it has helped lead to evolving treatment paradigms in the space. The group was led by **Ajai Chari, MD**, professor of medicine at the University of California San Francisco.

Additional panelists include **Natalie Callander, MD**, director of the University of Wisconsin Carbone Cancer Center Myeloma Clinical Program and faculty member in the Division of Hematology, Medical Oncology and Palliative Care within the Department of Medicine; **Matthew James Pianko, MD**, clinical assistant professor at University of Michigan Health; **Timothy Schmidt, MD**, assistant professor at the University of Wisconsin School of Medicine and Public Health; **C. Ola Landgren, MD, PhD**, professor of medicine, chief of the Division of Myeloma in the Department of Medicine, director of the Sylvester Myeloma Institute, coleader of the Translational and Clinical Oncology Program, and Paul J. DiMare Endowed Chair in Immunotherapy at the University of Miami Miller School of Medicine; and **Caitlin Costello, MD**, associate professor of medicine at University of California, San Diego Health.

Step-Up Dosing Regimens

To begin the discussion, results from the phase 1/2 MajesTEC-1 trial (NCT03145181; NCT04557098) were presented.[1] Top-line findings included 43% of patients achieving a complete response at 22 months. Additionally, at 22 months, the median duration of response was 24 months, the median progression-free survival was 12.5 months, and the median overall survival was 21.9 months.

During week 1 of treatment, patients were given 0.06 mg/kg and 0.3 mg/kg of teclistamab. During cycles 1 and onward, weekly teclistamab was given subcutaneously at 1.5 mg/kg and continued until progressive disease.

Hematologic adverse effects (AEs) were of grades 3 and 4 and included

neutropenia (72% vs 65%), anemia (54% vs 38%), and thrombocytopenia (42% vs 22%), respectively. A total of 72% of patients experienced infections and cytokine release syndrome (CRS), respectively. One patient in phase 1 experienced a dose reduction due to neutropenia. Currently, 49 patients remain on the study and approximately 90% have received dosing of once every 2 weeks.

Chari posed the question to his colleagues, wanting to know how the results from this trial changed their practice. Callander noted it has dramatically affected how she treats patients, with Landgren chiming in that he foresees this being an outpatient procedure in the future.

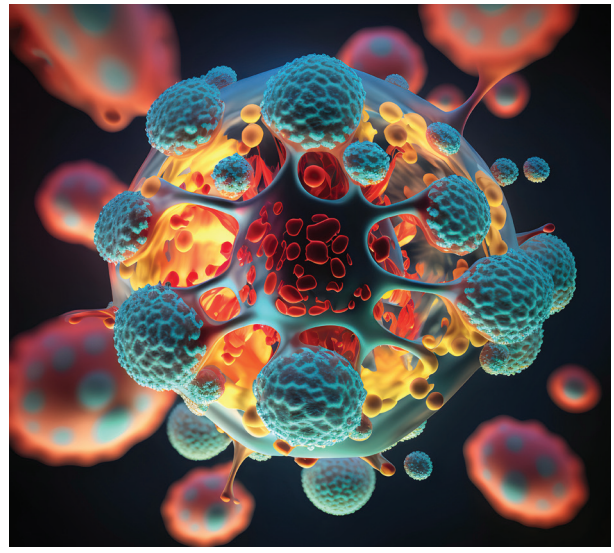
Often there is a lag time between a drug being approved and clinicians being allowed to use it in the clinic. For Callander, she began to use it almost immediately; however, Pianko had to wait approximately 2 months to gain access to the treatment, which was still relatively quick.

"These products, because of their highly active nature and the nature of the population who needs it, at most academic institutions, the time from approval to getting it to your patient was unprecedentedly short because of the dire need of these patients," said Pianko.

At Costello's institution, she noted some logistics needed to be worked out, specifically how to manage AEs and the increased need for hospital beds. Despite these challenges, Schmidt noted how important it was that this treatment was available for patients and how clinicians worked so hard to make it available.

While the clinicians have adjusted to the logistics of administering teclistamab, Chari wanted to know how step-up dosing was tackled. Pianko monitors patients for 48 hours and tries to shorten the step-up dosing schedule because it helps to limit inpatient time because of resource limitations. This hardship is not something institution specific but occurs at centers across the country.

"We took a very similar approach at our institution. I think I went to the formulary committee the day after the approval, and we had it up and going about a month later. We had read the fine print very carefully, and it said, as we know, 2 days apart, but there was a footnote saying that at the discretion of the clinician, it could be only 1 day apart. We made up the default rule, did day 1, day 3, and day 5," said Landgren.



As is common with a bispecific antibody, patients often experience CRS. Often tocilizumab (Actemra) will be given to help mitigate the effects, but typically only when it hits grade 2. Clinicians are finding that administering it during grade 1 after treatment with teclistamab has helped lessen the CRS experience.

Callander and Pianko don't use early tocilizumab because of pushback from the pharmacy and being conservative with cost. Landgren's institution uses tocilizumab as a prophylactic medication, as it was approved internally to do so. Landgren presented these findings at the 2023 American Society of Hematology (ASH) Annual Meeting & Exposition.[2]

Costello asked the panel where they are admitting these patients when AEs occur. She's begun admitting patients to the cellular therapy and transplant services, which causes issues with bed space. Landgren admits his patients to the myeloma inpatient service but cautions that clinicians should be aware of and able to manage the AEs that occur.

Bispecific Education

The conversation switched to how bispecifics are originally administered at an institution, specifically in those without experience with chimeric antigen receptor (CAR) T-cell therapy. Costello said her institution made sure all nurses in the clinic and inpatient centers were educated on AEs. Additionally, it would be helpful if the institution had a cellular therapy background or education. Patients also need to be educated on what to expect and when to contact the clinic.

In the bispecific space, the clinicians agreed that they have seen very little CRS and immune effector cell—associated neurotoxicity syndrome (ICANS). Landgren, who uses tocilizumab prophylactically, has seen very few cases of CRS but has seen more ICANS. However, he brings up the point that it can be hard to differentiate the 2 syndromes because of the occurrence of an AE and the ability to detect it.

Teclistamab Use in the Outpatient Setting

A study recently presented at ASH highlighted the use of teclistamab in an outpatient setting when step-up dosing was administered.[3] Of the 39 patients who received a dose of teclistamab, 37 were given step-up dosing. Of those, 32% developed CRS, and all were admitted to the hospital with a median stay of 1.7 days. Of note, only 1 patient experienced ICANS.

Komal/Stock.Adobe.com

Chari asked how the group practices admissions, and everyone answered inpatient, except for Costello, who utilizes outpatient treatment with parameters. Landgren and Pianko noted that there are plans to switch to outpatient soon.

Some conditions for outpatient treatment that Costello outlined included having caregiver support, close proximity to the treatment center, and vital monitoring systems. "There's cool options that are happening out there where people are wearing monitors that can be transmitted to a third party that can call the on-call doctor if there's changes," she said.

Callander said her hospital is pushing back on the idea of outpatient treatment with teclistamab because of the bed capacity. Typically, they are at 98% and 99% capacity, so if severe AEs are being experienced, they may not have enough room for these patients to be admitted. She also highlighted other institutions are beginning to have dedicated oncology doctors in the emergency department (ED), which she hopes to be able to have in the future.

Chari asked Costello what the triage process is like for patients experiencing AEs at home. She said that the University of California, San Diego Health, does have these same challenges. Those in the ED must be educated on how to handle these AEs, electronic health records must be set up to highlight that this patient is receiving immunotherapy, and an on-call oncologist should be notified immediately.

Another ASH presentation looked at step-up dosing of teclistamab using real-world data and all-payer claims. At the data cutoff, 99 patients had completed step-up dosing, with 87.9% completing step-up dosing in 1 inpatient admission, 4.0% fully outpatient, and 8.1% in hybrid inpatient/outpatient settings.

For patients who had more than 1 hospitalization due to teclistamab, the median length of stay was 8.0 days, and the mean was 8.3 days. The mean length of step-up dosing shortened from 12.1 to 1.2 days.

Based on these data, Callander said she would not feel comfortable giving a bispecific as an outpatient treatment because "[patients are] too debilitated from their disease, and they have too many end-organ issues."

Schmidt chimed in, saying it's important to look at the patient's comorbidities and determine whether cytotoxic chemotherapy and its rapid response have more pros than using a bispecific. Landgren disagreed, saying he'd give it to all his patients because there is no restriction for age or any other traditional factors.

FDA Decisions and Weighing In on Treatment Factors

In a statement in November 2023, the FDA brought forth that there was potential for T-cell malignancies to develop after treatment with B-cell maturation antigens or CD19-directed CAR T-cell therapies.[4] The panel noted that there were very few cases identified and stood by the FDA's position that the potential benefits would outweigh the risks of treatment.

"[The FDA] reviewed about 600 cases, of which there was only 1 patient with a T-cell malignancy, and that patient had T-cell abnormalities prior to the apheresis. It goes back to what [we discussed]; there's always patient disease and treatment factors, and if these are just heavily treated patients, that's not the treatment-related issue," said Pianko. ■

REFERENCES

1. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med.* 2022;387(6):495-505. doi:10.1056/NEJMoa2203478

2. Kowalski A, Lykon JL, Diamond B, et al. Tocilizumab prophylaxis for patients treated with teclistamab: a single-center experience. *Blood.* 2023;142(suppl 1):4709. doi.10.1182/blood-2023-187086

3. Sandahl TB, Soefje SA, Calay ES, et al. Real-world treatment outcomes of teclistamab under an outpatient model for step-up dosing administration. *Blood.* 2023;142(suppl 1):5154. doi.10.1182/blood-2023-174270

4. FDA investigating serious risk of T-cell malignancy following BCMA-directed or CD19-directed autologous chimeric antigen receptor (CAR) T cell immunotherapies. FDA. November 28, 2023. Accessed January 10, 2024. https://bit.ly/47CkPYY

> **"There [are] cool options that are happening out there where people are wearing monitors that can be transmitted to a third party that can call the on-call doctor if there [are] changes,"**
> – Caitlin Costello, MD

SWITCH TREATMENT AT THE CRITICAL MOMENT

Consider ICLUSIG for your appropriate patients

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

CML **Ph+ ALL**

ICLUSIG IS THE ONLY 3RD-GENERATION TKI IN CML AND PH+ ALL AND SHOWS ACTIVITY AGAINST ALL KNOWN SINGLE POINT MUTATIONS, INCLUDING T315I[1-8]

INDICATIONS AND USAGE

ICLUSIG is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.

Limitations of Use: ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

IMPORTANT SAFETY INFORMATION

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY

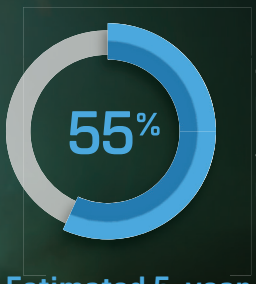
See full prescribing information for complete boxed warning.

- **Arterial occlusive events (AOEs), including fatalities, have occurred in ICLUSIG-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG based on severity. Consider benefit-risk to guide a decision to restart ICLUSIG.**
- **Venous thromboembolic events (VTEs) have occurred in ICLUSIG-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG based on severity.**
- **Heart failure, including fatalities, occurred in ICLUSIG-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ICLUSIG for new or worsening heart failure.**
- **Hepatotoxicity, liver failure and death have occurred in ICLUSIG-treated patients. Monitor liver function tests. Interrupt or discontinue ICLUSIG based on severity.**

Please see accompanying Brief Summary of full Prescribing Information on the following pages, and Important Safety Information, including Boxed Warning, throughout.

ICLUSIG DELIVERED CLINICALLY MEANINGFUL RESPONSES IN RESISTANT OR INTOLERANT CP-CML AND PH+ ALL[1]

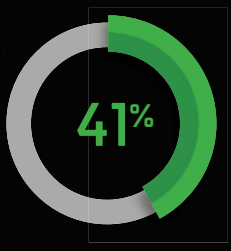
CP-CML[1,9]



achieved MCyR by 12 months
(n=148/267) (95% CI: 49, 62)

40% achieved MMR at any time
(n=105/267) (95% CI: 35, 47)

Ph+ ALL[1]



achieved MaHR by 6 months[1,2]
(n=13/32; 95% CI: 24, 59)[a,b]

Median time to MaHR 0.7 months
(range: 0.4-6.0)

Estimated 5-year survival in CP-CML[9]

73% overall survival (95% CI: 66, 79)

53% progression-free survival (95% CI: 45, 60)

Cytogenetic responses at any time[10]

38% CCyR (n=12/32)

47% MCyR (n=15/32)

SAFETY PROFILE[1]:

Serious adverse reactions occurred in **69%** of patients who received ICLUSIG. Serious adverse reactions in >2% of patients included AOEs (20%), pneumonia (10%), cardiac arrhythmias (8%), pancreatitis/lipase elevation (7%), abdominal pain (6%), cardiac failure (6%), hemorrhage (6%), sepsis (5%), VTEs (5%), fluid retention and edema (4.5%), pyrexia (4.5%), secondary malignancies (5%), anemia (3.3%), hypertension (3.1%), thrombocytopenia (3.1%), febrile neutropenia (2.9%), cellulitis (2.7%), and arthralgia (2.2%). Fatal adverse reactions occurred in 9% of patients who received ICLUSIG; the most frequent fatal adverse reactions were AOEs (2%), sepsis (1.6%), and hemorrhage (1.3%).

Permanent discontinuation of ICLUSIG due to an adverse reaction occurred in 21% of CP-CML, 12% of AP-CML, 15% of BP-CML, and 9% of Ph+ ALL patients. The most frequent adverse reactions that led to treatment discontinuation were thrombocytopenia (4.5%) and AOEs (4%).

Dose interruption of ICLUSIG for more than 3 days due to an adverse reaction occurred in 71% of patients and dose reduction of ICLUSIG due to an adverse reaction occurred in 68% of patients. Adverse reactions which required a dosage interruption or dose reduction in >5% of patients included thrombocytopenia (31%), pancreatitis/lipase elevation (17%), abdominal pain (14%), rash and related conditions (14%), neutropenia (14%), hepatic dysfunction (12%), AOEs (10%), arthralgia (8%), anemia (7%), ALT increased (6%), and AST increased (5%).

The most common (>20%) non-hematologic adverse reactions were rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, AOEs, diarrhea, vomiting, and myalgia.

Learn more at ICLUSIG.com/HCP

PACE TRIAL DESIGN[1,9]: PACE was a single-arm, phase 2 trial in adult patients with CML or Ph+ ALL who were resistant or intolerant to dasatinib or nilotinib, or who had the BCR::ABL1[IS] T315I mutation regardless of prior TKI use (N=449; n=270 CP-CML; n=32 Ph+ ALL). The primary efficacy endpoint for CP-CML was MCyR at 12 months. The primary efficacy endpoint for Ph+ ALL was MaHR by 6 months.

Starting dose for ponatinib was 45 mg once daily. Dose reductions to 30 mg or 15 mg once daily were applied to manage adverse events, per protocol, or implemented proactively in 2013: 15 mg once daily for CP-CML patients with MCyR, and 30 mg once daily for patients with CP-CML without MCyR, patients with AP-CML, and patients with BP-CML.

[a] The primary endpoint for Ph+ ALL of MaHR by 6 months combined complete hematologic responses (CHR) and no evidence of leukemia.[1]

[b] CHR: WBC ≤institutional ULN; ANC ≥1000/mm^3; platelets ≥100,000/mm^3; no blasts or promyelocytes in peripheral blood; bone marrow blasts ≤5; <5% myelocytes plus metamyelocytes in peripheral blood; basophils <5% in peripheral blood; no extramedullary involvement (including no hepatomegaly or splenomegaly).[1]

ANC=absolute neutrophil count; AP-CML=accelerated phase chronic myeloid leukemia; BCR::ABL1[IS]=BCR::ABL1 International Scale; CCyR=complete cytogenetic response; CHR=complete hematologic response; MaHR=major hematological response; MCyR=major cytogenetic response; Ph+ ALL=Philadelphia chromosome positive acute lymphoblastic leukemia; TKI=tyrosine kinase inhibitor; ULN=upper limit of normal for the lab; WBC=white blood cell.

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. The incidence of AOEs in OPTIC (45 mg→15 mg) was 14% of 94 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In OPTIC and PACE, AOEs were more frequent with increasing age.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded. In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG were excluded. Consider whether the benefits of ICLUSIG are expected to exceed the risks.

Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. VTEs included deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity.

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG. In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue ICLUSIG for new or worsening heart failure.

Hepatotoxicity: ICLUSIG can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL. Hepatotoxicity occurred in 28% of 94 patients in OPTIC and 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in OPTIC (6% of 94 patients) and PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at a reduced dose or discontinue ICLUSIG based on recurrence/severity.

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop ICLUSIG if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG and consider evaluating for renal artery stenosis.

Pancreatitis: Serious or severe pancreatitis has occurred in patients who received ICLUSIG. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2 weeks. Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

Increased Toxicity in Newly Diagnosed Chronic Phase CML: In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with CP-CML, single agent ICLUSIG 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy: Peripheral and cranial neuropathy occurred in patients in OPTIC and PACE. Some of these events in PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Ocular Toxicity: Serious or severe ocular toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

IMPORTANT SAFETY INFORMATION (cont'd)

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, occurred in patients in OPTIC and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led to hospitalization. Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in OPTIC and PACE. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1×10^9/L or platelets less than 50×10^9/L, interrupt ICLUSIG until ANC at least 1.5×10^9/L and platelets at least 75×10^9/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients upon resolution of RPLS is unknown.

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

The most common (>20%) adverse reactions are rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-817-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid coadministration or reduce ICLUSIG dose if coadministration cannot be avoided.

Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 6 days following last dose.

Females and Males of Reproductive Potential: Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG. Ponatinib may impair fertility in females, and it is not known if these effects are reversible.

Pre-existing Hepatic Impairment: Reduce the starting dose of ICLUSIG to 30mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function.

Please see accompanying Brief Summary of full Prescribing Information on the following pages, and Important Safety Information, including Boxed Warning, throughout.

References: 1. ICLUSIG (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc. 02/2022. **2.** Data on file. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc. 2022. **3.** Gozgit JM, Schrock AB, Chen TC, et al. Poster presented at: The American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. **4**. Eide CA, Zabriskie MS, Stevens SLS, et al. *Cancer Cell.* 2019;36(4):431-443. **5.** Deininger MW, Hodgson JG, Shah NP, et al. *Blood.* 2016;127(6):703-712. **6**. Jabbour E, Kantarjian H, Cortes J. *Clin Lymphoma Myeloma Leuk.* 2015;15(6):323-334. **7.** Zabriskie MS, Eide CA, Tantravahi SK, et al. *Cancer Cell.* 2014;26(3):428-442. **8.** O'Hare T, Shakespeare WC, Zhu X, et al. *Cancer Cell.* 2009;16(5):401-412. **9.** Cortes JE, Kim DW, Pinilla-Ibarz J, et al. *Blood.* 2018;132(4):393-404. **10.** Cortes JE, Kim DW, Pinilla-Ibarz J, et al. *N Engl J Med.* 2013;369(19):1783-1796.

Takeda | ONCOLOGY

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION
ICLUSIG® (PONATINIB)

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY

Arterial Occlusive Events:

- **Arterial occlusive events (AOEs), including fatalities, have occurred in Iclusig-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue Iclusig based on severity. Consider benefit-risk to guide a decision to restart Iclusig *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.**

Venous Thromboembolic Events:

- **Venous thromboembolic events (VTEs) have occurred in Iclusig-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue Iclusig based on severity *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.**

Heart Failure:

- **Heart failure, including fatalities, occurred in Iclusig-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue Iclusig for new or worsening heart failure *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.**

Hepatotoxicity:

- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor liver function tests. Interrupt or discontinue Iclusig based on severity *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)]*.**

1 INDICATIONS AND USAGE

Iclusig is indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.

Limitations of Use: Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML *[see Warnings and Precautions (5.7)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Arterial Occlusive Events

Arterial occlusive events (AOEs), including fatalities, occurred in patients who received Iclusig in OPTIC and PACE *[see Adverse Reactions (6.1)]*.

Of the 94 patients who received a starting dose of 45 mg (45 mg → 15 mg) in OPTIC, 14% experienced AOEs, of which 7%, 4.3%, and 2.1% experienced cardiovascular, cerebrovascular or peripheral vascular AOEs, respectively. The median time to onset of the first cardiovascular, cerebrovascular, or peripheral vascular event was 4.7 months (range: 12 days to 2.1 years), 11.7 months (range 15 days to 1.6 years), and 3.6 months (range: 23 days to 6.3 months), respectively. Grade 3 or 4 AOEs occurred in 6% of patients; the most frequent Grade 3 or 4 AOEs were myocardial infarction, acute coronary syndrome, arterial thrombosis, ischemic stroke, ischemic cerebral infarction, and unstable angina (1.1% each). Fatal AOEs occurred in 2 patients (2.1%); both of which were sudden death. AOEs were more frequent with increasing age *[see Use in Specific Populations (8.5)]*.

In PACE, 26% of 449 patients experienced AOEs, of which 15%, 7%, and 11% experienced cardiovascular, cerebrovascular, and peripheral vascular AOEs, respectively. Some patients experienced recurrent or multisite vascular occlusion. The median time to onset of the first cardiovascular, cerebrovascular, and peripheral vascular AOEs was 1 year (range: 1 day to 4.1 years), 1.4 years (range: 2 days to 4.5 years), and 2 years (range: 10 days to 4.9 years), respectively. Grade 3 or 4 AOEs occurred in 14% of patients; the most frequent Grade 3 or 4 AOEs were peripheral arterial occlusive disease (3.1%), myocardial infarction (2%), coronary artery disease (1.6%), and cerebral infarction (1.6%). Fatal AOEs occurred in 9 patients (2%); the most frequent fatal AOE was cardiac arrest (0.9%).

In PACE, fatal and life-threatening AOEs occurred within 2 weeks of starting treatment at 45 mg, and at dose levels as low as 15 mg per day. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced AOEs. AOEs were more frequent with increasing age *[see Use in Specific Populations (8.5)]* and in patients with history of ischemia, hypertension, diabetes, or hypercholesterolemia. The most common risk factors in patients with AOEs were history of hypertension (67%; 77/115), hypercholesterolemia (59%; 68/115), and non-ischemic cardiac disease (43%; 49/115).

In PACE, patients developed heart failure concurrent or subsequent to a myocardial ischemic event *[see Warnings and Precautions (5.3)]*. Patients required revascularization procedures (coronary, cerebrovascular, and peripheral arterial). Iclusig caused stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery). Patients developed digital or distal extremity necrosis and required amputations. Renal artery stenosis associated with worsening, labile or treatment-resistant hypertension occurred in some Iclusig-treated patients *[see Warnings and Precautions (5.5)]*.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, congestive heart failure, venous thromboembolism, or clinically significant atrial/ventricular arrhythmias, were excluded. In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease, including any history of clinically significant atrial/ventricular arrhythmias or history of myocardial infarction, unstable angina, or congestive heart failure within the 3 months prior to the first dose of Iclusig, were excluded *[see Adverse Reactions (6.1)]*. Consider whether the benefits of Iclusig are expected to exceed the risks.

Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue Iclusig based on recurrence/severity *[see Dosage and Administration (2.2)]*. Consider benefit-risk to guide a decision to restart Iclusig.

5.2 Venous Thromboembolic Events

Serious or severe VTEs have occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, 1 patient experienced a VTE (Grade 1 retinal vein occlusion).

In PACE, VTEs occurred in 6% of 449 patients, including serious or severe (Grade 3 or 4) in 5.8%. VTEs included deep venous thrombosis (2.2%), pulmonary embolism (1.8%), superficial thrombophlebitis (0.7%), retinal vein occlusion (0.7%), and retinal vein thrombosis (0.4%) with vision loss. VTEs occurred in 10% of the 62 patients with BP-CML, 9% of the 32 patients with Ph+ ALL, 6% of the 270 patients with CP-CML, and 3.5% of the 85 patients with AP-CML.

Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue Iclusig based on recurrence/severity *[see Dosage and Administration (2.2)]*.

5.3 Heart Failure

Fatal, serious or severe heart failure events have occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, heart failure events occurred in 13% of patients; 1.1% experienced serious or severe (Grade 3 or 4) heart failure. The most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%).

Fatal or serious heart failure occurred in PACE. Heart failure events occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher) heart failure. The most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%) and decreased ejection fraction (2.9%), and cardiac failure (2%).

Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue Iclusig for new or worsening heart failure *[see Dosage and Administration (2.2)]*.

5.4 Hepatotoxicity

Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in 3 patients, with hepatic failure occurring within 1 week of starting Iclusig in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, hepatotoxicity occurred in 28% of patients; 6% experienced Grade 3 or 4 hepatotoxicity. The median time to onset of hepatotoxicity was 1.9 months, with a range of 3 days to 4.1 years. The most frequent hepatotoxic events were elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and gamma-glutamyl transferase (GGT). In 29% of the 21 patients who reported ALT or AST elevation, the event was not resolved by the date of last follow-up.

In PACE, hepatotoxicity occurred in 32% of 449 patients; 13% experienced Grade 3 or 4 hepatotoxicity. The median time to onset of hepatotoxicity was 3.1 months, with a range of 1 day to 4.9 years. The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. In 9% of the 88 patients who reported ALT or AST elevation, the event was not resolved by the date of last follow-up.

Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at reduced dose or discontinue Iclusig based on recurrence/severity *[see Dosage and Administration (2.2)]*.

5.5 Hypertension

Serious or severe hypertension, including hypertensive crisis, has occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, hypertension events were reported in 32% of patients; 12% experienced serious or severe hypertension. Based on vital sign data, Grade 1 blood pressure elevation occurred in 8 out of 18 (44%) patients with normal initial blood pressure, Grade 2 occurred in 28 out of 81 (35%) patients with initial blood pressure of less than Grade 2, and Grade 3 occurred in 18 out of 92 (20%) patients with initial blood pressure of less than Grade 3. Three patients (3.2%) experienced hypertensive crisis.

In PACE, hypertension events were reported in 32% of 449 patients; 13% experienced serious or severe hypertension. Any post-baseline elevation of systolic or diastolic BP of Grade 2 or higher in patients with normal baseline blood pressure occurred in 44% of 449 patients. Grade 1 BP elevation occurred in 26%, Grade 2 in 45%, and Grade 3 in 26%. Two patients (<1%) experienced Grade 4 hypertension (hypertensive crisis).

Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath *[see Adverse Reactions (6.1)]*. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop Iclusig if hypertension is not medically controlled *[see Dosage and Administration (2.2)]*. For significant worsening, labile or treatment-resistant hypertension, interrupt Iclusig and consider evaluating for renal artery stenosis.

5.6 Pancreatitis

Serious or severe pancreatitis has occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, pancreatitis occurred in 23% of patients; 15% experienced serious or severe (Grade 3 or 4) pancreatitis. Pancreatitis resulted in discontinuation in 1.1% of patients and interruption and/or dose reduction in 20% of patients. The median time to onset of pancreatitis was 23 days (range: 3 days to 5.6 months). In two patients with clinical pancreatitis that led to dose modification or treatment discontinuation, pancreatitis resolved within 2 weeks. Laboratory abnormalities of amylase elevation occurred in 11% of patients, while lipase elevation occurred in 34% of patients.

In PACE, pancreatitis occurred in 26% of 449 patients; 17% experienced serious or severe (Grade 3 or 4) pancreatitis. Pancreatitis resulted in discontinuation in 0.4% of patients and interruption and/or dose reduction in 17% of patients. The median time to onset of pancreatitis was 29 days (range: 1 day to 4 years). Nineteen of the 28 cases of clinical pancreatitis that led to dose modification or treatment discontinuation resolved within 2 weeks. Laboratory abnormalities of amylase elevations occurred in 18% of patients, while lipase elevations occurred in 39% of patients.

Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose or discontinue Iclusig based on severity *[see Dosage and Administration (2.2)]*. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

5.7 Increased Toxicity in Newly Diagnosed Chronic Phase CML

In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with CP-CML, single agent Iclusig 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety.

Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the Iclusig arm compared to the imatinib arm. Compared to imatinib-treated patients, Iclusig-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

5.8 Neuropathy

Of the 94 patients who received a starting dose of 45 mg in OPTIC, neuropathy occurred in 9% of patients. Peripheral neuropathy occurred in 6% of patients. The most frequently reported peripheral neuropathies were hypoesthesia (2.1%), muscular weakness (2.1%), and paresthesia (2.1%). Cranial neuropathy developed in 2 patients. The median time to onset of peripheral neuropathy and cranial neuropathy was 7.7 months (range: 1.5 months to 1.4 years) and 2.1 years (range: Day 1 to 4.2 years), respectively.

In PACE, neuropathy occurred in 22% of patients; 2.4% experienced Grade 3 or 4 neuropathy. Peripheral neuropathy occurred in 20% of 449 patients; 1.8% experienced Grade 3 or 4 peripheral neuropathy. The most frequent peripheral neuropathies were paresthesia (5%), neuropathy peripheral (4.5%), and hypoesthesia (3.6%). Cranial neuropathy developed in 3% of patients; 0.7% were Grade 3 or 4. The median time to onset of peripheral neuropathy and cranial neuropathy was 5.3 months (range: 1 day to 4.6 years) and 1.2 years (range: 18 days to 4 years), respectively.

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Interrupt, then resume at the same or reduced dose or discontinue Iclusig based on recurrence/severity *[see Dosage and Administration (2.2)]*.

5.9 Ocular Toxicity

Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patients.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, ocular toxicities occurred in 11% of patients; 1.1% experienced a serious or severe ocular toxicity. The most frequent ocular toxicities were blurred vision and eye pain. Retinal toxicities, including age-related macular degeneration and retinal vein occlusion, occurred in 2.1% of patients.

In PACE, ocular toxicities occurred in 30% of 449 patients; 3.6% experienced a serious or severe ocular toxicity. The most frequent ocular toxicities were dry eye, blurred vision, and eye pain. Retinal toxicities occurred in 3.6% of patients. The most frequent retinal toxicities were macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters (0.7% each).

Conduct comprehensive eye exams at baseline and periodically during treatment.

5.10 Hemorrhage

Fatal and serious hemorrhage events have occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, hemorrhage occurred in 12% of patients; 1 patient experienced a serious subdural hematoma.

In PACE, hemorrhage occurred in 28% of 449 patients; 6% experienced a serious hemorrhage and 1.3% experienced a fatal hemorrhage. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages, each occurring in 0.9% of patients. Most hemorrhages occurred in patients with Grade 4 thrombocytopenia *[see Warnings and Precautions (5.13)]*.

Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue Iclusig based on recurrence/severity *[see Dosage and Administration (2.2)]*.

5.11 Fluid Retention

Fatal and serious fluid retention events have occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, fluid retention occurred in 5% of patients. The most frequent fluid retention events were peripheral edema (2.1%) and pleural effusion (2.1%).

In PACE, fluid retention events occurred in 33% of 449 patients; 4.5% experienced serious fluid retention. One instance of brain edema was fatal. Serious fluid retention included pleural effusion (1.6%), pericardial effusion (1.6%), and angioedema (0.4%). The most frequent fluid retention events were peripheral edema (17%), pleural effusion (9%), pericardial effusion (4.2%) and peripheral swelling (3.8%).

Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue Iclusig based on recurrence/severity *[see Dosage and Administration (2.2)]*.

5.12 Cardiac Arrhythmias

Of the 94 patients who received a starting dose of 45 mg in OPTIC, cardiac arrhythmias occurred in 16% of patients; 4.3% experienced Grade 3 or 4 cardiac arrhythmias. Grade 3 or 4 cardiac arrhythmias included atrial fibrillation, cardio-respiratory arrest, supraventricular extrasystoles, and syncope.

In PACE, cardiac arrhythmias occurred in 20% of 449 patients; 7% experienced Grade 3 or 4 cardiac arrhythmias. Ventricular arrhythmias occurred in 3.4% of the 89 patients who reported an arrhythmia, with one event being Grade 3 or 4. Symptomatic bradyarrhythmias that led to pacemaker implantation occurred in 1% of patients. Atrial fibrillation was the most frequent cardiac arrhythmia (8%), with 3.3% being Grade 3 or 4. Other Grade 3 or 4 arrhythmia events included syncope (2%), tachycardia and bradycardia (0.4% each), and QT interval prolongation, atrial flutter, sinus bradycardia, supraventricular tachycardia, ventricular tachycardia, atrial tachycardia, atrioventricular block complete, cardio-respiratory arrest, loss of consciousness, and sinus node dysfunction (0.2% each). For 31 patients, the arrythmia led to hospitalization.

Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue Iclusig based on recurrence/severity.

5.13 Myelosuppression

Of the 94 patients who received a starting dose of 45 mg in OPTIC, neutropenia occurred in 55% (Grade 3 or 4 occurred in 22%), thrombocytopenia occurred in 65% (Grade 3 or 4 occurred in 31%), and anemia occurred in 35% of patients (Grade 3 or 4 occurred in 14%). The median time to onset of Grade 3 or 4 myelosuppression was 1.4 months (range: 1 day to 1.2 years).

In PACE, neutropenia occurred in 56% (Grade 3 or 4 occurred in 34%), thrombocytopenia occurred in 63% (Grade 3 or 4 occurred in 40%), and anemia occurred in 52% of patients (Grade 3 or 4 occurred in 20%). The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. Severe myelosuppression (Grade 3 or 4) was observed early in treatment, with a median onset time of 29 days (range: 1 day to 4.1 years).

Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1×10^9/L or platelets less than 50×10^9/L, interrupt Iclusig until ANC at least 1.5×10^9/L and platelets at least 75×10^9/L, then resume at same or reduced dose *[see Dosage and Administration (2.2)]*.

5.14 Tumor Lysis Syndrome

Of the 94 patients who received a starting dose of 45 mg in OPTIC, serious tumor lysis syndrome (TLS) developed in 1.1% of patients. Hyperuricemia occurred in 2.1% of patients.

In PACE, serious TLS developed in 0.4% of 449 patients. One case occurred in a patient with advanced AP-CML and 1 case occurred in a patient with BP-CML. Hyperuricemia occurred in 7% of patients.

Ensure adequate hydration and treat high uric acid levels prior to initiating Iclusig.

5.15 Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS; also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received Iclusig. Patients can present with hypertension, seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis. Interrupt Iclusig until resolution. The safety of resumption of Iclusig in patients upon resolution of RPLS is unknown.

5.16 Impaired Wound Healing and Gastrointestinal Perforation

Impaired wound healing occurred in patients receiving Iclusig *[see Adverse Reactions (6.2)]*. Withhold Iclusig for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Iclusig after resolution of wound healing complications has not been established.

Gastrointestinal perforation or fistula occurred in patients receiving Iclusig *[see Adverse Reactions (6.2)]*. Permanently discontinue in patients with gastrointestinal perforation.

5.17 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Iclusig can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of ponatinib to pregnant rats during organogenesis caused adverse developmental effects at exposures lower than human exposures at the recommended human dose. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Iclusig and for 3 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions identified in the Highlights of the Prescribing Information are from a pooled safety population of 543 patients with CML or Ph+ ALL who received Iclusig at a starting dose of 45 mg orally once daily. In this pooled safety population, the most common (>20%) adverse reactions were rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction, and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>20%) were platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

Previously Treated CP-CML

The safety of Iclusig was evaluated in OPTIC *[see Clinical Studies (14)]*. Patients received one of three starting doses of Iclusig: 45 mg orally once daily (n=94), 30 mg orally once daily (n=94) or 15 mg orally once daily (n=94). Patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, congestive heart failure, venous thromboembolism, or clinically significant atrial/ventricular arrhythmias, were excluded. Only the safety information for the recommended starting dosage (45 mg) is described below. Patients who received a starting dose of Iclusig 45 mg orally once daily had a mandatory dose reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1^{IS}. Of these patients, 76% were exposed for 1 year or longer and 38% were exposed for greater than two years. The median time to the response-based dose reduction to 15 mg was 6.4 months (range 3.1 months to 1.8 years).

Serious adverse reactions occurred in 34% of patients who received Iclusig at a starting dose of 45 mg. Serious adverse reactions in >2% of patients included AOEs (9%; of which 2.1% were sudden death), cardiac arrhythmias (6%), thrombocytopenia (5%), pyrexia (4.3%), anemia (3.2%), abdominal pain (3.2%), atrial fibrillation (2.1%), pancreatitis/lipase elevation (2.1%), neutropenia (2.1%), and hypertension (2.1%). Fatal adverse reactions occurred in 2 patients (2.1%), both of which were sudden death.

Permanent discontinuation of Iclusig due to an adverse reaction occurred in 19% of patients who received Iclusig at a starting dose of 45 mg. Adverse reactions which resulted in permanent discontinuation in >2% of patients included AOEs, thrombocytopenia, hypertension, and sudden death.

Dose modifications (dose interruption or reductions) of Iclusig due to an adverse reaction occurred in 71% of patients who received Iclusig at a starting dose of 45 mg. Adverse reactions which required dose interruptions or reductions in >5% of patients included thrombocytopenia, pancreatitis/lipase elevation, neutropenia, hepatic dysfunction, rash and related conditions, and anemia.

The most common (>20%) adverse reactions were rash and related conditions, hypertension, arthralgia, hyperlipidemia, hepatic dysfunction, pancreatitis/lipase elevation, and abdominal pain. The most common (>20%) Grade 3 or 4 laboratory abnormalities were platelet count decreased and neutrophil cell count decreased.

Table 4 summarizes the adverse reactions in OPTIC for patients who received Iclusig at a starting dose of 45 mg.

Table 4: Adverse Reactions (≥10%) in Patients with CP-CML Who Received Iclusig at Starting Dose of 45 mg Followed by Reduction to 15 mg After Achievement of ≤1% BCR-ABL1^{IS} in OPTIC

Adverse Reaction	Iclusig 45 mg → 15 mg (N = 94)	
	All Grades (%)	Grade 3 or 4 (%)
Skin and Subcutaneous Tissue Disorders		
Rash and related conditions	51	3.2
Dry Skin	12	0
Vascular Disorders		
Hypertension	32	12
Arterial occlusive events	14	6
Hemorrhage	12	2.1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia[(a)]	30	0
Metabolism and Nutrition Disorders		
Hyperlipidemia[(b)]	28	2.1
Gastrointestinal Disorders		
Abdominal Pain[(c)]	25	3.2
Pancreatitis/lipase elevation	23	15
Constipation	11	0
Hepatobiliary Disorders		
Hepatotoxicity	28	6
Nervous System Disorders		
Headache	17	0
General Disorders and Administration Site Conditions		
Pyrexia	16	1.1
Fatigue or asthenia	10	1.1
Cardiac Disorders		
Cardiac arrhythmias	16	4.3
Cardiac Failure	13	1.1

Graded using CTCAE v5.0

(a) Arthralgia includes arthralgia, arthritis, back pain, intervertebral disc degeneration, osteoarthritis, pain, neck pain, pain in extremity, pain of skin, sciatica, spinal pain, tendonitis, tenosynovitis

(b) Hyperlipidemia includes blood cholesterol increased, blood triglycerides increased, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, low density lipoprotein increased

(c) Abdominal pain includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, chronic gastritis, colitis, enteritis, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal pain, gastroesophageal reflux disease, Helicobacter gastritis

Clinically relevant adverse reactions in ≤10% of patients who received Iclusig at a starting dose of 45 mg: neuropathy (9%), fluid retention and edema (5%), and hypothyroidism (3.2%).

Table 5 summarizes the laboratory abnormalities in OPTIC for patients who received Iclusig at a starting dose of 45 mg.

Table 5: Select Laboratory Abnormalities (>20%) that Worsened from Baseline in Patients with CP-CML Who Received Iclusig at Starting Dose of 45 mg in OPTIC

Laboratory Abnormality	Iclusig 45 mg → 15 mg (N = 94)	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic Laboratory Tests		
Platelet count decreased	65	31
White blood cell decreased	56	13
Neutrophil cell count decreased	55	22
Lymphocyte decreased	42	7
Hemoglobin decreased	35	14
Liver Function Tests		
ALT increased	49	1.1
AST increased	40	0
Alkaline phosphatase increased	23	1.1
Chemistry		
Glucose increased	48	1.1
Triglycerides increased	44	3.2
Phosphate decreased	27	3.2
Bicarbonate decreased	27	0
Pancreatic Enzymes		
Lipase increased	34	12

ALT = alanine aminotransferase, AST = aspartate aminotransferase

Graded using CTCAE v5.0 (except glucose increased which is graded using CTCAE v4.03)

Previously Treated CML or Ph+ ALL

The safety of Iclusig was evaluated in PACE *[see Clinical Studies (14)]*. Eligible patients had CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior kinase inhibitor, including those with the BCR-ABL T315I mutation. Patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease, including any history of clinically significant atrial/ventricular arrhythmias or history of myocardial infarction, unstable angina, or congestive heart failure within the 3 months prior to the first dose of Iclusig, were excluded. Patients received a starting dose of Iclusig 45 mg orally once daily (N=449). Dose reductions to 30 mg orally once daily or 15 mg orally once daily were allowed for the management of adverse reactions. After approximately 2 years of follow-up, patients who were still taking a 45 mg orally once daily dose were recommended to undergo a dose reduction in response to the continued occurrence of AOEs and VTEs in the clinical trial *[see Warnings and Precautions (5.1)]*. At study completion (60 months of follow-up), the median duration of treatment with Iclusig was 32 months in patients with CP-CML, 19 months in patients with AP-CML, 2.9 months in patients with BP-CML, and 2.7 months in patients with Ph+ ALL.

Serious adverse reactions occurred in 69% of patients who received Iclusig. Serious adverse reactions in >2% of patients included AOEs (20%), pneumonia (10%), cardiac arrhythmias (8%), pancreatitis/lipase elevation (7%), abdominal pain (6%), cardiac failure (6%), hemorrhage (6%), sepsis (5%), VTEs (5%), fluid retention and edema (4.5%), pyrexia (4.5%), secondary malignancies (5%), anemia (3.3%), hypertension (3.1%), thrombocytopenia (3.1%), febrile neutropenia (2.9%), cellulitis (2.7%), and arthralgia (2.2%). Fatal adverse reactions occurred in 9% of patients who received Iclusig; the most frequent fatal adverse reactions were AOEs (2%), sepsis (1.6%), and hemorrhage (1.3%).

Permanent discontinuation of Iclusig due to an adverse reaction occurred in 21% of CP-CML, 12% of AP-CML, 15% of BP-CML, and 9% of Ph+ ALL patients. The most frequent adverse reactions that led to treatment discontinuation were thrombocytopenia (4.5%) and AOEs (4%).

Dose interruption of Iclusig for more than 3 days due to an adverse reaction occurred in 71% of patients and dose reduction of Iclusig due to an adverse reaction occurred in 68% of patients. Adverse reactions which required a dosage interruption or dose reduction in >5% of patients included thrombocytopenia (31%), pancreatitis/lipase elevation (17%), abdominal pain (14%), rash and related conditions (14%), neutropenia (14%), hepatic dysfunction (12%), AOEs (10%), arthralgia (8%), anemia (7%), ALT increased (6%), and AST increased (5%).

The most common (>20%) non-hematologic adverse reactions were rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, AOEs, diarrhea, vomiting, and myalgia.

Table 6 summarizes the adverse reactions in PACE.

Table 6: Adverse Reactions (>10%) in Patients with CML or Ph+ ALL Who Received Iclusig in PACE

Adverse Reaction	CP-CML (N = 270)		AP-CML (N = 85)		BP-CML (N = 62)		Ph+ ALL (N = 32)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and Subcutaneous Tissue Disorders								
Rash and related conditions	75	9	68	12	55	7	50	3.1
Dry skin	42	3.3	32	1.2	26	1.6	25	0
Alopecia	8	0	11	0	8	0	6	0
Musculoskeletal and Connective Tissue Disorders								
Arthralgia	61	9	58	6	52	4.8	41	0
Myalgia	24	1.1	21	0	18	0	6	0
Muscle spasms	14	0	7	0	4.8	0	13	0
Bone pain	14	0.4	13	1.2	11	3	9	3
Musculoskeletal pain	11	1.5	7	0	8.1	0	6	3
Gastrointestinal Disorders								
Abdominal pain	54	11	49	9	45	13	34	6
Constipation	42	2.6	29	2.4	27	0	53	3.1
Pancreatitis/lipase elevation	32	19	21	15	19	16	9	6
Nausea	29	0.7	32	0	34	1.6	22	0
Diarrhea	20	0.7	29	2.4	24	3.2	13	3.1
Vomiting	19	1.5	27	0	27	1.6	25	0
Oral mucositis[a]	16	1.1	20	1.2	24	0	9	3.1
General Disorders								
Fatigue or asthenia	44	3.7	47	8	36	4.8	34	3.1
Fluid retention and edema	31	3.7	37	3.5	32	4.8	41	6
Pyrexia	26	1.1	40	7	37	3.2	25	0
Chills	8	0	12	0	13	1.6	9	0
Nervous System Disorders								
Headache	43	3.3	31	1.2	31	3.2	25	0
Neuropathy	26	3.3	18	2.4	13	0	13	0
Dizziness	17	0.4	11	0	4.8	0	3.1	0
Vascular Disorders								
Hypertension[b]	42	30	53	28	48	6	31	25
Arterial occlusive events	31	17	22	12	13	10	13	6
Hemorrhage	23	3	38	12	37	8	31	13
Hepatobiliary Disorders								
Hepatotoxicity	32	10	39	14	34	19	16	13
Cardiac Disorders								
Cardiac arrhythmias	19	7	17	4.7	24	8	25	6
Cardiac failure	9	5	8	4.7	16	10	6	3.1
Respiratory, Thoracic, and Mediastinal Disorders								
Cough[c]	19	0	24	0	21	0	6	0
Dyspnea[d]	19	3	20	3.5	23	6	16	0

Table 6: Adverse Reactions (>10%) in Patients with CML or Ph+ ALL Who Received Iclusig in PACE (continued)

Adverse Reaction	CP-CML (N = 270)		AP-CML (N = 85)		BP-CML (N = 62)		Ph+ ALL (N = 32)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections								
Upper respiratory tract infection[e]	14	1.1	13	0	13	1.6	3.1	0
Urinary tract infection[f]	12	2.2	14	3.5	1.6	1.6	9	0
Nasopharyngitis	12	0	18	0	3.2	0	3.1	0
Pneumonia	8	4.8	18	11	18	13	22	16
Cellulitis	4.4	1.9	8	3.5	13	4.8	0	0
Sepsis[g]	2.6	1.9	11	6	18	6	28	25
Metabolism and Nutrition Disorders								
Decreased appetite	13	0.4	14	1.2	8	0	31	0
Hyperlipidemia	13	0.7	7	0	3.2	0	3.1	0
Investigations								
Weight decreased	10	0.4	9	0	4.8	0	13	0
Psychiatric Disorders								
Insomnia	11	0	13	0	11	0	13	0
Anxiety	4.8	0	18	0	8	0	6	0
Blood and Lymphatic System Disorders								
Febrile neutropenia	1.1	1.1	4.7	4.7	13	13	25	25

Graded using CTCAE v4.03.

[a] Oral mucositis includes aphthous ulcer, gingival pain, lip blister, lip pain, lip swelling, mouth ulceration, oropharyngeal pain, oral mucosal blistering, oral mucosal eruption, oral pain, pharyngeal ulceration, stomatitis, and tongue ulceration

[b] Derived from blood pressure (BP) measurement

[c] Cough includes cough, productive cough, and upper airway cough syndrome

[d] Dyspnea includes dyspnea and dyspnea exertional

[e] Upper respiratory tract infection includes upper respiratory tract infection and viral upper respiratory tract infection

[f] Urinary tract infection includes escherichia urinary tract infection, urinary tract infection, and urinary tract infection bacterial

[g] Sepsis includes abdominal sepsis, bacteremia, device-related sepsis, escherichia bacteremia, fungemia, klebsiella bacteremia, klebsiella sepsis, neutropenic sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal sepsis, streptococcal bacteremia, and urosepsis

Clinically relevant adverse reactions occurring in ≤10% of patients: impaired glucose tolerance (9%)*, venous thromboembolic events (6%)*, secondary malignancies* (6%), and hypothyroidism (3%).

* Grouped terms: secondary malignancies includes basal cell carcinoma, squamous cell carcinoma of the skin, melanoma, chronic myelomonocytic leukemia, colon cancer, epithelioid mesothelioma, large cell lung cancer recurrent, lung neoplasm, malignant ascites, myelodysplastic syndrome, neuroendocrine carcinoma metastatic, non-Hodgkin lymphoma, pancreatic cancer, thyroid neoplasm, vulval cancer; venous thromboembolic events includes deep vein thrombosis, pulmonary embolism, retinal vein occlusion, retinal vein thrombosis, superficial thrombophlebitis, venous embolism, venocclusive liver disease, portal vein thrombosis; impaired glucose tolerance includes blood glucose increased, diabetes mellitus, glucose tolerance impaired, glycosylated hemoglobin increased, hyperglycemia, insulin resistance, and type 2 diabetes mellitus

Tables 7 and 8 summarize the Grade 3 or 4 hematologic laboratory abnormalities or all grades non-hematologic abnormalities in PACE.

Table 7: Select Grade 3 or 4* Hematologic Laboratory Abnormalities in Patients Who Received Iclusig in PACE

Laboratory Abnormality	CP-CML (N = 270) (%)	AP-CML (N = 85) (%)	BP-CML (N = 62) (%)	Ph+ ALL (N = 32) (%)
Hematology				
Platelet count decreased	35	49	45	47
Neutrophil cell count decreased	23	52	48	59
White blood cell decreased	12	37	48	63
Lymphocyte decreased	10	25	32	19
Hemoglobin decreased	8	31	52	34

* Graded using CTCAE v4.03

Table 8: Select Non-Hematologic Laboratory Abnormalities (≥20%) in Patients Who Received Iclusig in PACE

Laboratory Abnormality	Pooled Safety Population (N = 449)	
	All Grades* (%)	Grade 3 or 4 (%)
Chemistry		
Glucose increased	54	7
Phosphate decreased	34	10
Calcium decreased	30	0.9
Sodium decreased	27	4.9
Creatinine increased	21	0.2
Potassium increased	20	2.2
Bicarbonate decreased	20	0.2
Liver Function Tests		
ALT increased	41	6
Alkaline phosphatase increased	40	2
AST increased	35	3.6
Albumin decreased	28	0.2
Bilirubin increased	13	0.9
Pancreatic Enzymes		
Lipase increased	40	14
Amylase increased	18	3.6

ALT = alanine aminotransferase, AST = aspartate aminotransferase

* Graded using CTCAE v4.03

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders: Thrombotic microangiopathy

Endocrine Disorders: Hyperthyroidism

Gastrointestinal Disorders: Gastrointestinal perforation, fistula

Metabolism and Nutrition Disorders: Dehydration

Nervous System Disorders: Reversible posterior leukoencephalopathy syndrome (RPLS)

Skin and Subcutaneous Tissue Disorders: Severe cutaneous reaction (e.g., Erythema multiforme, Stevens-Johnson syndrome), impaired wound healing

Vascular Disorders: Arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Iclusig

Strong CYP3A Inhibitors

Coadministration of Iclusig with a strong CYP3A inhibitor increases ponatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Iclusig adverse reactions. Avoid coadministration of Iclusig with strong CYP3A inhibitors. If coadministration of Iclusig with strong CYP3A inhibitors cannot be avoided, reduce the Iclusig dosage *[see Dosage and Administration (2.3)]*.

Strong CYP3A Inducers

Coadministration of Iclusig with a strong CYP3A inducer decreases ponatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of Iclusig with strong CYP3A inducers unless the benefit outweighs the risk of decreased ponatinib exposure. Monitor patients for reduced efficacy. Selection of concomitant medication with no or minimal CYP3A induction potential is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Iclusig can cause fetal harm when administered to a pregnant woman. There are no available data on Iclusig use in pregnant women. In animal reproduction studies, oral administration of ponatinib to pregnant rats during organogenesis caused adverse developmental effects at doses lower than human exposures at the recommended human dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

Ponatinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 0.3 mg/kg/day, 1 mg/kg/day, and 3 mg/kg/day during organogenesis (25 rats per group). At the maternally toxic dose of 3 mg/kg/day (equivalent to the AUC in patients receiving the recommended dose of 45 mg/day), ponatinib caused embryo-fetal toxicity as shown by increased resorptions, reduced body weight, external alterations, multiple soft tissue and skeletal alterations, and reduced ossification. Embryo-fetal toxicities also were observed at 1 mg/kg/day (approximately 24% the AUC in patients receiving the recommended dose) and involved multiple fetal soft tissue and skeletal alterations, including reduced ossification.

8.2 Lactation

Risk Summary

There is no data on the presence of ponatinib in human milk or the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child from ponatinib, advise women not to breastfeed during treatment with Iclusig and for 6 days following the last dose.

8.3 Females and Males of Reproductive Potential

Iclusig can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Iclusig.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Iclusig and for 3 weeks after the last dose.

Infertility

Based on animal data, ponatinib may impair fertility in females of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Juvenile Animal Toxicity Data

A juvenile toxicity study in 15 day old rats was conducted with daily oral gavage administration of ponatinib at 0.75 mg/kg/day, 1.5 mg/kg/day, or 3 mg/kg/day for 21 days. There were no adverse effects of ponatinib on juvenile rat developmental parameters (vaginal opening, preputial separation or bone measurements) observed in this study. Once daily oral administration of 3 mg/kg/day ponatinib to juvenile rats beginning on Day 15 postpartum (pp) resulted in mortality related to inflammatory effects after 6 to 7 days following initiation of treatment. The dose of 3 mg/kg/day is approximately 0.32 times the clinical dose on a mg/m^2 basis for a child.

8.5 Geriatric Use

Of the 94 patients with CP-CML who received Iclusig at a starting dose of 45 mg in OPTIC, 17% were 65 years and older and 2.1% were 75 years and older. Patients aged 65 years and older had a lower ≤1% BCR-ABL1^{IS} rate at 12 months (27%) as compared with patients less than 65 years of age (47%). AOEs occurred in 38% (6/16) of patients 65 years and older and 9% (7/78) of patients less than 65 years of age *[see Warnings and Precautions (5.1)]*.

Of the 449 patients who received Iclusig in PACE, 35% were 65 years and older and 8% were 75 years and older. In patients with CP-CML, patients aged 65 years and older had a lower major cytogenetic response rate (40%) as compared with patients less than 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients aged 65 years and older had a similar hematologic response rate (45%) as compared with patients less than 65 years of age (44%). AOEs occurred in 35% (54/155) of patients 65 years and older and in 21% (61/294) of patients less than 65 years of age *[see Warnings and Precautions (5.1)]*.

Patients aged 65 years or older are more likely to experience adverse reactions including vascular occlusion, decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Patients with hepatic impairment are more likely to experience adverse reactions compared to patients with normal hepatic function. Reduce the starting dose of Iclusig for patients with pre-existing hepatic impairment (Child-Pugh A, B, or C) *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*. The safety of multiple doses, or doses higher than 30 mg, has not been studied in patients with hepatic impairment.

17 PATIENT COUNSELING INFORMATION

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

Arterial Occlusive Events and Venous Thromboembolic Events

Inform patients that serious arterial thromboses (including arterial stenosis sometimes requiring revascularization) and VTEs have occurred. Advise patients to immediately contact their healthcare provider with any symptoms suggestive of a blood clot such as chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain, or leg swelling *[see Warnings and Precautions (5.1, 5.2)]*.

Heart Failure and Cardiac Arrhythmias

Inform patients of the possibility of heart failure, and abnormally slow or fast heart rates. Advise patients to contact their healthcare provider if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting *[see Warnings and Precautions (5.3, 5.12)]*.

Hepatotoxicity

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their healthcare provider if signs of liver failure occur, including jaundice, anorexia, bleeding or bruising *[see Warnings and Precautions (5.4)]*.

Hypertension

Inform patients of the possibility of new or worsening of existing hypertension. Advise patients to contact their healthcare provider for elevated blood pressure or if symptoms of hypertension occur including confusion, headache, dizziness, chest pain, or shortness of breath *[see Warnings and Precautions (5.5)]*.

Pancreatitis

Inform patients of the possibility of developing pancreatitis that may be accompanied by nausea, vomiting, abdominal pain, or abdominal discomfort, and to promptly report these symptoms *[see Warnings and Precautions (5.6)]*.

Neuropathy

Inform patients of the possibility of developing peripheral or cranial neuropathy while being treated with Iclusig. Advise patients to report symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness *[see Warnings and Precautions (5.8)]*.

Ocular Toxicity

Inform patients of the possibility of ocular toxicity while being treated with Iclusig. Advise patients to report symptoms of ocular toxicity, such as blurred vision, dry eye, or eye pain *[see Warnings and Precautions (5.9)]*.

Hemorrhage

Inform patients of the possibility of serious bleeding and to immediately contact their healthcare provider with any signs or symptoms suggestive of hemorrhage such as unusual bleeding or easy bruising *[see Warnings and Precautions (5.10)]*.

Fluid Retention

Inform patients of the possibility of developing fluid retention and to contact their healthcare provider for symptoms such as leg swelling, abdominal swelling, weight gain, or shortness of breath *[see Warnings and Precautions (5.11)]*.

Myelosuppression

Inform patients of the possibility of developing low blood cell counts; inform patients to report immediately should fever develop, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.13)]*.

Tumor Lysis Syndrome

Inform patients of the possibility of developing TLS and to immediately contact their healthcare provider for any signs or symptoms associated with TLS *[see Warnings and Precautions (5.14)]*. Advise patients to be adequately hydrated when taking Iclusig to reduce the risk of TLS.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS – also known as Posterior Reversible Encephalopathy Syndrome)

Inform patients of the possibility of developing Reversible Posterior Leukoencephalopathy Syndrome while being treated with Iclusig. Advise patients to report symptoms such as seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances *[see Warnings and Precautions (5.15)]*.

Impaired Wound Healing and Gastrointestinal Perforation

Inform patients that impaired wound healing and gastrointestinal fistula or perforation have been reported. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.16)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Iclusig and for 3 weeks after the last dose *[see Warnings and Precautions (5.17), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with Iclusig and for 6 days after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females of reproductive potential of the potential for reduced fertility from Iclusig *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Instructions for Taking Iclusig

Advise patients to take Iclusig exactly as prescribed and not to change their dose or to stop taking Iclusig unless they are told to do so by their healthcare provider. Iclusig may be taken with or without food. Iclusig tablets should be swallowed whole. Patients should not cut, crush or dissolve the tablets.

Patients should not take two doses at the same time to make up for a missed dose.

Advise patients not to drink grapefruit juice or eat grapefruit as it may increase the amount of Iclusig in their blood and therefore increase their risk of adverse reactions.

Lactose

Inform patients that Iclusig tablets contain lactose monohydrate.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Lexington, MA 02421

ICL348 R9

CONTINUING MEDICAL EDUCATION (CME)

Pediatric-Inspired Asparaginase Regimens for Patients With Acute Lymphocytic Leukemia

FACULTY
Rachel Rau, MD

Attending Physician,
Cancer and Blood Disorders Center
Seattle Children's Hospital
Associate Professor of Pediatrics,
Hematology/Oncology
University of Washington School
of Medicine
Principal Investigator
Ben Towne Center for Childhood Cancer Research
Seattle, WA

This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

CME PROVIDER CONTACT INFORMATION
Physicians' Education Resource®, LLC
2 Commerce Drive
Cranbury, NJ 08512
Toll-Free: 888-949-0045
Local: 609-378-3701
Fax: 609-257-0705
info@gotoper.com

PER® Physicians' Education Resource, LLC
gotoper.com

LEARNING OBJECTIVES

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

- Discuss the use of asparaginase to treat pediatric and adult acute lymphocytic leukemia.
- Identify and manage toxicities associated with asparaginase therapy.

RELEASE DATE: February 1, 2024
EXPIRATION DATE: February 1, 2025

INSTRUCTIONS FOR PARTICIPATION AND HOW TO RECEIVE CREDIT

1. Read this activity in its entirety.
2. Go to **https://gotoper.com/piar23all-postref** to access and complete the posttest.
3. Answer the evaluation questions.
4. Request credit using the drop-down menu.

YOU MAY IMMEDIATELY DOWNLOAD YOUR CERTIFICATE

FACULTY, STAFF, AND PLANNERS' DISCLOSURES

In accordance with ACCME Guidelines, PER® has identified and resolved all COI for faculty, staff, and planners prior to the start of this activity by using a multistep process.

Disclosures (Dr Rau): *Consultant*: Jazz Pharmaceuticals; *Advisory Board*: Jazz Pharmaceuticals.

The staff of PER® have no relevant financial relationships with commercial interests to disclose.

OFF-LABEL DISCLOSURE AND DISCLAIMER

This activity may or may not discuss investigational, unapproved, or off-label use of drugs. Learners are advised to consult prescribing information for any products discussed. The information provided in this activity is for accredited continuing education purposes only and is not meant to substitute for the independent clinical judgment of a health care professional relative to diagnostic, treatment, or management options for a specific patient's medical condition. The opinions expressed in the content are solely those of the individual faculty members, and do not reflect those of PER® or any of the companies that provided commercial support for this activity.

This activity is funded by PER®.

ACCREDITATION/CREDIT DESIGNATION

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Asparaginase treatment is a cornerstone of acute lymphocytic leukemia (ALL) chemotherapy. This enzyme has a unique mechanism of action and toxicity profile that presents a distinct set of challenges in the clinical setting. In this article, Rachel Rau, MD, explores the use of asparaginase formulations in pediatric and adult ALL.

Q: Please provide a brief description of the unique mechanism of action of asparaginase therapy.

RAU: Asparaginase is quite distinct in terms of how it functions as an antileukemic agent compared with most of our standard chemotherapies. Asparaginase is an enzyme that breaks down the amino acid asparagine into aspartic acid and ammonia.[1] Normal cells can synthesize their own asparagine and, therefore, continue to function in the absence of it. However, leukemic cells lack the machinery to form their own asparagine, and so they depend on scavenging it from their environment. When you give a person with leukemia asparaginase, the leukemic cells can't produce proteins and they die.

Q: Can you comment on the differences between asparaginase formulations currently used in clinical practice? When do you use each formulation?

RAU: That has been a rapidly evolving landscape over the past few years. Our frontline preferred agent is asparaginase derived from *Escherichia coli* bacteria that has been engineered to be long-acting—it has had polyethylene glycol moieties added to that bacterial enzyme.[1] There are currently 2 FDA-approved formulations of long-acting, pegylated *E coli*–derived asparaginase. One is pegaspargase, which has been around the longest and has been used in most of our frontline trials over the past several decades. Currently, in the United States, that formulation is only available to individuals 22 years and older.

The other long-acting formulation is calaspargase.[1] It is a pegylated *E coli*–derived asparaginase with a different linker that results in a much longer duration of activity compared with pegaspargase. Pegaspargase is given no more often than once every 2 weeks, whereas calaspargase is given no more often than once every 3 weeks. Currently, calaspargase is only approved in the United States and for use in individuals 21 years or younger. Clinical trials are ongoing to examine its use in older individuals.[2]

If patients have a hypersensitivity reaction to one of those frontline *E coli*-derived asparaginases, we have to switch them to something that they wouldn't have antibodies to. Our available products are asparaginase derived from a different bacteria called *Erwinia chrysanthemi*.[1] Currently, in the United States our only *Erwinia*-based asparaginase therapy is recombinant *Erwinia chrysanthemi*.

There are only short-acting versions available of *Erwinia*-derived asparaginase.[1] For 1 dose of pegaspargase that lasts in the system for 2 weeks, you would have to give 6 doses of *Erwinia* asparaginase on a Monday, Wednesday, Friday schedule, or 7 doses every 48 hours. But we can effectively replace our long-acting asparaginase with *Erwinia*-based products in patients who need it.

Infusion reactions are difficult to distinguish from allergic reactions caused by neutralizing antibodies, especially in the heat of the moment when you have a sick child in clinic with emergent symptoms.

Q: What are best practices for monitoring serum asparaginase levels?

RAU: In the United States, we now have the capacity to monitor asparaginase activity levels in patients clinically. There are 2 commercial laboratories for which these assays are available and usually, you get results back within 3 days. Best practice is to send levels 7 to 14 days after a full dose of long-acting asparaginase to ensure that they still have adequate levels.[3] If the serum asparaginase levels are low at those time points, that probably indicates that the patient has silent inactivation where antibodies are neutralizing the drug, resulting in its rapid clearance from the system. Those patients are not benefitting from the drug, and that situation would prompt you to switch to the *Erwinia*-based asparaginase.

Certainly, if you're giving patients premedication, it is advisable to send levels because you might have masked a hypersensitivity reaction that you could then uncover by looking at asparaginase activity levels.[3] Serum asparaginase levels also should be determined for those patients who have had presumed hypersensitivity responses to judge whether these effects are related to an infusion reaction vs an antibody-mediated reaction.

The correct time to monitor serum asparaginase levels in individuals receiving the short-acting, *Erwinia*-based product is even less defined. A lot of institutions are not checking them at all, because that is the last line of therapy that the patient has; therefore, how those values should be used is unclear. Presumably, if a patient has multiple consecutive trough levels 48 hours after an *Erwinia*-based asparaginase product, this could indicate silent inactivation, prompting discontinuation.

Q: What are some of the serious toxicities associated with asparaginase therapy?

RAU: Asparaginase therapy has a unique and distinct toxicity profile

compared with our other chemotherapies.[1] The first toxicity that everybody thinks about are those hypersensitivity reactions. Asparaginases are foreign-derived proteins; thus it is not surprising that our body can mount an immune response against them. True, antibody-mediated hypersensitivity reactions with our long-acting, pegylated products occur in 10% to 20% of patients.[4]

We most often give our long-acting asparaginases by intravenous (IV) infusion.[1] When you give a drug by IV infusion, there is a chance of the patient experiencing an infusion reaction. An infusion reaction, simply defined, is a set of clinical symptoms that develop during or shortly after infusion of a drug. These reactions are due to the drug infusion itself and can be from a cytokine release or other mechanisms distinct from something antibody-mediated. This is relatively common with asparaginases, because they cleave asparagine into aspartic acid and ammonia, leading to a rapid increase in patients' serum ammonia levels. As a result of this spike in ammonia, patients can get a full-body rash, nausea, vomiting, a feeling of impending doom, and vital sign changes. Infusion reactions are difficult to distinguish from allergic reactions caused by neutralizing antibodies, especially in the heat of the moment when you have a sick child in clinic with emergent symptoms. Asparaginase activity levels can help you sort that out, because really low levels would suggest that there were antibodies present to cause the reaction. If you have decent levels after that reaction, you can feel more confident that it was probably just secondary to the infusion itself. This is an important distinction because with an antibody-mediated hypersensitivity reaction, you would need to change asparaginase formulations; with infusion reactions, you can consider rechallenging with some modification to the infusion such as premedications and slowing of the infusion rate.

The next toxicity that comes to mind for most individuals is pancreatitis. This is a complication that can occur usually 10 to 14 days after the dose or the start of a course.[5] Pancreatitis is much more common in older individuals. We see it in around 5% of the younger kids and somewhere around 10% to 15% of our adolescents and young adult (AYA) population. Pancreatitis can range in severity from transient, mild abdominal pain to fulminant pancreatitis with pancreatic necrosis, pseudocyst formation, insulin-dependent diabetes, and even death. Other than the age of the patient, there are no great ways to predict the risk for pancreatitis. There also are no great ways to prevent it. The big question after having an episode of pancreatitis, is which patients can be rechallenged? The answer to this question depends on balancing the patient's risk of leukemic relapse with the risk of having a recurrence of pancreatitis.

Patients at NCI high risk who missed 1 or more courses of asparaginase due to toxicity or the *Erwinia*-based asparaginase shortage had a 50% increase in relapse risk.

The final toxicity that I will mention is liver toxicity. We see a fair amount of a distinct liver toxicity with this asparaginase, particularly during induction therapy.[1] We know that individuals who are obese are at risk for liver toxicity including really high levels of direct bilirubin.[6] Symptoms usually manifest a couple of weeks after their first dose of a long-acting, *E coli*–derived asparaginase, which is given during the first week of their first block of treatment. Strategies like capping the asparaginase dose at 1 vial for obese individuals are being explored, but we do not yet know whether that is going to solve the problem for individuals at risk.

There are some other strategies being looked at as well. We have L-carnitine as a preventative agent, which is being explored in a currently ongoing clinical trial.[7] Delaying the dose is another strategy. Instead of giving asparagine in the first week, wait until the second or third week, when the liver may be a little more calmed from a leukemia perspective, and see if that lessens the risks.[1]

Q: What is the impact of dose interruptions and discontinuations on therapeutic outcomes and future adverse events?

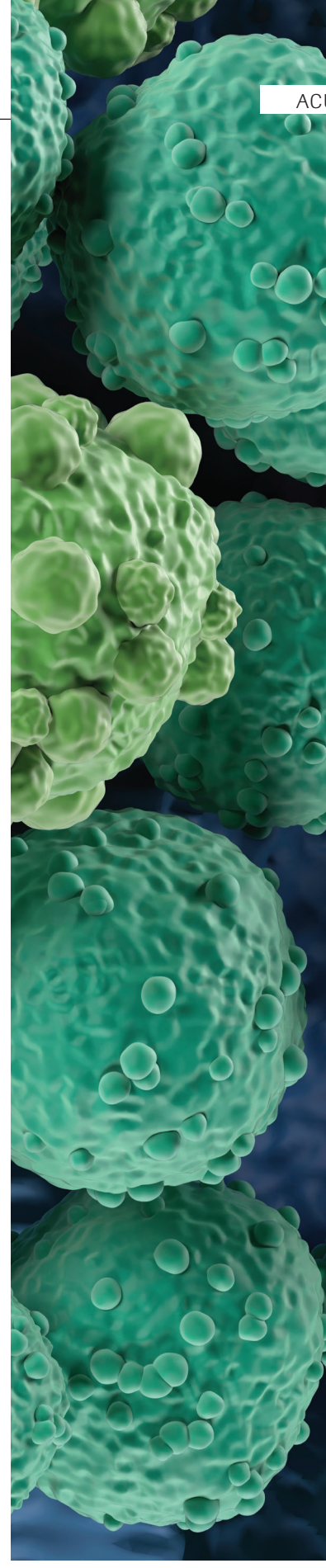
RAU: During recent shortages of *Erwinia*-derived asparaginase, we had a lot of patients who had a reaction to long-acting, *E coli*–based asparaginase, and we had no other options to switch to. We had to discontinue their asparaginase courses altogether, missing 1 or more of those planned during their therapy. We found that those missed doses really impacted outcomes, particularly for our higher-risk patients.[8] In the Children's Oncology Group (COG) study done by Sumit Gupta, MD, we found that NCI high-risk patients, who missed 1 or more courses of asparaginase due to toxicity or the Erwinia-based asparaginase shortage, had a 50% increase

in relapse risk.[8] Likewise, the Nordic Society for Pediatric Hematology and Oncology group showed that if you had to truncate your asparaginase therapy courses, you had an increased risk of relapse.[9] Similar results also were shown by the Dana-Farber consortia.[10] The impact of those missed courses was more than we hoped, which highlights the need to avoid drug shortages and to come up with strategies to prevent those toxicities that can be dose-limiting.

Q: How do you determine whether rechallenge vs switching formulations is the appropriate choice?

RAU: There's only 1 indication for switching formulations, and that is a hypersensitivity reaction to *E coli*–based asparaginase.[3] None of these other complications that we have discussed has an indication for switching from *E coli*–derived asparaginase to an *Erwinia*-based product, so the decision then becomes if you rechallenge with asparaginase or discontinue it altogether. Pancreatitis is perhaps the toxicity where the decision of whether or not to rechallenge is most difficult. About 50% of patients who have an episode of pancreatitis will have a recurrence regardless of severity of the first episode.[5] In our COG protocols, if a patient has mild grade 3 pancreatitis, meaning fewer than 72 hours of symptoms with no diabetes or pseudocyst or other severe complications, you can consider rechallenge.[11] If it is a more severe episode, we would advise discontinuing asparaginase. However, for all patients with pancreatitis, you must balance the risk of relapse vs the risk of recurrence of the pancreatitis.

For liver toxicity, you will almost always rechallenge. It is unlikely that you are going to get that severe hyperbilirubinemia during subsequent courses, as that tends to be most prominent during induction. Thrombosis is another potential complication that can be severe and scary, but once you have patients on a stable anticoagulant regimen and the symptoms of their initial event have stabilized or resolved, then you can rechallenge them with asparaginase.



LASZLO@STOCK.ADOBE.COM

Q: What are the key considerations to keep in mind when using pediatric-inspired regimens in adults?

RAU: That would be the toxicity profile. Many toxicities, such as pancreatitis, liver toxicity, and thrombosis, are more common as patients become older.[1] I think the exception is hypersensitivity. That seems to be pretty even across the board. Undoubtedly there is an inflection point where the risk of toxicities outweighs the benefits in terms of relapse risk, but the existing data strongly support that a pediatric-inspired regimen that includes asparaginase is beneficial in terms of relapse prevention in AYAs and even in patients in middle adulthood. ■

Key References

1. Juluri KR, Siu C, Cassaday RD. Asparaginase in the treatment of acute lymphoblastic leukemia in adults: current evidence and place in therapy. *Blood Lymphat Cancer.* 2022;12:55-79. doi:10.2147/blctt.S342052

3. van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica.* 2016;101(3):279-285. doi:10.3324/haematol.2015.137380

8. Gupta S, Wang C, Raetz EA, et al. Impact of asparaginase discontinuation on outcome in childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. *J Clin Oncol.* 2020;38(17):1897-1905. doi:10.1200/jco.19.03024

For full list of references visit https://gotoper.com/piar23all-postref

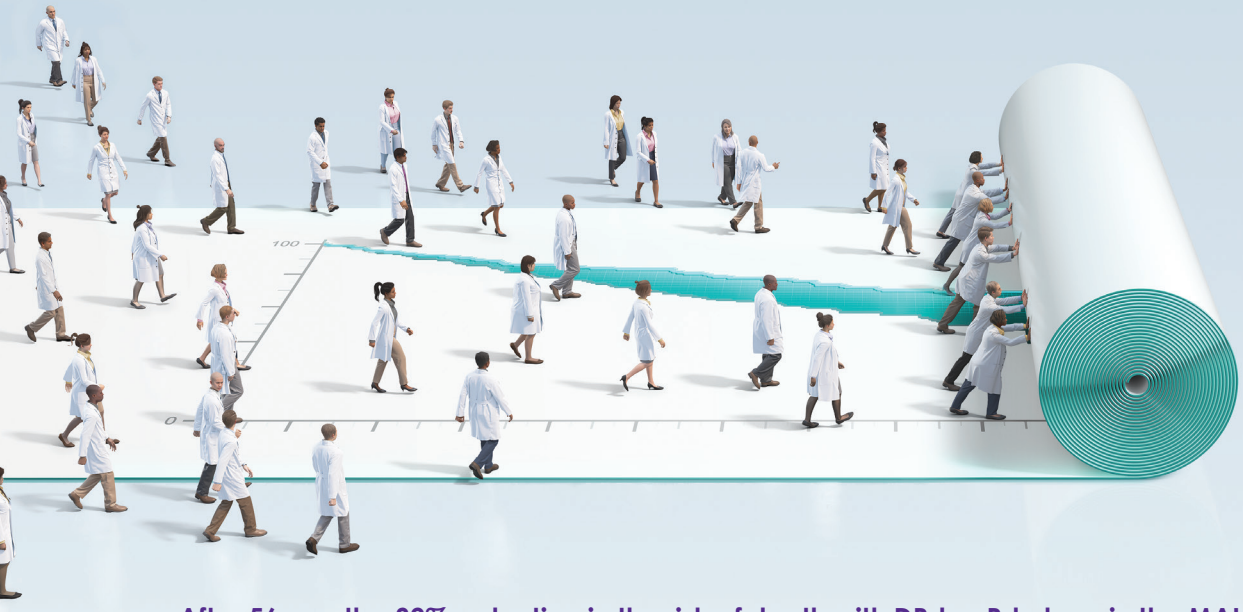
DARZALEX® (daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

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

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

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

Help your patients live longer than Rd alone with DRd, an established frontline treatment proven to significantly extend overall survival[1]



After 56 months: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial
(HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).*[1]

*Median follow-up was 56 months in the DRd group (range: 53.0-60.1 months) and in the Rd group (range: 52.5-59.4 months)[1,2]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions.

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DARZALEX® (daratumumab) + Rd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma.

Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) and OS was a secondary endpoint.[1]

Powerful efficacy to start the treatment journey[1,3]

At follow-up of 28 months, **median progression-free survival (mPFS) was not reached** with DARZALEX® + Rd vs 31.9 months (95% CI, 28.9 to not reached) with Rd alone*

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

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

Efficacy results in long-term follow-up[1,4]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, not evaluable) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm

45% **reduction in the risk of disease progression or death** with DARZALEX® + Rd vs Rd alone (HR=0.55; 95% CI, 0.45-0.67)

Secondary endpoint of overall survival (OS)[1,2]
After 56 months of follow-up:

- 66% of patients were still alive with DRd vs 53% with Rd alone (DRd: 95% CI, 60.8-71.3; Rd: 95% CI, 47.2-58.6)†
- Median OS was not reached for either arm

32% **reduction in the risk of death** in patients treated in the DRd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013)

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

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

Safety results in long-term follow-up
(median follow-up of 64.5 months)[4]

This information is not included in the current Prescribing Information and has not been evaluated by the FDA.

- Most frequent TEAEs for DRd occurring in ≥30% of patients were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms‡
- Grade 3/4 infections were 43% for DRd vs 30% for Rd‡
- Grade 3/4 TEAEs occurring in ≥10% of patients were neutropenia (54% for DRd vs 37% for Rd), pneumonia (20% vs 11%), and anemia (17% vs 22%)‡

Treatment-emergent adverse events are reported as observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[1,3]
†Kaplan-Meier estimate.[3]
‡Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after the start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

See the rolled-out data.
Visit darzalexhcp.com

IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

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

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj): Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

Local Reactions

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

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

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

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

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

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

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

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

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

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

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

DARZALEX®: ADVERSE REACTIONS

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

DARZALEX *FASPRO*®: ADVERSE REACTIONS

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

INDICATIONS

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

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

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

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

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

cp-248517v3

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(11):1582-1596. doi:10.1016/s1470-2045(21)00466-6 **3.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med.* 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249 **4.** Kumar SK, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA.

07/23 cp-352216v2

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

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

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

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

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

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

Interference with Serological Testing

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

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

Infections

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

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

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

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

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

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

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies.

Postmarketing Experience

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

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

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

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

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

For patent information: www.janssenpatents.com

cp-271933v4

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

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

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

Interference with Serological Testing

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

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

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

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

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

Postmarketing Experience

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

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

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

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

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

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

For patent information: www.janssenpatents.com

cp-267681v3

cancernetwork®

Frontline FORUM

Frontline Forum is a live, 90-minute moderator-guided workshop featuring KOLs who discuss real-world evidence, data readouts, and more from conferences around a specific disease state or topic.

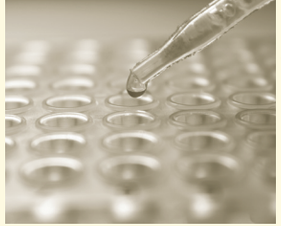
This new program provides real-time feedback from trusted experts. Our KOLs work on the frontline of patient care.

Scan to view

or visit: CancerNetwork.com/frontline-forum

Follow us

@cancernetwork | @cancernetwrk



Indiana University Health Medical Center

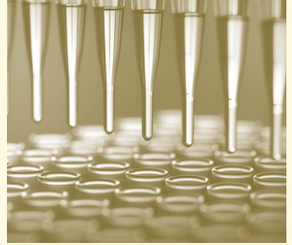
A reputation of providing world-class cancer care and groundbreaking research.

HONORED TO BE RANKED #1 IN INDIANA BY U.S. NEWS & WORLD REPORT

Together in partnership with IU School of Medicine, IU Health Medical Center provides world-class care and is known for leadership and groundbreaking research in the prevention, detection and treatment of cancer, notably breast, colon, pancreatic, genitourinary and hematologic cancers.

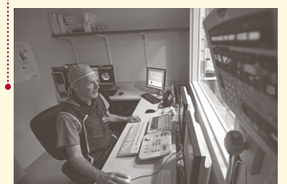
Discover more at **iuhealth.org/OncologyPioneers**

Indiana University Health



Indiana University Health Medical Center

Pioneers on the leading edge of cancer care.



Indiana University Health

Over a century of clinical breakthroughs and excellence in treating every form of cancer.

1887
Indiana University School of Medicine established what is believed to be the country's first department of urology
founded by William N. Wishard, MD

1960
Pioneered the surgical technique of retroperitoneal lymph node dissection (RPLND) for patients with testis cancer
by John Donohue, MD

1970s
Led the country in developing and refining the medical approach to testis cancer

Developed the treatment and cared for first patient with testis cancer through cisplatin-based chemotheraphy
by Lawrence Einhorn, MD

Physicists and engineers at Indiana University School of Medicine pioneered high intensity focused ultrasound (HIFU) for treatment of prostate cancer
by Naren Sanghbi

1987
Use of Indiana Pouch for patients with bladder cancer or other urologic conditions published
by Richard Bihrle, MD and others at Indiana University School of Medicine

The first population based study for screening colonoscopy performed in the United States
by Douglas Rex, MD

1988
The first cord blood transplant made possible by the basic scientific proof-of-concept research at IU School of Medicine
by the late Hal Broxmeyer, PhD

1992
The National Cancer Institute (NCI) awards a planning grant to IU School of Medicine for a cancer center, establishing the Indiana University Cancer Center

1999
The IU Cancer Center earns National Cancer Institute designation.

2006
The IU Cancer Center becomes the Indiana University Melvin and Bren Simon Cancer Center to reflect the philanthropic support of Melvin and Bren Simon

2007
The Komen Tissue Bank is established at Indiana Univeristy Melvin and Bren Simon Cancer Center

First to publish on HIFU treatment for prostate cancer in the U.S.
by Michael Koch, MD and Thomas Gardner, MD

2010
One of the first five programs in the country to initiate robotic surgery for the pancreas, bile ducts and gallbladder

2016
One of the first in the U.S. to pioneer PSMA guided imaging for prostate cancer
Clint Bahler, MD

One of the first to perform focal HIFU procedure for treatment of prostate cancer
Michael Koch, MD

2017
Pioneered the regimen of high-dose chemotherapy with autologous peripheral-blood stem-cell transplantion for relapsed germ cell tumors
by Nabil Adra, MD, Rafat Abonour, MD, Sandra K. Althouse, MD, Costantine Albany, MD, Nasser H. Hanna, MD, and Lawrence H. Einhorn, MD

2019
The IU Simon Cancer Center earns Comprehensive Cancer Center status, the NCI's highest designation

2021
New England Journal of Medicine published findings on preventing a common complication to lifesaving blood stem cell transplantation in leukemia, acute graft-versus-host disease (GVHD)
Sherif Farag, MD, PhD

2022
The Indiana University Melvin and Bren Simon Comprehensive Cancer Center becomes a member of the National Comprehensive Cancer Network

2022
IU Health completed the first study using tumor gene fingerprints to define therapy in patients with high-risk disease for breast cancer

Indiana University Health