GAZYVA Infusion-Related Reactions Guide

Indications

GAZYVA is a CD20-directed cytolytic antibody indicated:

- In combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma (FL)
- In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)

Select Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Please see additional important safety information throughout, and click here for full prescribing information, including BOXED WARNING.

GAZYVA®
obinutuzumab
injection | 1,000mg/40mL

GAZYVA Infusion-Related Reactions Guide

This guide has been created to help provide information on approved GAZYVA-based regimens for the treatment of your appropriate patients with[1]:

- Previously untreated stage II bulky, III, or IV follicular lymphoma (FL)
- Previously untreated chronic lymphocytic leukemia (CLL)

In addition to information on the preparation, dosing, and administration of GAZYVA, you will also find further information on identifying, reducing the risk of, and managing infusion reactions in your patients.

For your convenience, this guide has been organized with 2 sections that highlight the differences in GAZYVA use by indication. Please be sure to refer to the appropriate section for the patient you are treating.

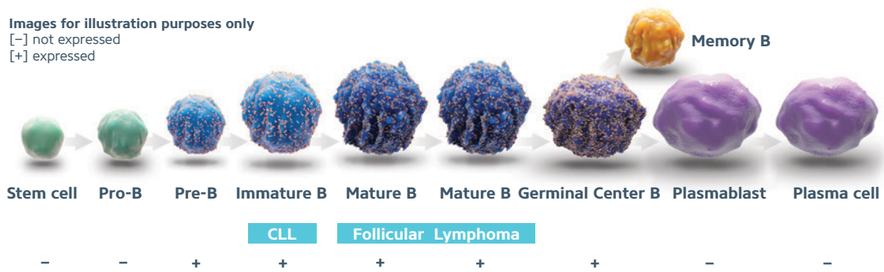
Table of Contents

B-Cell Lineage and CD20

CD20 is a surface antigen that is expressed on the majority of B cells[2-4]

- CD20 is absent in stem cells, plasma cells, and cells of other lineages

B-cell differentiation[2-4]



CD20 expression (ligands are not reflective of real data)

Important Safety Information

Contraindications

- GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g. anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use

Warnings and Precautions

Hepatitis B Virus Reactivation

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies including GAZYVA. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (ie, HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive)

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Monoclonal Antibodies Are Therapeutic Proteins Commonly Used in Cancer Treatment[5]

- Some are genetically engineered to target a specific antigen or receptor (eg, CD20) on the surface of a target cell[1,5]
- When a monoclonal antibody such as GAZYVA binds to CD20, an immune response is thought to be triggered, which can lead to the destruction of the target cell and may affect healthy cells[1]

GAZYVA is a type of humanized monoclonal antibody[1,6,7]

Humanized
>90% human

Generic suffix
-zumab

Types of monoclonal antibodies include[8]:

- **Murine:** derived solely from mouse immunoglobulin[5,7,9]
- **Chimeric:** composed of protein sequences from murine and human origin[6]
- **Humanized:** human antibody combined with murine antibody. Humanized antibodies contain a very small percentage of murine material[5,6]
- **Human:** fully or nearly 100% human composition; produced with genetically engineered, knockout, or transgenic mice or through the use of phage display[6,8,9]

Select Important Safety Information

Hepatitis B Virus Reactivation (cont'd)

- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level, or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, ie, increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with GAZYVA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult healthcare providers with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy

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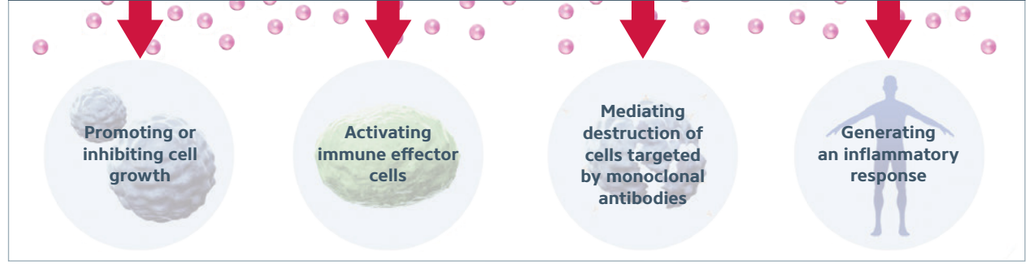
Antibody Binding to CD20 May Result in Cytokine Release, Leading to Infusion Reactions

Cytokines are important mediators of immune function

- Cytokines are proteins that are secreted by cells and transmit signals between cells[3]
  - –Common cytokines include interleukins (ILs), interferons (IFNs), and tumor necrosis factors (TNFs)
  - –Cytokines mediate normal immune function, including response to monoclonal antibody therapy, by transmitting signals between cells
- Cytokines are often involved in the body's response to monoclonal antibody therapy[5]

Most cytokines have several functions and act on many cell types[3,10]



The release of cytokines during therapeutic monoclonal antibody administration is thought to be an underlying cause of infusion-related reactions[5,10,11]

Cytokine-mediated infusion-related reactions have 3 main steps[5,10,11]

1. Monoclonal antibodies bind to target cells
2. Subsequent immune response destroys target cells
3. Circulating cytokines may trigger common infusion-related reaction symptoms

- As cytokines circulate through the body, they activate lymphocytes, trigger inflammation, and attract leukocytes, which may lead to systemic symptoms[10]
- When cytokines reach the brain, they can trigger the hypothalamus to raise core body temperature, eliciting a fever[11,12]

Signs and symptoms of infusion-related reactions can range from mild to severe, and potentially fatal, and may include but are not limited to[13]

- Fever
- Rash
- Pruritus
- Dizziness
- Headache
- Urticaria
- Nausea
- Myalgia
- Hypotension
- Hypertension
- Hypoxemia
- Chills/rigors
- Vomiting
- Angioedema
- Bronchospasm

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Cytokine-Mediated Infusion-Related Reactions vs Allergic Reactions

Cytokine-mediated infusion reactions are distinct from allergic reactions

- These types of reactions may appear similar clinically, but have different origins, time of occurrence, and treatment strategies[13]

CYTOKINE-MEDIATED INFUSION-RELATED REACTIONS[10,13]	ALLERGIC (TYPE 1 HYPERSENSITIVITY) REACTIONS[10,13]
• Dependent on cytokines	• Mediated by IgE*
• Occur commonly with monoclonal antibody therapy	• Occur less frequently with monoclonal antibody therapy
• Most often occur during or within 24 hours of infusion	• May occur during infusion or long after, usually occur with repeated exposure to antigen
• Decrease in frequency and severity with subsequent infusions	• Stay the same or worsen in severity with subsequent infusions
• Manage with premedication, slowing or interrupting the infusion, and supportive care	• Manage with supportive care

*IgE, immunoglobulin E.

- Typically, allergic reactions become more severe with repeated exposure to an antigen. However, the presentation of allergic reactions may be clinically indistinguishable from common infusion reactions[10,13]
- Infusion-related reactions and allergic reactions may be fatal or require permanent discontinuation of therapy[1]
- The immune system identifies monoclonal antibodies as foreign proteins, and may react by generating natural antibodies[14]
  –HAHA (human anti-humanized antibody)
- Clinical significance of antibodies against anti-CD20 therapies is unknown[1]

Nurses should consult the treating physician and follow their respective institution's protocols for managing infusion-related and allergic reactions.

Please see additional important safety information throughout, and click here for full prescribing information, including BOXED WARNING.

Proposed Mechanisms of Action of GAZYVA

Select Important Safety Information

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- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Warnings and Precautions: Hypersensitivity Reactions Including Serum Sickness

- Hypersensitivity reactions have been reported in patients treated with GAZYVA. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion-related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure
- If a hypersensitivity reaction is suspected during or after an infusion, stop the infusion and permanently discontinue treatment. GAZYVA is contraindicated in patients with known hypersensitivity reactions to GAZYVA, including serum sickness with prior obinutuzumab use

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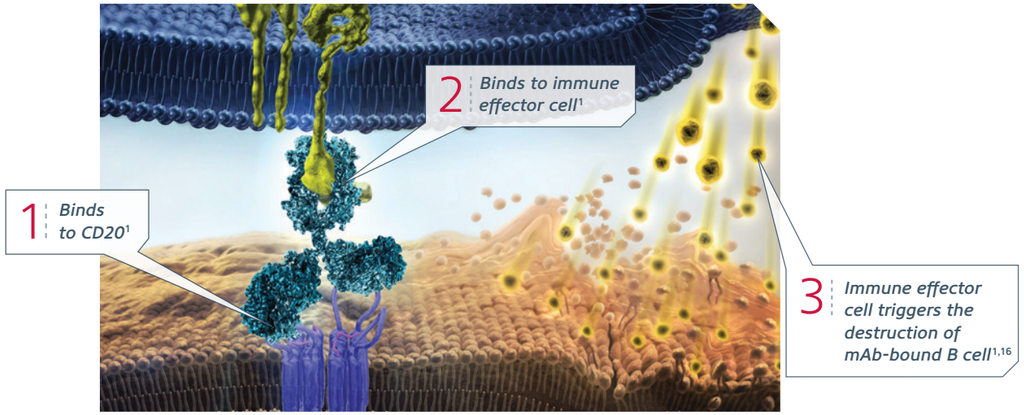
GAZYVA: an Engineered Anti-CD20 Monoclonal Antibody

GAZYVA is a humanized type II anti-CD20 monoclonal antibody that binds to the CD20 antigen. It is engineered for reduced fucose content[1,15,16]

Proposed GAZYVA Mechanisms of Action

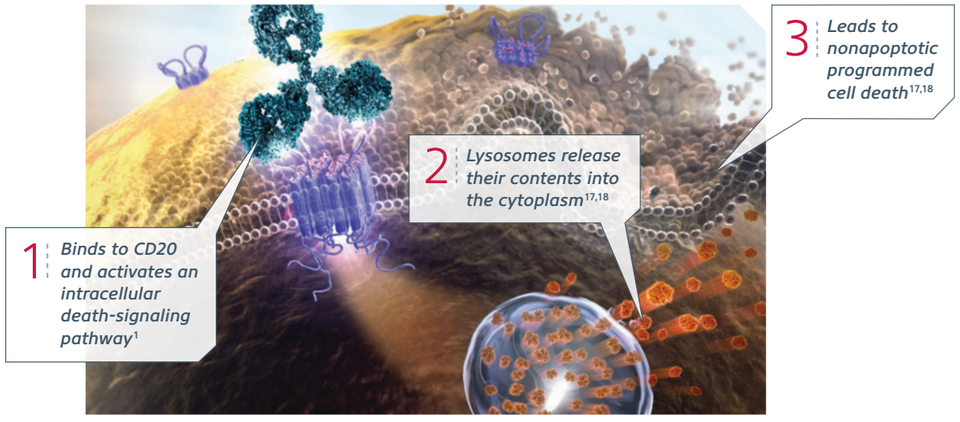
Antibody-Dependent Cellular Cytotoxicity (ADCC)

- GAZYVA binds to and activates immune effector cells in preclinical studies[1,15]



Direct Cell Death

- GAZYVA, a type II antibody, directly activates intracellular death signaling pathways as shown in preclinical studies[1,15,16]



Complement-Dependent Cytotoxicity

- GAZYVA has also been shown to trigger the activation of the complement cascade in preclinical studies[1]

Proposed GAZYVA Mechanisms of Action

GAZYVA was engineered to induce greater ADCC and direct cell death vs rituximab in preclinical studies[1,15,16]

Mechanism	GAZYVA dosing schedule[1]
Antibody-dependent cellular cytotoxicity (ADCC)[1]	• GAZYVA was engineered for enhanced ADCC in preclinical studies[15,16] • GAZYVA delivered up to a 35-fold increase[a] in ADCC[15]
Direct cell death[1]	• GAZYVA activated intracellular death signaling pathways in preclinical studies[1,15,16] • Direct cell death is an internal cell-killing mechanism different from apoptosis[15]

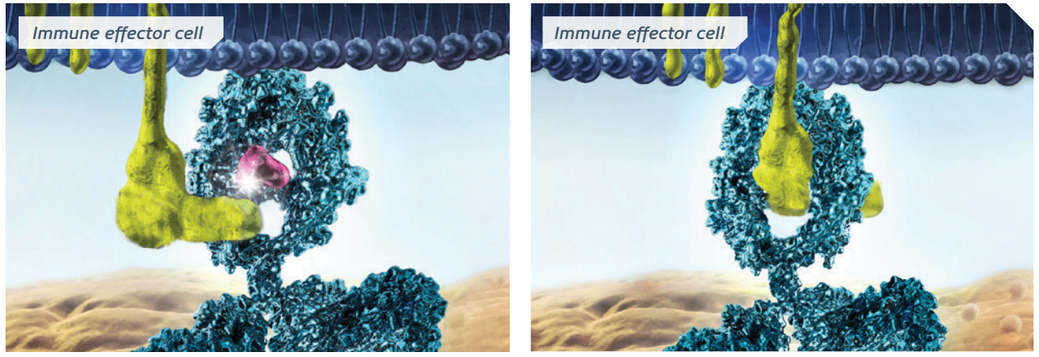
[a]As calculated by EC_{50} in preclinical studies.

- GAZYVA and rituximab bind with similar affinity to overlapping epitopes on CD20

GAZYVA: Engineered for reduced fucose content[1,16]

- Reduced fucose content enhanced binding and activation of immune effector cells in preclinical studies

FC receptor binding



rituximab (presence of a core fucose residue) *GAZYVA (reduced core fucose content)*

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GAZYVA for Previously Untreated Follicular Lymphoma

Studied head-to-head vs rituximab* in **stage II bulky, III, and IV patients**[1]

*GAZYVA and rituximab were each combined with bendamustine, CHOP, or CVP, and followed by GAZYVA or rituximab monotherapy, respectively, in patients who responded.

Indication

GAZYVA, in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma (FL).

Select Important Safety Information

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- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

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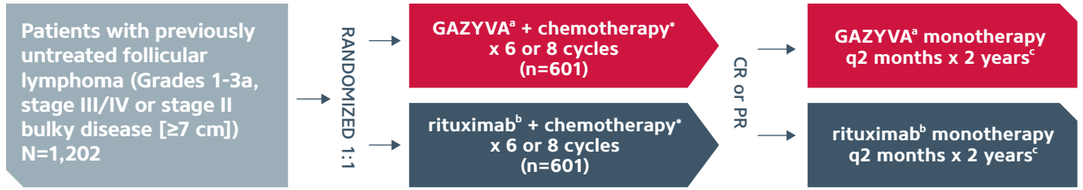
GALLIUM Trial: GAZYVA vs rituximab in Previously Untreated FL[1]

With chemotherapy for stage II bulky, III, and IV patients*

This Phase III, open-label, randomized trial was designed to answer one primary question: In patients with previously untreated FL, did the GAZYVA based regimen deliver superior PFS compared with the rituximab-based regimen?[1]



- **Primary endpoint:** PFS as assessed by Independent Review Committee (IRC)
- **Additional endpoints:** Response rates at end of induction (IRC-assessed, assessed by CT ± PET), PFS by chemotherapy regimen (IRC-assessed)

[a]Each dose of GAZYVA was 1,000 mg IV on Days 1, 8, and 15 of Cycle 1, and 1,000 mg on Day 1 of subsequent treatment cycles.[1]

[b]Each dose of rituximab was 375 mg/m^2 IV administered on Day 1 of each cycle.[19]

[c]In patients achieving a CR or PR at the end of 6-8 cycles, GAZYVA or rituximab monotherapy was administered every 2 months until disease progression or for a maximum of 2 years.[1]

*GAZYVA and rituximab were each studied in combination with bendamustine, CHOP, or CVP, and followed by GAZYVA or rituximab monotherapy, respectively[1,19]:

- When combined with GAZYVA or rituximab, bendamustine was administered at 90 mg/m^2/day IV (Days 1-2) for six 28-day cycles, and prednisone or equivalent was administered 100 mg orally (Day 1, Cycle 1)
- When CHOP was used in combination with GAZYVA or rituximab, cyclophosphamide was administered 750 mg/m^2 IV (Day 1), doxorubicin was administered 50 mg/m^2 IV (Day 1), vincristine was administered 1.4 mg/m^2 IV (maximum = 2 mg) (Day 1), and prednisone (or equivalent prednisolone or methylprednisolone) was administered 100 mg orally on Days 1 to 5 for six 21-day cycles. Subsequently, 2 additional cycles of GAZYVA or rituximab were given without chemotherapy for a total of 8 cycles
- When CVP was used in combination with GAZYVA or rituximab, cyclophosphamide was administered 750 mg/m^2 IV (Day 1), vincristine was administered 1.4 mg/m^2 IV (maximum = 2 mg) (Day 1), and prednisone (or equivalent prednisolone or methylprednisolone) was administered 100 mg orally on Days 1 to 5 for eight 21-day cycles
- Each investigator site chose CHOP, CVP, or bendamustine; all patients with FL at that site received the chosen chemotherapy for the duration of induction. At randomization, patients were stratified by disease characteristics (ie, FLIPI score), chemotherapy regimen, and geographic region.[19]

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Dosing Schedule in Previously Untreated FL

GAZYVA dosing schedule[1]			
Day of treatment cycle		**Dose**	**Rate of infusion**
Cycle 1 (loading doses)	Day 1	1,000 mg	**Rate of infusion:** • Administer at 50 mg/hr • The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
	Day 8	1,000 mg	**Rate of infusion:** • If no infusion-related reaction or an infusion-related reaction of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr • If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 15	1,000 mg	
Cycles 2-6 or 2-8	Day 1	1,000 mg	
Monotherapy	Every 2 months for up to 2 years	1,000 mg	

- Patients who achieve a complete or partial response to the initial 6 or 8 cycles of GAZYVA treatment in combination with chemotherapy should continue on GAZYVA 1,000 mg as monotherapy every 2 months until disease progression or for a maximum of 2 years
- If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible. During GAZYVA and chemotherapy treatment, adjust the dosing schedule accordingly to maintain the time interval between chemotherapy doses. During monotherapy, maintain the original dosing schedule for subsequent doses. Initiate monotherapy approximately 2 months after the last induction dose of GAZYVA

Administer GAZYVA with one of the following chemotherapy regimens[1]:

- Six 28-day cycles in combination with bendamustine
- Six 21-day cycles in combination with CHOP, followed by 2 additional 21-day cycles of GAZYVA alone
- Eight 21-day cycles in combination with CVP

Premedication & administration[1]

- Premedicate before each infusion
- Provide prophylactic hydration and antihyperuricemics to patients at high risk of tumor lysis syndrome
- Administer only as an intravenous infusion through a dedicated line
- Do not administer as an intravenous push or bolus
- Monitor blood counts at regular intervals
- GAZYVA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur

Recommended Premedications

The following premedications are recommended before beginning the GAZYVA infusion to reduce the risk of IRRs[1]

Complete before infusion	**Cycle 1:** Days 1	**All Subsequent Infusions**		
	All patients	**All patients**	**Patients with an IRR (Grade 1-2)** with the previous infusion	**Patients with a Grade 3 IRR** with the previous infusion OR with a lymphocyte count >25 x 10^9/L prior to next treatment
60 MINUTES **PRIOR** Intravenous glucocorticoid[a,b]	✓			✓
30 MINUTES **PRIOR** Antihistamine[c]	✓		✓	✓
30 MINUTES **PRIOR** Acetaminophen[d]	✓	✓	✓	✓

[a]20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion-related reactions.
[b]If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.
[c]Eg, 50 mg diphenhydramine.
[d]650-1,000 mg.

Premedication and close monitoring are recommended for all patients[1]

- Patients with preexisting cardiac or pulmonary conditions are at a greater risk of experiencing more severe infusion reactions
- Hypotension may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration
- Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L), or renal impairment are considered at risk of tumor lysis syndrome and should receive prophylaxis. Premedicate with antihyperuricemics (eg, allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed
- Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis for patients with severe and long lasting (>1 week) neutropenia.

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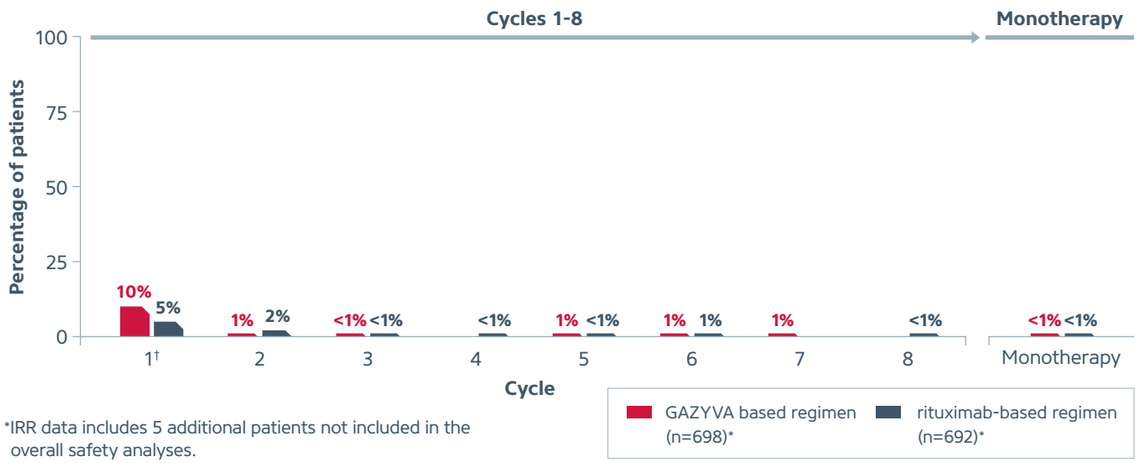
Incidence of Infusion-Related Reactions by Treatment Cycle in GALLIUM

IRRs with GAZYVA may be severe and life threatening, and can occur at any time[1]

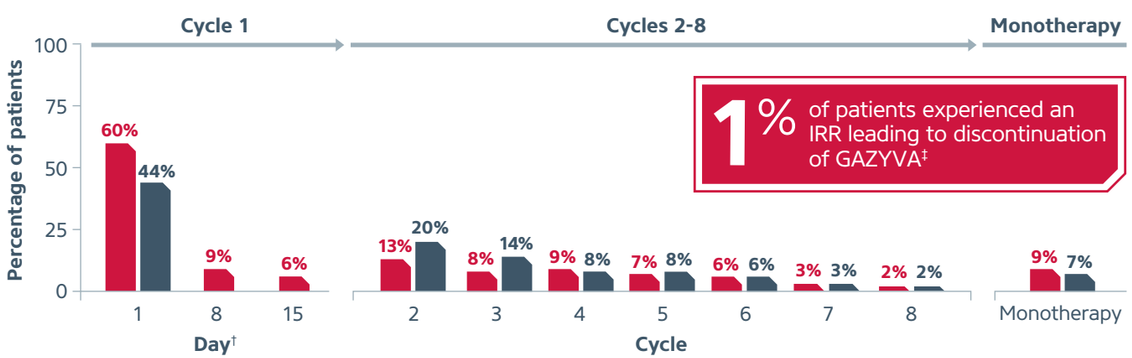
- Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema)
- Most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, constipation, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills

Grades 3 to 4 infusion-related reactions in the GAZYVA and rituximab arms[19]



*IRR data includes 5 additional patients not included in the overall safety analyses.

Infusion-related reaction (all grades) in the GAZYVA and rituximab arms[1,19]



†Per study protocol, GAZYVA was administered on Days 1, 8 and 15 of Cycle 1 and rituximab was administered on Day 1 of Cycle 1.

‡In the rituximab arm, <1% of patients experienced an IRR leading to treatment discontinuation.

Adjusting Infusions in Case of IRRs[1]

If a patient experiences an infusion-related reaction of any grade during infusion, adjust the infusion as follows:

Infusion Reactions	CTCAE v4.0 Description[20]	Recommendations per Prescribing Information[1]
Grade 4 (life-threatening)	Life-threatening consequences; pressor or ventilatory support indicated	Stop infusion immediately and permanently discontinue GAZYVA therapy
Grade 3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Interrupt infusion and manage symptoms • Upon resolution of symptoms, consider restarting GAZYVA infusion at no more than half the previous rate (the rate being used at the time that the infusion-related reaction occurred), and if patient does not experience any further infusion-related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose • Permanently discontinue treatment if patients experience a Grade 3 infusion-related reaction at rechallenge
Grades 1-2 (mild to moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Reduce infusion rate or interrupt infusion and manage symptoms • Upon resolution of symptoms, continue or resume GAZYVA infusion, and if patient does not experience any further infusion-related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose
	Mild reaction; infusion interruption not indicated; intervention not indicated	

CTCAE, Common Terminology Criteria for Adverse Events.

- Closely monitor patients during the entire infusion. Infusion reactions within 24 hours of receiving GAZYVA have occurred
- Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion reactions as needed

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GAZYVA in Combination With Chlorambucil for the First-line Treatment of Chronic Lymphocytic Leukemia

Indication

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

Select Important Safety Information

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- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

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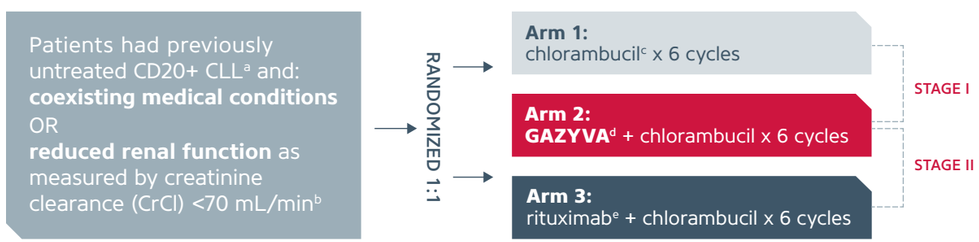
CLL-11: Designed to Determine the Superior Anti-CD20 Regimen for First-line CLL Patients

GAZYVA + Clb was evaluated against rituximab + Clb in first-line CLL patients[1,21]



- **Primary endpoint:** progression-free survival (PFS), as evaluated by an independent review committee
- **Secondary endpoints:** overall response rate, complete response rate, response duration, and minimal residual disease negativity
- The safety and efficacy of GAZYVA + Clb was evaluated in a Stage I comparison of Arm 1 vs Arm 2 in 356 patients and a Stage II comparison of Arm 2 vs Arm 3 in 663 patients

[a]All patients required treatment according to NCI criteria, and had a life expectancy >6 months.[19]
[b]Patients with creatinine clearance <30 mL/min or inadequate liver function were excluded.[21]
[c]Each oral dose of chlorambucil is 0.5 mg/kg of body weight. Cycles 1-6: Days 1 and 15.[1]
[d]Each dose of GAZYVA is 1,000 mg with the exception of Cycle 1 Day 1 (100 mg) and Cycle 1 Day 2 (900 mg). Cycle 1: Days 1, 2, 8, and 15; Cycles 2-6: Day 1.[14]
[e]Each dose of rituximab is 500 mg/m^2 with the exception of Cycle 1 Day 1 (375 mg/m^2). Cycles 1-6: Day 1.[21]

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First-line CLL 6-Cycle Dosing Schedule

Each dose of GAZYVA is 1,000 mg administered intravenously with the exception of the first infusions in Cycle 1, which are administered on Day 1 (100 mg) and Day 2 (900 mg)[1]

GAZYVA dosing schedule[1]			
Day of treatment cycle		**Dose**	**Rate of infusion**
Cycle 1 (loading doses)	Day 1	100 mg	**Rate of infusion:** • Administer at 25 mg/hr • Do not increase the infusion rate
	Day 2	900 mg	**Rate of infusion:** • Administer at 50 mg/hr • The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
	Day 8	1,000 mg	**Rate of infusion:** • If no infusion-related reaction or an infusion-related reaction of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr • If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 15	1,000 mg	
Cycles 2-6	Day 1	1,000 mg	

Chlorambucil should be given 0.5 mg/kg orally on Days 1 and 15 of Cycles 1-6[1]

- If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible and adjust dosing schedule accordingly
- If appropriate, patients who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose
- Consider treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a ≥Grade 2 non-hematologic toxicity

Premedication & administration[1]

- Premedicate before each infusion
- Provide prophylactic hydration and antihyperuricemics to patients at high risk of tumor lysis syndrome
- Prepare Day 1 (100 mg) and Day 2 (900 mg) infusion bags at the same time using one vial (1,000 mg/40 mL) on Day 1
- Administer only as an intravenous infusion through a dedicated line
- Do not administer as an intravenous push or bolus
- Monitor blood counts at regular intervals
- GAZYVA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur

Please see additional important safety information throughout, and click here for full prescribing information, including BOXED WARNING.

Recommended Premedications

The following premedications are recommended before GAZYVA infusion begins to reduce the risk of infusion-related reactions (IRRs)[1]

	Cycle 1: Days 1 and 2			
Complete before infusion	**All patients**	**All patients**	**Patients with an IRR (Grade 1-2)** with the previous infusion	**Patients with a Grade 3 IRR** with the previous infusion OR with a lymphocyte count >25 x 10^9/L prior to next treatment
60 MINUTES **PRIOR** Intravenous glucocorticoid[a,b]	✓			✓
30 MINUTES **PRIOR** Antihistamine[c]	✓		✓	✓
30 MINUTES **PRIOR** Acetaminophen[d]	✓	✓	✓	✓

[a]20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion-related reactions.

[b]If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.

[c]Eg, 50 mg diphenhydramine.

[d]650-1,000 mg.

Premedication and close monitoring are recommended for all patients[1]

- Patients with preexisting cardiac or pulmonary conditions are at a greater risk of experiencing more severe infusion-related reactions
- Hypotension may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration
- Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L), or renal impairment are considered at risk of tumor lysis syndrome and should receive prophylaxis. Premedicate with antihyperuricemics (eg, allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed
- Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis for patients with severe and long lasting (>1 week) neutropenia.

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Incidence of Infusion-Related Reactions in CLL-11

IRRs with GAZYVA may be severe and life threatening and can occur at any time[1]

- Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (eg, bronchospasm, larynx and throat irritation, wheezing, laryngeal edema)
- Most frequently reported symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills

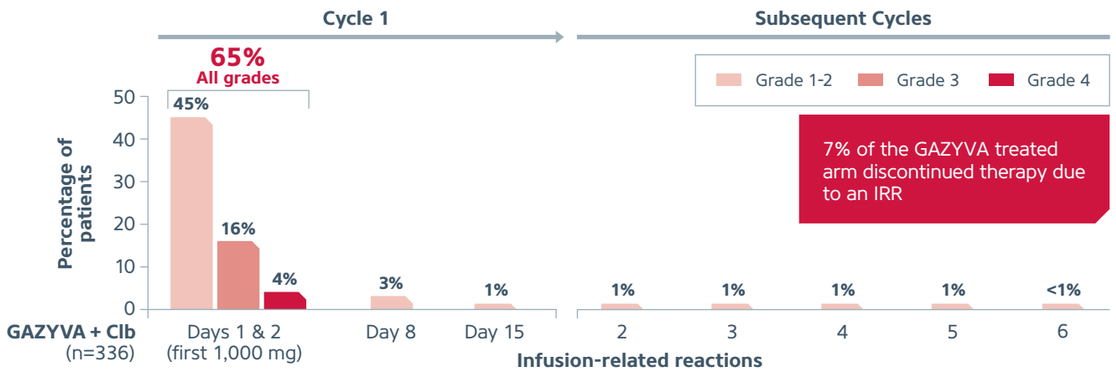
First 1,000 mg infused: 65% of patients experienced IRRs with GAZYVA[1]

- Grade 3 or 4 reactions occurred in 20% of patients

Subsequent infusions: IRRs also occurred[1]

- The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg and <1% thereafter
- There were no Grade 3 or 4 IRRs reported after the first 1,000 mg infused

Incidence of infusion-related reactions by cycle[1,19]



- In the rituximab + Clb arm (n=321), the incidence of IRRs during Cycle 1 was 27% (24% Grades 1-2, 3% Grades 3-4)[19]
  - –In Cycle 2, the incidence of IRRs was 13% (12% Grades 1-2, 1% Grades 3-4)
  - –The incidence of IRRs was 6% for Cycle 3, 2% for Cycle 4, 2% for Cycle 5, and 1% for Cycle 6
  - –<1% of the rituximab treated arm discontinued therapy due to an IRR

Protocol modifications were implemented to help mitigate infusion-related reactions[1]

- Protocol modifications in CLL-11 required premedication with a corticosteroid,* an antihistamine, and acetaminophen. The first 1,000 mg dose was also divided into 2 infusions (100 mg on Day 1 and 900 mg on Day 2)

BEFORE PROTOCOL MODIFICATIONS (N=53)

- **89%** of patients experienced an infusion-related reaction

AFTER PROTOCOL MODIFICATIONS (N=140)

- **53%** of patients experienced an infusion-related reaction with the first 1,000 mg and <3% thereafter

*Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion-related reactions.

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Infusion-Related Reaction Symptoms Occurring in ≥5% of Patients in CLL-11 Stage II[19]

Body System/Adverse Event	GAZYVA + Clb Patients N (%) (n=336)	rituximab + Clb Patients N (%) (n=321)
General/Administration Site Disorders	**119 (35)**	**69 (21)**
Chills	78 (23)	45 (14)
Pyrexia	70 (21)	26 (8)
Vascular Disorders	**109 (32)**	**41 (13)**
Hypotension	65 (19)	20 (6)
Flushing	41 (12)	19 (6)
Hypertension	20 (6)	7 (2)
Gastrointestinal Disorders	**94 (28)**	**37 (12)**
Nausea	73 (22)	27 (8)
Vomiting	54 (16)	15 (5)
Diarrhea	16 (5)	6 (2)
Respiratory, Thoracic, and Mediastinal Disorders	**65 (19)**	**28 (9)**
Dyspnea	47 (14)	16 (5)
Bronchospasm	18 (5)	5 (2)
Nervous System Disorders	**33 (10)**	**8 (2)**
Headache	18 (5)	5 (2)
Dizziness	17 (5)	3 (<1)
Cardiac Disorders	**22 (7)**	**9 (3)**
Tachycardia	20 (6)	8 (2)

Select Important Safety Information

Hepatitis B Virus Reactivation

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies including GAZYVA. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (ie, HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive)
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level, or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, ie, increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death

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Adjusting Infusions in Case of IRRs

If a patient experiences an infusion-related reaction (IRR) of any grade during infusion, adjust the infusion as follows:

Infusion-Related Reactions	CTCAE v4.0 Description[20]	Recommendations per Prescribing Information[1]
Grade 4 (life-threatening)	Life-threatening consequences; pressor or ventilatory support indicated	Stop infusion immediately and permanently discontinue GAZYVA therapy
Grade 3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Interrupt infusion and manage symptoms • Upon resolution of symptoms, consider restarting GAZYVA infusion at no more than half the previous rate (the rate being used at the time that the infusion-related reaction occurred), and if patient does not experience any further infusion-related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose • Permanently discontinue treatment if patients experience a Grade 3 infusion-related reaction at rechallenge –For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further
Grades 1-2 (mild to moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Reduce infusion rate or interrupt infusion and manage symptoms • Upon resolution of symptoms, continue or resume GAZYVA infusion, and if patient does not experience any further infusion-related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose –For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further
	Mild reaction; infusion interruption not indicated; intervention not indicated	

CTCAE, Common Terminology Criteria for Adverse Events.

- Closely monitor patients during the entire infusion. Infusion-related reactions within 24 hours of receiving GAZYVA have occurred
- Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion-related reactions as needed

Please see additional important safety information throughout, and click here for full prescribing information, including BOXED WARNING.

Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Contraindications

- GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g. anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use

Warnings and Precautions

Hepatitis B Virus Reactivation

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies including GAZYVA. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (ie, HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive)
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level, or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, ie, increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with GAZYVA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult healthcare providers with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy
- Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with GAZYVA
- In patients who develop reactivation of HBV while receiving GAZYVA, immediately discontinue GAZYVA and any concomitant chemotherapy and institute appropriate treatment. Resumption of GAZYVA in patients whose HBV reactivation resolves should be discussed with healthcare providers with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming GAZYVA in patients who develop HBV reactivation

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Important Safety Information (cont'd)

Progressive Multifocal Leukoencephalopathy (PML)

- JC virus infection resulting in PML, which can be fatal, occurred in patients treated with GAZYVA. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue GAZYVA therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML

Infusion-Related Reactions

- GAZYVA can cause severe and life-threatening infusion-related reactions (IRRs). Sixty-five percent of patients with CLL experienced a reaction to the first 1,000 mg of GAZYVA infused. Thirty-seven percent of patients with relapsed or refractory NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 of GAZYVA infusion. IRRs have occurred within 24 hours of receiving GAZYVA. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills
- Premedicate patients with acetaminophen, an antihistamine, and a glucocorticoid. Closely monitor patients during the entire infusion. Reduce infusion rate, interrupt infusion or permanently discontinue GAZYVA for IRRs based on severity. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed
- For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the GAZYVA infusion-related reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each GAZYVA infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication

Hypersensitivity Reactions Including Serum Sickness

- Hypersensitivity reactions have been reported in patients treated with GAZYVA. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion-related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure
- If a hypersensitivity reaction is suspected during or after an infusion, stop the infusion and permanently discontinue treatment. GAZYVA is contraindicated in patients with known hypersensitivity reactions to GAZYVA, including serum sickness with prior obinutuzumab use

Please see additional important safety information throughout, and click here for full prescribing information, including BOXED WARNING.

Tumor Lysis Syndrome (TLS)

- Tumor lysis syndrome, including fatal cases, has been reported in patients receiving GAZYVA. Patients with high tumor burden, high circulating lymphocyte count (>25 x 10^9/L) or renal impairment are at greater risk for TLS
- Administer appropriate tumor lysis prophylaxis with antihyperuricemics (eg, allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA for patients at risk for TLS. During the initial days of GAZYVA treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated

Infections

- Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. When GAZYVA is administered with chemotherapy followed by GAZYVA monotherapy, Grade 3 to 5 infections have been reported in up to 8% of patients during combination therapy, up to 13% of patients during monotherapy, and up to 8% of patients after treatment
- In GALLIUM, more Grade 3 to 5 infections were reported in the recipients of GAZYVA and bendamustine (117/410 patients, 29%), as compared to GAZYVA plus CHOP or CVP (43/281 patients, 15%). More fatal infections were reported in patients treated with GAZYVA and bendamustine (3%), as compared to GAZYVA plus CHOP or CVP (<1%), including during the monotherapy phase and after completion of treatment
- Do not administer GAZYVA to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection

Neutropenia

- Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with GAZYVA. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider dose delays for Grade 3 or 4 neutropenia. Consider administration of granulocyte colony-stimulating factors (GCSF) in patients with Grade 3 or 4 neutropenia
- Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days)
- Patients with severe and long lasting (>1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis

Thrombocytopenia

- Severe and life-threatening thrombocytopenia has been reported during treatment with GAZYVA in combination with chemotherapy. Fatal hemorrhagic events have been reported in patients with NHL treated with GAZYVA in combination with chemotherapy, including during Cycle 1
- Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider dose delays of GAZYVA and chemotherapy or dose reductions of chemotherapy. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications that may increase bleeding risk (platelet inhibitors or anticoagulants), especially during the first cycle

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Important Safety Information (cont'd)

Immunization

- The safety and efficacy of immunization with live or attenuated viral vaccines during or following GAZYVA therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings in animals, GAZYVA can cause B-cell depletion in infants exposed to obinutuzumab in-utero. Advise pregnant women of the potential risk to a fetus. Mothers who have been exposed to GAZYVA during pregnancy should discuss the safety and timing of live virus vaccinations for their infants with their child's healthcare providers. Advise females of reproductive potential to use effective contraception while receiving GAZYVA and for 6 months after the last dose

Lactation

- Human IgG is known to be present in human milk. Because of the potential of serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with GAZYVA and for 6 months after the last dose

Geriatric Use

- Of 336 patients with previously untreated CLL who received GAZYVA in combination with chlorambucil, 81% were 65 years and older, while 46% were 75 and older. Of the patients 75 years and older, 46% experienced serious adverse reactions and 7% experienced adverse reactions leading to death. Of the patients younger than 75, 33% experienced a serious adverse reaction and 2% an adverse reaction leading to death. No significant differences in efficacy were observed between younger and older patients
- Of the 691 patients in GALLIUM treated with GAZYVA plus chemotherapy as first-line therapy, 33% were 65 and over, while 7% were 75 and over. Of patients 65 and over, 63% experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal, while in patients under 65, 43% experienced serious adverse reactions and 13% had an adverse reaction leading to treatment withdrawal. No clinically meaningful differences in efficacy were observed between these patients and younger patients

Additional Important Safety Information

Previously Untreated CLL

- The most common Grade 3 to 4 adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were neutropenia, infusion-related reactions, and thrombocytopenia
- The most common adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were infusion-related reactions, neutropenia, thrombocytopenia, and diarrhea
- Adverse reactions rates and laboratory abnormalities from the Stage 2 phase are consistent with the rates in Stage 1. In addition to the adverse reactions observed in Stage 2, in Stage 1 back pain (5% vs 2%), anemia (12% vs 10%) and cough (10% vs 7%) were observed at a higher incidence in the GAZYVA treated patients. The incidence of Grade 3 to 4 back pain (<1% vs 0%), cough (0% vs <1%) and anemia (5% vs 4%) was similar in both treatment arms. With regard to laboratory abnormalities, in Stage 1 hyperkalemia (33% vs 18%), creatinine increased (30% vs 20%) and alkaline phosphatase increased (18% vs 11%) were observed at a higher incidence in patients treated with GAZYVA with similar incidences of Grade 3 to 4 abnormalities between the two arms

Previously Untreated NHL

- A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1,385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%)
- Serious adverse reactions occurred in 50% of patients on the GAZYVA arm and 43% of patients on the rituximab product arm. Fatal adverse reactions were reported during treatment in 3% in the GAZYVA arm and 2% in the rituximab product arm, most often from infections in the GAZYVA arm. During treatment and follow-up combined, fatal adverse reactions were reported in 5% of the GAZYVA arm and 4% of the rituximab product arm, with infections and second malignancies being leading causes. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm
- Neutropenia, infusion related reactions, febrile neutropenia and thrombocytopenia were the most common Grade 3 to 5 adverse reactions (incidence ≥5%) observed more frequently in the GAZYVA arm
- Throughout treatment and follow-up, the most common adverse reactions (incidence ≥20%) observed at least 2% more in the GAZYVA arm were infusion related reactions (72%), neutropenia (53%), upper respiratory tract infection (50%), cough (35%), constipation (32%) and diarrhea (30%)
- During the monotherapy period, the common adverse reactions (incidence ≥10%) observed at least 2% more with GAZYVA were upper respiratory infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%) and herpesvirus infection (13%)

You are encouraged to report side effects to Genentech and the FDA. You may contact Genentech by calling 1-888-835-2555. You may contact the FDA by visiting www.fda.gov/medwatch, or calling 1-800-FDA-1088.

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Counseling Patients on Infusion Reactions

Understanding infusion reactions is important

Patients and caregivers should understand the adverse reactions that may develop with monoclonal antibody use

- Advise patients and caregivers about signs and symptoms to watch for during and after infusion, including dizziness, nausea, chills, fever, vomiting, diarrhea, breathing problems, or chest pain
- Inform patients that infusion reactions may be mild to moderate and can be managed, but also that fatal adverse reactions can occur with monoclonal antibody therapy
- Encourage patients to report any symptoms they experience, especially during the first few hours of infusion

Please see additional important safety information throughout, and click here for full prescribing information, including BOXED WARNING.

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