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

It's Time to Rethink GAZYVA

FDA-Approved Regimens Across FL & CLL

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 bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen
- 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**

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

Please see Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

8

Eight FDA-Approved Regimens Across FL & CLL, With Many Studies Ongoing[1-4]

Approved in 2013
1L CLL

GAZYVA + chlorambucil[1]

GAZYVA in combination with chlorambucil is indicated for the treatment of patients with previously untreated CLL.

Approved in 2016
R/R FL

GAZYVA + bendamustine[1]

GAZYVA in combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab product-containing regimen.

Approved in 2017
1L FL

GAZYVA + bendamustine[1]

followed by GAZYVA monotherapy.

GAZYVA + CHOP[1]

followed by GAZYVA monotherapy.

GAZYVA + CVP[1]

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).

Approved in 2019
1L CLL/SLL

GAZYVA + ibrutinib[2,*]

Ibrutinib is indicated for the treatment of adult patients with CLL/SLL.

GAZYVA + venetoclax tablets[3,*]

Venetoclax tablets are indicated for the treatment of adult patients with CLL/SLL.

GAZYVA + acalabrutinib[4,*]

Acalabrutinib is indicated for the treatment of adult patients with CLL/SLL.

***Refer to the full Prescribing Information for ibrutinib, venetoclax tablets, and acalabrutinib for additional information including Indications, Safety, and Dosing.**

2020+

GAZYVA continues to be studied in CLL and FL.

Select Important Safety Information

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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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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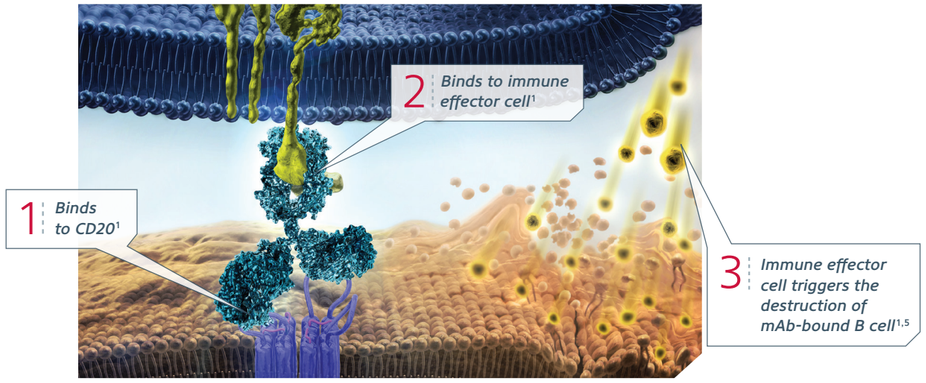
GAZYVA: An Engineered Anti-CD20 Monoclonal Antibody

GAZYVA is a humanized type II anti-CD20 monoclonal antibody that binds to the CD20 antigen, a proven target for CD20+ B cells. It is engineered for reduced fucose content[1,5,6]

Proposed GAZYVA Mechanisms of Action

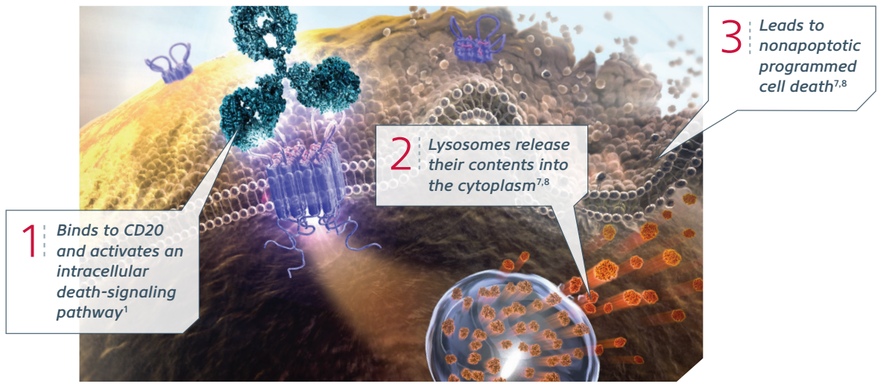
Antibody-Dependent Cellular Cytotoxicity (ADCC)

- GAZYVA binds to and activates immune effector cells in preclinical studies[1,5]



Direct Cell Death

- GAZYVA, a type II antibody, directly activates intracellular death signaling pathways as shown in preclinical studies[1,5,6]



Complement-Dependent Cytotoxicity

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

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Proposed GAZYVA Mechanisms of Action

GAZYVA was engineered to induce greater ADCC and direct cell death vs rituximab product in preclinical studies [1,5,6]

Mechanism	Compared to rituximab product
Antibody-dependent cellular cytotoxicity (ADCC)[1]	• GAZYVA was engineered for enhanced ADCC in preclinical studies[5,6] • **GAZYVA delivered up to a 35-fold increase[a] in ADCC[5]**
Direct cell death[1]	• GAZYVA activated intracellular death signaling pathways in preclinical studies[1,5,6] • Direct cell death is an internal cell-killing mechanism different from apoptosis[5]

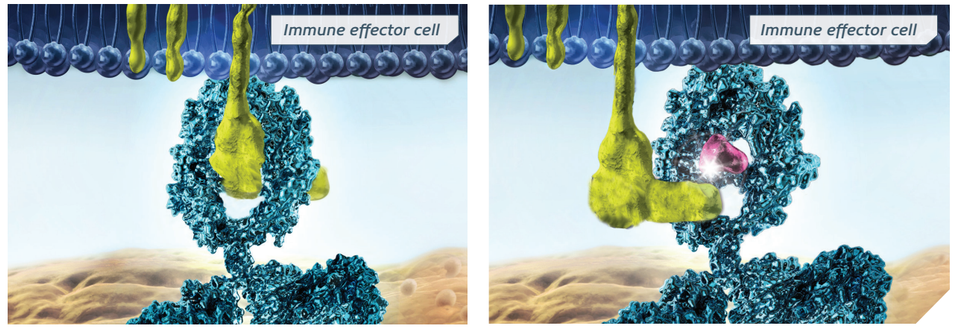
[a] As calculated by EC_{50} in preclinical studies.

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

GAZYVA: Engineered for reduced fucose content[1,6]

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

FC receptor binding



GAZYVA (reduced core fucose content)

rituximab product (presence of a core fucose residue)

Select Important Safety Information

Hepatitis B Virus Reactivation (cont'd)

- 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

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In Follicular Lymphoma (FL), the Duration of PFS on First-line Therapy Is Crucial[9]

FL is characterized by a pattern of remission and relapse, with shorter remissions following each relapse[10]

In FL, PFS is generally longest in first-line treatment

Shorter PFS is common following each relapse

In an analysis from the multicenter, observational National LymphoCare Study (NLCS), patients with FL treated with R-CHOP in first-line who experienced progression within 2 years of diagnosis had an increased risk of poor outcomes after first-line treatment compared to those who did not.[11]

Several different prognostic indices have been developed to try and inform patient prognoses, with varying results[12-16]

Select Important Safety Information

Hepatitis B Virus Reactivation (cont'd)

- 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

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

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Multiple Studies Show That It Is Difficult to Reliably Predict Early Progression of Disease

- Beyond the NLCS, several studies have attempted to use baseline clinical, biologic, or metabolic features to predict the course of a patient's disease[17]
- While these prognostic indices categorize a proportion of patients as high-risk, both lower- and higher-risk patients in each index may experience early progression or death[12-16]

Correlation of Prognostic Indices and Incidence of Early Progression[17]

Prognostic Index	Definition of High Risk	% of Patients Scored as High Risk	% of Patients Scored as High Risk Who Experienced Early Progression or Death
FLIPI[11]	≥3 risk factors	**28%**	**55%**
TMTV[12]	>510 cm^3	**29%**	**56%**
M7-FLIPI[13,14]	Calculated from FLIPI and mutational analysis of 7 genes	**28%**	**76%**
23-gene model[15]	Calculated from expression levels of 23 genes	**21-35%**	**38%**

TMTV = total metabolic tumor volume.

While some of these factors may be correlated with early progression or death, there is no single factor or index that can consistently predict patients who will progress early[11]

Select Important Safety Information

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

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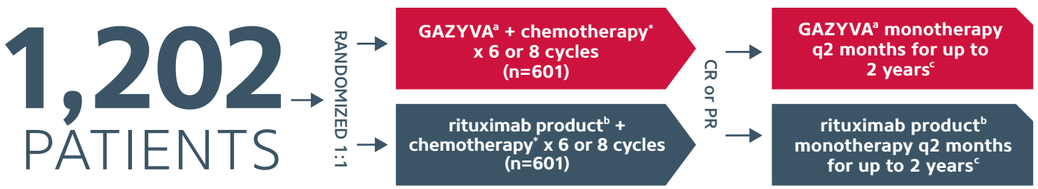
FL Treatment Goals

GALLIUM: GAZYVA vs rituximab product Is the Largest 1L FL Study Ever Conducted[1]

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 product-based regimen?[1]



The GALLIUM trial studied patients with previously untreated follicular lymphoma (Grades 1-3a, stage III/IV or stage II bulky disease [≥7 cm])

- **Primary endpoint:** PFS as assessed by Independent Review Committee (IRC)

[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 product was 375 mg/m^2 IV administered on Day 1 of each cycle.[18]

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

*GAZYVA and rituximab product were each studied in combination with bendamustine, CHOP, or CVP, and followed by GAZYVA or rituximab product monotherapy, respectively, in patients who responded[1,18]:

- When combined with GAZYVA or rituximab product, 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 product, 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 product were given without chemotherapy for a total of 8 cycles
- When CVP was used in combination with GAZYVA or rituximab product, 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

Select Important Safety Information

Infusion-Related Reactions (cont'd)

- 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

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Bulky Disease and Advanced Staging Prevalent at Baseline[1,18]

The GAZYVA and rituximab product arms were generally well balanced with respect to demographic factors and baseline disease characteristics[18]

79% FLIPI SCORE >2

56% STAGE IV DISEASE, 35% STAGE III, 7% STAGE II

44% BULKY DISEASE (≥7 cm)

97% ECOG PS 0-1 (3% ECOG PS 2)

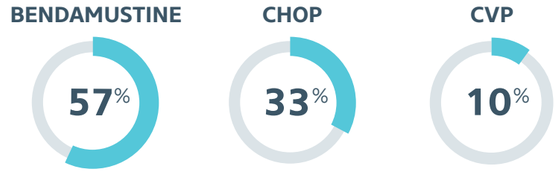
34% ≥1 B-SYMPTOM AT BASELINE†

59 MEDIAN AGE (range 23-88)

†Fever, night sweats, or weight loss.[18]

GALLIUM evaluated GAZYVA vs rituximab product when each was combined with bendamustine, CHOP, or CVP and followed by GAZYVA or rituximab product monotherapy, respectively

Percentage of Patients Who Received Each Chemotherapy Regimen[1,‡]



‡Each investigator site chose CHOP, CVP, or bendamustine; all patients with FL at that site received the chosen chemotherapy for the duration of induction. Patients were stratified by disease characteristics (ie, FLIPI score), chemotherapy regimen, and geographic region at randomization, and the treatment arms were generally balanced with respect to these factors.[18]

Select Important Safety Information

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

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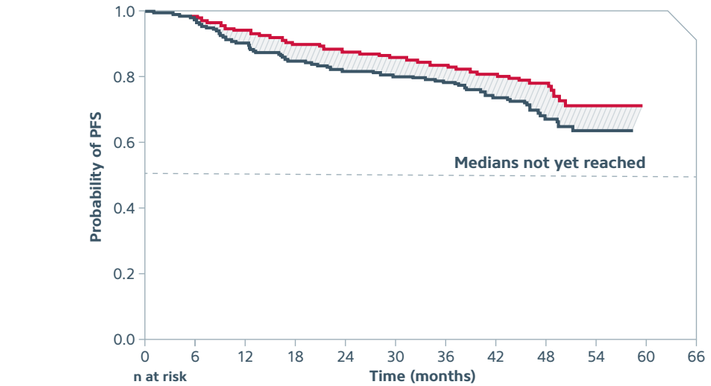
The GAZYVA Based Regimen* Is the First and Only Approved Therapy That Demonstrated Superior PFS vs the rituximab product-based Regimen* in Previously Untreated FL[1]

For stage II bulky, III, and IV patients

Primary Endpoint: PFS (IRC-assessed)[1]



HR=0.72

28%
reduction in the risk of disease progression or death

95% CI, 0.56-0.93; *P*=0.0118; PFS events, 108 (18%) in the GAZYVA arm vs 141 (23%) in the rituximab product arm; 38-month median observation time

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

Additional endpoints[1]

- CT-assessed response rates at the end of induction (IRC-assessed) were similar between arms
  - CT-assessed overall response rates at the end of induction (IRC-assessed) were 91% for the GAZYVA based regimen and 88% for the rituximab product-based regimen
  - CT-assessed complete response rates at the end of induction (IRC-assessed) were 28% for the GAZYVA based regimen and 27% for the rituximab product-based regimen

The GAZYVA based regimen delivered superior PFS vs the rituximab product-based regimen as assessed by IRC, reducing patients' risk of disease progression or death by 28% (38-month median observation time; HR=0.72; 95% CI, 0.56-0.93; *P*=0.0118; median PFS was not reached in either arm).[1]

Select Important Safety Information

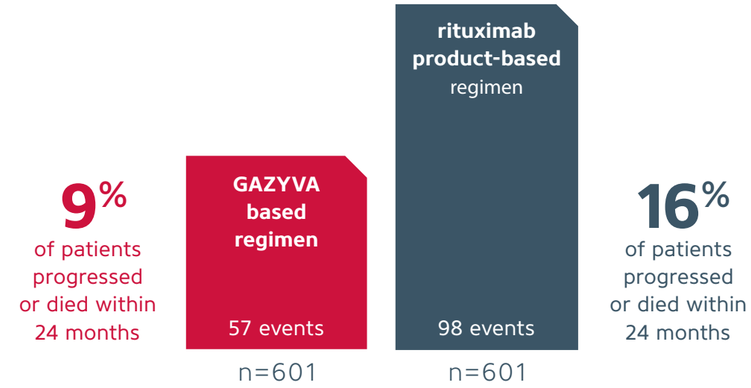
Hypersensitivity Reactions Including Serum Sickness (cont'd)

- 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 as well as accompanying full Prescribing Information, including BOXED WARNINGS.

GAZYVA vs rituximab product: Disease Progression at 24 Months in the GALLIUM Study

Retrospective, Exploratory Analysis: Events of disease progression in the 24 months after randomization[19,†]



†This endpoint was exploratory and no formal inference may be drawn.

Events of progression in this analysis were defined as progression of disease or death due to disease progression within 24 months of randomization.

Based on data from the National Lymphocare Study, ~20% of previously untreated patients treated with a chemo-immunotherapy standard of care progressed within 24 months of diagnosis[11]

- Early progression of FL predicts poor prognosis, but early progressors may be difficult to identify in advance[11]

Select Important Safety Information

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

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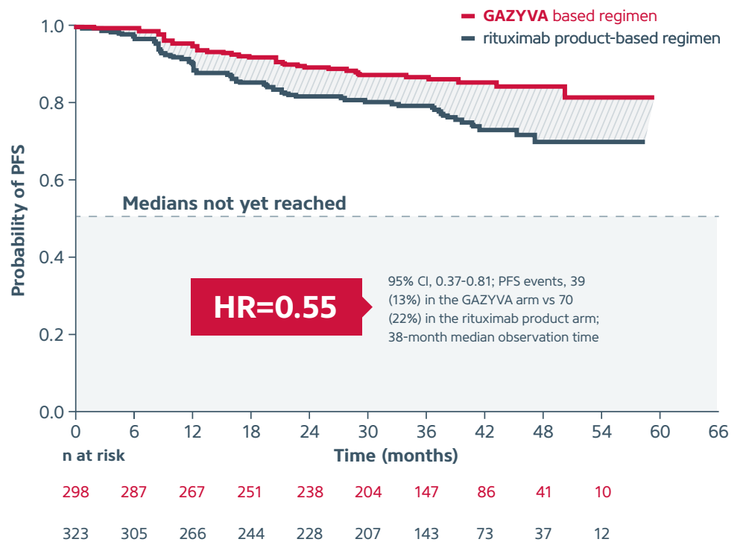
GALLIUM Exploratory Analysis: Should Treatment Decisions Factor in Patient Age?

- The median age of patients in the GALLIUM Trial was 59 years (range 23-88)
- IRC-assessed PFS by age subgroup was an exploratory analysis and was not powered to demonstrate statistically significant differences between treatment arms. These analyses are descriptive only

PFS based on age: <60 years (IRC-assessed)[18]



PFS event was defined as disease progression or death.

Select Important Safety Information

Infections

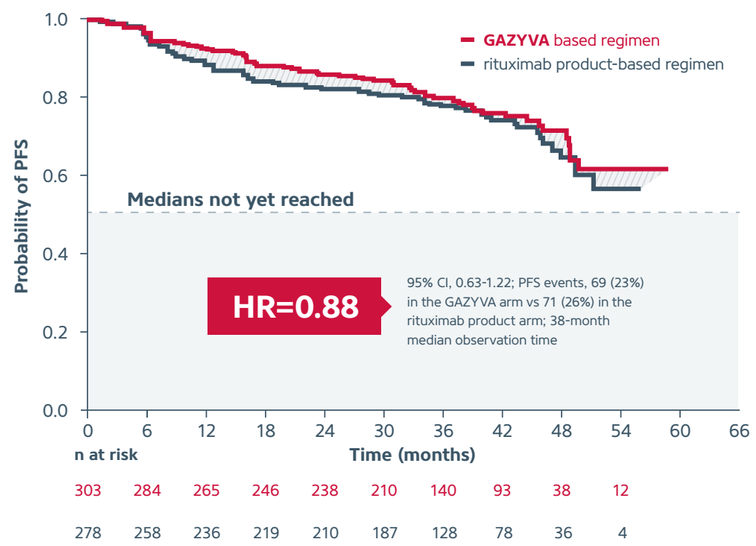
- Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. When GAZYVA is administered with chemotherapy followed by GAZYVA monotherapy, Grade 3 to 5 infections have been reported in up to 8% of patients during combination therapy, up 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

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Prespecified Exploratory Analysis of PFS by Age Subgroups[18]

- The median age of patients in the GALLIUM Trial was 59 years (range 23-88)
- IRC-assessed PFS by age subgroup was an exploratory analysis and was not powered to demonstrate statistically significant differences between treatment arms. These analyses are descriptive only

PFS based on age: ≥60 years (IRC-assessed)[18]



PFS event was defined as disease progression or death.

Select Important Safety Information

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

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The Safety Profile of the GAZYVA Based Regimen* Was Consistent Overall With the rituximab product-based Regimen*

Common adverse reactions (≥10% incidence and ≥2% greater in the GAZYVA arm), in patients with previously untreated NHL[1]

Body System Adverse Reactions[a,b]	GAZYVA + chemotherapy followed by GAZYVA monotherapy (n=691)		rituximab product + chemotherapy followed by rituximab product monotherapy (n=694)	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
Infusion-related reactions[c]	72	12	60	8
Neutropenia[d]	53	49	47	41
Thrombocytopenia[d]	14	7	8	3
Upper respiratory tract infection	50	3	43	1
Herpesvirus infection	18	3	14	1
Pneumonia	14	7	12	6
Cough	35	<1	28	<1
Constipation	32	<1	29	<1
Diarrhea	30	3	26	2
Headache	18	<1	15	<1
Arthralgia	16	0	14	<1
Insomnia	15	<1	12	<1
Decreased appetite	14	<1	12	<1
Alopecia	13	0	10	<1
Pruritus	11	<1	9	0

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

[a]Includes adverse reactions reported throughout study treatment and follow-up.

[b]Includes grouped preferred terms as defined by the FDA. Definitions can be found in the GAZYVA Prescribing Information.

[c]Except where noted, individual events that meet the definition of "infusion-related reaction" are excluded from the table above, as they are already included in the group term "Infusion-Related Reaction". The most common individual terms within the group term "Infusion Related Reaction" in decreasing order of frequency are nausea, chills, pyrexia and vomiting.

[d]Includes adverse reactions reported as infusion-related reactions.

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%).

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

GALLIUM Trial: Safety Information

Common new or worsening laboratory abnormalities (≥10% incidence and ≥2% greater in the GAZYVA arm) in patients with previously untreated NHL[1]

Laboratory Abnormalities[a]	GAZYVA + chemotherapy followed by GAZYVA monotherapy (n=691)		rituximab product + chemotherapy followed by rituximab product monotherapy (n=694)	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Lymphopenia	97	83	95	67
Leukopenia	92	49	89	39
Neutropenia	84	59	76	50
Thrombocytopenia	68	11	50	4
ALT/SGPT increased	50	3	43	2
AST/SGOT increased	44	1	41	1
Hypophosphatemia	36	5	33	5
Hypoalbuminemia	33	1	25	1
Hypoproteinemia	32	0	30	0
Hypocalcemia	32	1	26	1
Hyperuricemia	28	28	22	22
Hyponatremia	26	4	20	3
Hyperkalemia	23	1	17	1
Hypernatremia	16	<1	13	0

[a]Includes lab abnormalities, reported throughout treatment and follow-up, that were new or worsening, or worsening from baseline unknown.

GAZYVA monotherapy investigator-reported adverse reactions[1]

- The common adverse reactions (incidence ≥10%) observed at least 2% more with GAZYVA were upper respiratory tract infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%) and herpesvirus infection (13%)

GAZYVA monotherapy hematological laboratory abnormalities[1]

- New-onset Grade 3 or 4 neutropenia was reported in 21% of patients in the GAZYVA arm (Grade 4, 10%) and 17% of patients in the rituximab product arm (Grade 4, 9%)

Adverse reactions leading to treatment withdrawal[1]

- 18% in the GAZYVA arm vs 15% in the rituximab product arm

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A Retrospective Analysis of Adverse Reactions Based on Age: <60 and ≥60 Years[18]

Event	GAZYVA + chemotherapy followed by GAZYVA monotherapy (n=595)		rituximab product + chemotherapy followed by rituximab product monotherapy (n=595)	
	<60 y (n=298)	≥60 y (n=297)	<60 y (n=320)	≥60 y (n=277)
Total number of patients with ≥1 event (adverse reaction or death), n (%)	298 (100.0)	295 (99.3)	314 (98.1)	274 (98.9)
Number of patients with , n (%):				
Serious adverse reactions	115 (38.6)	166 (55.9)	111 (34.7)	135 (48.7)
Adverse reactions leading to death (Grade 5)	3 (1.0)	21 (7.1)	5 (1.6)	16 (5.8)
Adverse reactions leading to treatment withdrawal	35 (11.7)	63 (21.2)	39 (12.2)	49 (17.7)

- This safety analysis by age subgroup was a retrospective exploratory analysis and was not powered to demonstrate statistically significant differences between treatment arms. These analyses are descriptive only

Select Important Safety Information

Geriatric Use (GALLIUM)

- 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

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Select GALLIUM Safety Information

Clinical Trial Experience: Adverse Reactions for GAZYVA + Chemotherapy Followed by GAZYVA Monotherapy vs rituximab Product + Chemotherapy Followed by rituximab Product Monotherapy

Infusion-Related Reactions (IRR): Overall 72% of patients in the GAZYVA treated arm experienced IRRs (all grades). The incidence of Grade 3 to 4 IRRs for these patients was 12%. In Cycle 1, the incidence of IRRs (all grades) was 62% in the GAZYVA treated arm with Grade 3 to 4 IRRs reported in 10%. The incidence of IRRs (all grades) was highest on Day 1 (60%) and decreased on Days 8 and 15 (9% and 6% respectively). During Cycle 2, the incidence of IRRs (all grades) in the GAZYVA treated arm was 13% and decreased with subsequent cycles. During GAZYVA monotherapy treatment, IRRs (all grades) were observed in 9% of patients. Overall, 1% of patients experienced an IRR leading to discontinuation of GAZYVA.

Neutropenia: The incidence of neutropenia was higher in the GAZYVA treated arm (53%) compared to the rituximab product treated arm (47%). Cases of prolonged neutropenia (1%) and late onset neutropenia (4%) were also reported in the GAZYVA treated arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with chemotherapy (45%) compared to the GAZYVA monotherapy treatment phase (20%).

Infection: The incidence of infection was 82% in the GAZYVA treated arm and 73% in the rituximab product treated arm, with Grade 3 to 4 events reported in 21% and 17%, respectively. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm. The incidence of Grade 3 to 4 infections in the GAZYVA and rituximab product treated arms was lower in patients receiving GCSF prophylaxis (14%; 16%) compared with patients not receiving GCSF prophylaxis (24%; 18%). The incidence of fatal infections in patients receiving GCSF prophylaxis in the GAZYVA and rituximab product treated arms was 2% and 0%, respectively, and was 2% and <1% in patients not receiving GCSF prophylaxis.

Thrombocytopenia: Thrombocytopenia was reported as an adverse reaction in 14% of the GAZYVA treated arm and 8% of the rituximab product treated arm, with the incidence of Grade 3 to 4 events being 7% and 3% respectively. The difference in incidences between the treatment arms is driven by events occurring during the first cycle. The incidence of thrombocytopenia (all grades) in the first cycle were 9% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 5% and 1%, respectively. Both treatment arms had a 12% overall incidence of hemorrhagic events and a <1% incidence of fatal hemorrhagic events.

Tumor Lysis Syndrome (TLS): The incidence of Grade 3 or 4 TLS was 0.9% in the GAZYVA treated arm.

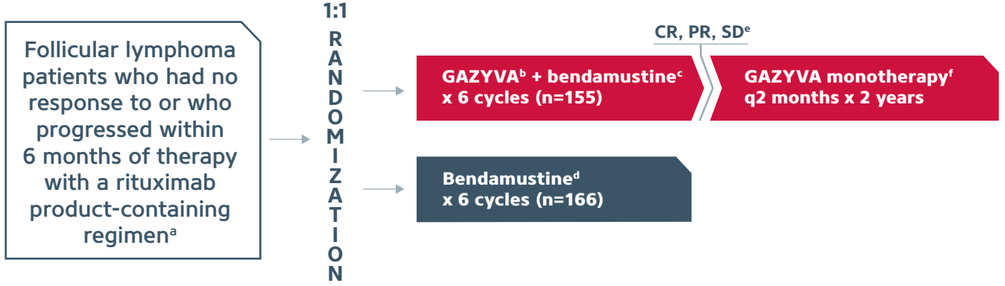
Musculoskeletal Disorders: Musculoskeletal disorders were reported in 54% of patients in the GAZYVA treated arm and 49% of patients in the rituximab product treated arm.

Gastrointestinal Perforation: Cases of gastrointestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

Worsening of Pre-existing Cardiac Conditions: Fatal cardiac events have been reported in patients treated with GAZYVA.

GADOLIN: Studied in a Rituximab-Refractory Population and Approved in R/R FL

This Phase III randomized controlled trial was designed to establish the clinical benefit in terms of progression-free survival (PFS) of GAZYVA in combination with bendamustine followed by GAZYVA monotherapy, compared to bendamustine alone[1,18]



- **Primary endpoint:** PFS assessed by an independent review committee (IRC)
- **Secondary endpoints:** PFS as assessed by investigator, best overall response (complete response [CR] and partial response [PR]), duration of response, and overall survival

[a]Patients were stratified according to rituximab product-refractory type (refractory to prior rituximab product monotherapy vs rituximab product in combination with chemotherapy) and the number of prior therapies (≤2 vs >2).

[b]Each dose of GAZYVA in Cycles 1-6 was 1,000 mg IV and was administered on Days 1, 8, and 15 in Cycle 1; and Day 1 of Cycles 2-6. Cycles 1-6 were 28 days in duration each.

[c]Bendamustine, in combination with GAZYVA, was administered on Days 1 and 2 for Cycles 1-6 at 90 mg/m^2/day IV.

[d]Bendamustine alone was administered on Days 1 and 2 of Cycles 1-6 at 120 mg/m^2/day IV.

[e]Patients in the GAZYVA + bendamustine arm who did not have disease progression (patients with a CR, PR, or stable disease [SD]) at the end of the 6 cycles continued receiving GAZYVA monotherapy for 2 years.

[f]Each dose of GAZYVA monotherapy was 1,000 mg IV and was administered every 2 months for 2 years unless disease progression occurred during the treatment. At the time of interim analysis, 114 patients started GAZYVA monotherapy.

The GADOLIN trial was stopped at the pre-planned interim analysis because patients had a significant improvement in PFS with GAZYVA + bendamustine followed by GAZYVA monotherapy vs bendamustine alone[1,18]

Select Important Safety Information

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

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

GADOLIN: Rituximab-Refractory* Patients Who Progressed Early and Had 1-10 Prior Therapies[1]

Median of 2 Prior Therapies (range 1-10)	
1 prior therapy	46% (n=148)
2 prior therapies	33% (n=106)
3-10 prior therapies	21% (n=67)

72% (n=107)[18]
of these patients progressed within 24 months of first-line therapy

- 95% ECOG PS of 0-1
- 5% ECOG PS of 2
- Median age: 63 (range 34-87)

The follicular lymphoma patients studied in this trial were refractory to rituximab product-containing regimens that primarily included R-CHOP, R-CVP, and rituximab product monotherapy[1,18]

Only 2 patients enrolled into the trial had prior bendamustine exposure.

*Rituximab-refractory was defined as patients who had no response to or who progressed within 6 months of therapy.

Select Important Safety Information

Thrombocytopenia (cont'd)

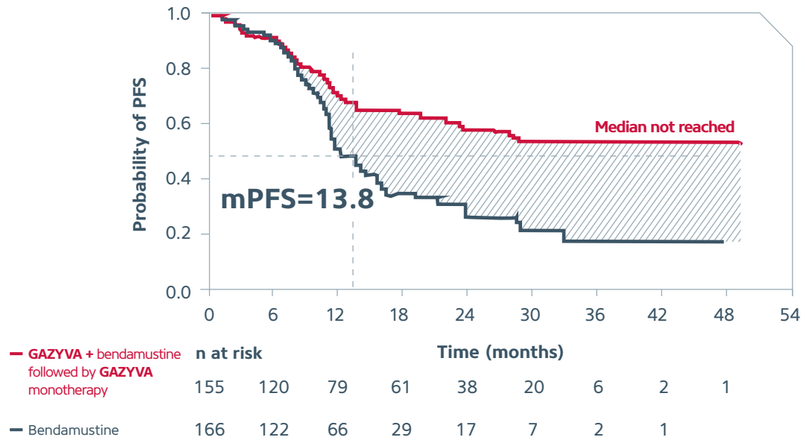
- Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider dose delays of GAZYVA and chemotherapy or dose reductions of chemotherapy. 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

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

GADOLIN: Superior PFS[1]

For FL patients who were refractory to a rituximab product-containing regimen

Primary Endpoint: PFS (IRC-assessed)[1]



HR=0.48

52% reduction in the risk of disease progression or death

95% CI, 0.34-0.68; *P*<0.0001;

21.1-month median observation time

GAZYVA + bendamustine followed by GAZYVA monotherapy more than doubled the median investigator-assessed PFS vs bendamustine alone[1]

Secondary Endpoint: Investigator-Assessed Median PFS

29.2 MONTHS **GAZYVA** + bendamustine followed by **GAZYVA** monotherapy (n=155)

13.7 MONTHS Bendamustine (n=166)

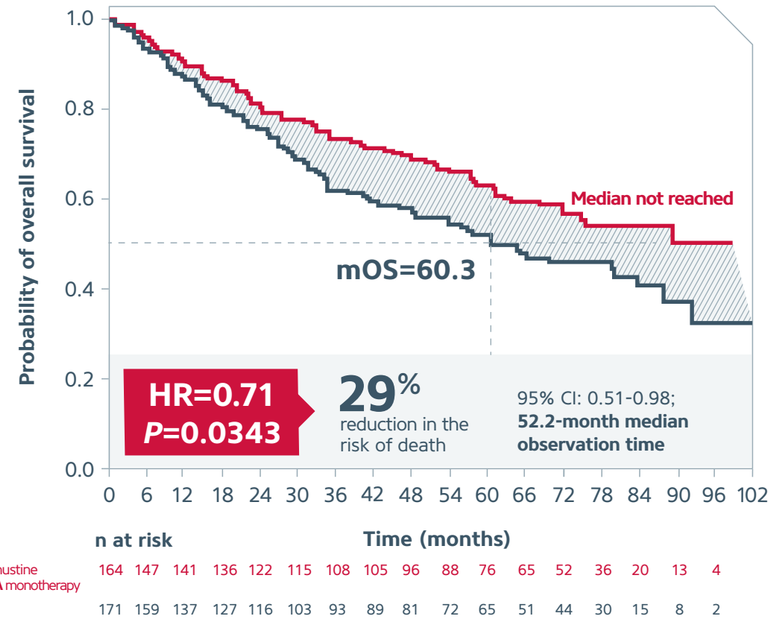
PFS HR=0.48; 95% CI, 0.35-0.67; *P*<0.0001; 21.1-month median observation time

GADOLIN: Superior Overall Survival[1]

For FL patients who were refractory to a rituximab product-containing regimen

- The final efficacy analysis included 335 patients with 171 randomized to bendamustine alone and 164 to GAZYVA in combination with bendamustine: Median observation time was 52.2 months

Secondary Endpoint: Overall Survival[1]



HR=0.71
***P*=0.0343**

29% reduction in the risk of death

95% CI: 0.51-0.98;
52.2-month median observation time

Select Important Safety Information

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

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Select Important Safety Information

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

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

GADOLIN Trial: Investigator-Reported Adverse Reactions

Adverse reactions (incidence ≥10% and ≥2% greater in the GAZYVA arm) in patients with relapsed or refractory NHL[1]

Body system adverse reactions[a,b]	GAZYVA + bendamustine followed by GAZYVA monotherapy (n=204)		Bendamustine (n=203)	
	All Grades %	Grades 3-5 %	All Grades %	Grades 3-5 %
Infusion-related reactions[c]	67	11	63	5
Fatigue	40	3	36	3
Pyrexia	19	1	15	1
Neutropenia	37	35[d]	29	27
Upper respiratory tract infection	36	3	23	1
Respiratory tract infection, unspecified	14	1	8	0
Urinary tract infection	13	3	7	0
Cough	31	<1	21	0
Musculoskeletal pain	28	1	20	0
Arthralgia	12	<1	5	0
Rash	17	<1	14	<1
Pruritus	11	0	6	0

[a]Includes adverse reactions reported throughout study treatment and follow-up.
[b]Includes grouped terms.
[c]Except where noted, individual events that meet the definition of "infusion-related reaction" are excluded from the table above, as they are included in the grouped term "Infusion-Related Reaction".
[d]Includes 1 fatal event.

The GADOLIN study evaluated safety in 407 patients with relapsed or refractory NHL, including follicular lymphoma (81%), small lymphocytic lymphoma, and marginal zone lymphoma. In the population of patients with follicular lymphoma, the profile of adverse reactions was consistent with the overall NHL population.

Investigator-reported adverse reactions[1]

- The most common adverse reactions (incidence ≥20%) in GAZYVA recipients included infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infection, and musculoskeletal pain
- During GAZYVA monotherapy (158 patients), adverse reactions in ≥10% of patients included upper and lower respiratory tract infections, cough, neutropenia, musculoskeletal pain, fatigue, diarrhea, rash, and urinary tract infection

Adverse events leading to treatment withdrawal[1]

- Discontinuation of any study drug due to adverse reactions occurred in 20% of the GAZYVA + bendamustine followed by GAZYVA monotherapy arm vs 17% in the bendamustine-only arm

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

GADOLIN Trial: Laboratory Abnormalities

New or worsening laboratory abnormalities (incidence ≥10% and ≥2% greater in the GAZYVA arm[a]) in patients with relapsed or refractory NHL[1]

Laboratory Abnormalities	GAZYVA + bendamustine followed by GAZYVA monotherapy (n=204)		Bendamustine (n=203)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Lymphopenia	97	92	96	84
Leukopenia	84	47	87	34
Neutropenia	76	53	75	42
Hypophosphatemia	41	8	38	7
Hypocalcemia	39	3	24	1
ALT/SGPT increased	36	2	31	3
Alkaline phosphatase increased	27	0	23	0
Hyperbilirubinemia	21	2	17	2
Hyperkalemia	20	3	18	0

[a]Two percent difference in either any-grade or Grade 3 to 4 laboratory abnormalities.

Hematologic laboratory abnormalities in the GAZYVA treated arm[1]

- The most frequently reported hematologic Grade 3-4 laboratory abnormalities were lymphopenia (92%), neutropenia (53%), and leukopenia (47%)

Non-hematologic laboratory abnormalities in the GAZYVA treated arm[1]

- The most frequently reported non-hematologic Grade 3-4 laboratory abnormalities were hypophosphatemia (8%), hypocalcemia (3%), hyperkalemia (3%), ALT/SGPT increased (2%), and hyperbilirubinemia (2%)

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

Select GADOLIN Safety Information

Clinical Trial Experience: Adverse reactions for GAZYVA + bendamustine followed by GAZYVA monotherapy vs bendamustine alone

Infusion-Related Reactions: Overall, 67% of patients in the GADOLIN study experienced an IRR (all grades) during treatment with GAZYVA in combination with bendamustine. The incidence of Grade 3 to 4 IRRs in GADOLIN was 11%. In Cycle 1, the incidence of IRRs (all grades) was 53% in patients receiving GAZYVA in combination with bendamustine of which 34 (9%) were Grade 3 to 4 in severity. In patients receiving GAZYVA in combination with bendamustine, the incidence of IRRs was highest on Day 1 (37%), and gradually decreased on Days 2, 8 and 15 (23%, 6% and 4%, respectively). During Cycle 2, the incidence of IRRs was 24% in patients receiving GAZYVA in combination with bendamustine and decreased with subsequent cycles. During GAZYVA monotherapy in GADOLIN, IRRs (all grades) were observed in 8% of patients. One Grade 3 and no Grade 4 IRRs were reported during GAZYVA monotherapy. Overall, 2% of patients in GADOLIN experienced an IRR leading to discontinuation of GAZYVA.

Neutropenia: The incidence of neutropenia in GADOLIN was higher in the GAZYVA plus bendamustine arm (37%) compared to the arm treated with bendamustine alone (30%). Cases of prolonged neutropenia (3%) and late onset neutropenia (8%) were also reported in the GAZYVA plus bendamustine arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with bendamustine (30%) compared to the GAZYVA monotherapy treatment phase (13%).

Infections: The incidence of infection in GADOLIN was 68% in the GAZYVA plus bendamustine arm and 59% in the bendamustine arm, with Grade 3 to 4 events reported in 20% and 16%, respectively. Fatal events were reported in 3% of patients in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm.

Thrombocytopenia: The incidence of thrombocytopenia in GADOLIN was lower in the GAZYVA plus bendamustine arm (15%) compared to the arm treated with bendamustine alone (25%). The incidence of hemorrhagic events in GAZYVA plus bendamustine treated patients compared to bendamustine alone was 12% and 11%, respectively. Grade 3 to 4 hemorrhagic events were similar in both treatment arms (4% in the GAZYVA plus bendamustine arm and 2% in the bendamustine arm).

Tumor Lysis Syndrome: The incidence of Grade 3 or 4 tumor lysis syndrome in GADOLIN was 0.5% in GAZYVA treated patients.

Musculoskeletal Disorders: Adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA plus bendamustine treated arm with higher incidence than in the bendamustine alone arm (44% vs 30%).

Gastrointestinal Perforation: Cases of gastrointestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

Worsening of Pre-existing Cardiac Conditions: Fatal cardiac events have been reported in patients treated with GAZYVA.

Select Important Safety Information

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 (CLL-11 & GADOLIN)

- 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 204 patients in GADOLIN with relapsed or refractory NHL treated with GAZYVA plus bendamustine, 44% were 65 and over, while 14% were 75 and over. In patients 65 and over, 55% of patients experienced serious adverse reactions and 28% experienced adverse reactions leading to treatment withdrawal while in patients under 65, 37% and 14% experienced serious adverse reactions and adverse reactions leading to treatment withdrawal, respectively. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GADOLIN

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

Follicular Lymphoma Dosing Schedule

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	

- 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

Chemotherapy Regimen Dosing

Previously untreated FL[1]:

- **Bendamustine:** When combined with GAZYVA, bendamustine is administered at 90 mg/m^2 IV on Days 1 and 2 with prednisone 100 mg orally or equivalent on Day 1 of Cycle 1 for six 28-day cycles
- **CVP:** When combined with standard dosing of CVP, GAZYVA is administered over eight 21-day cycles
- **CHOP:** When combined with standard dosing of CHOP, GAZYVA is administered over six 21-day cycles followed by 2 additional cycles of GAZYVA alone, for a total of 8 GAZYVA cycles
- 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 for up to 2 years

Relapsed or refractory FL:

- **Bendamustine:** When combined with GAZYVA, bendamustine is administered at 90 mg/m^2 IV on Days 1 and 2 for six 28-day cycles
- Patients who achieve a complete response, partial response, or stable disease to the first 6 cycles of GAZYVA + bendamustine should continue on GAZYVA monotherapy every 2 months for up to 2 years

Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Follicular Lymphoma Recommended Premedications

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

Complete before infusion	**Cycle 1:** Day 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-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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Adjusting Infusions in Case of IRRs for Follicular Lymphoma[1]

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

Infusion-Related Reactions	Recommendations per Prescribing Information
Grade 4 (life-threatening)	Stop infusion immediately and permanently discontinue GAZYVA therapy
Grade 3 (severe)	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 IRR occurred), and if patient does not experience any further IRR 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 IRR at rechallenge
Grades 1-2 (mild to moderate)	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 IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose

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

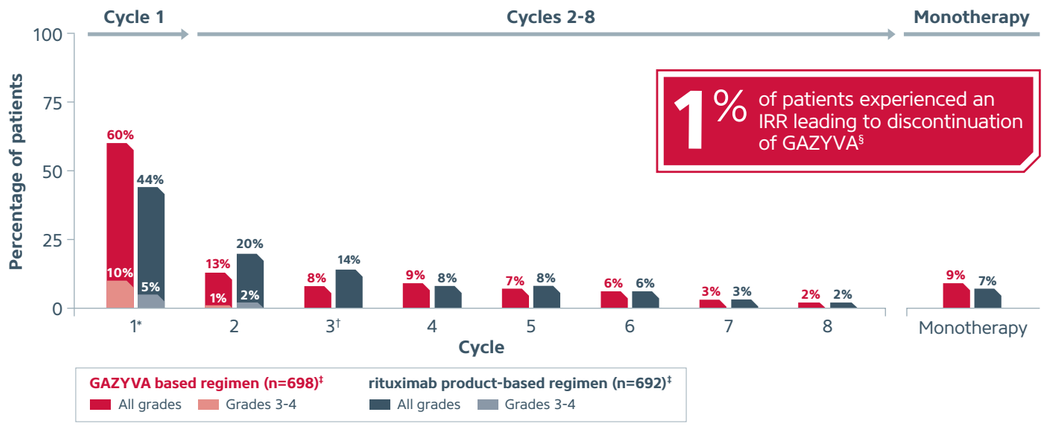
Please see additional Important Safety Information throughout as well as accompanying full Prescribing Information, including BOXED WARNINGS.

Follicular Lymphoma: Incidence of IRRs

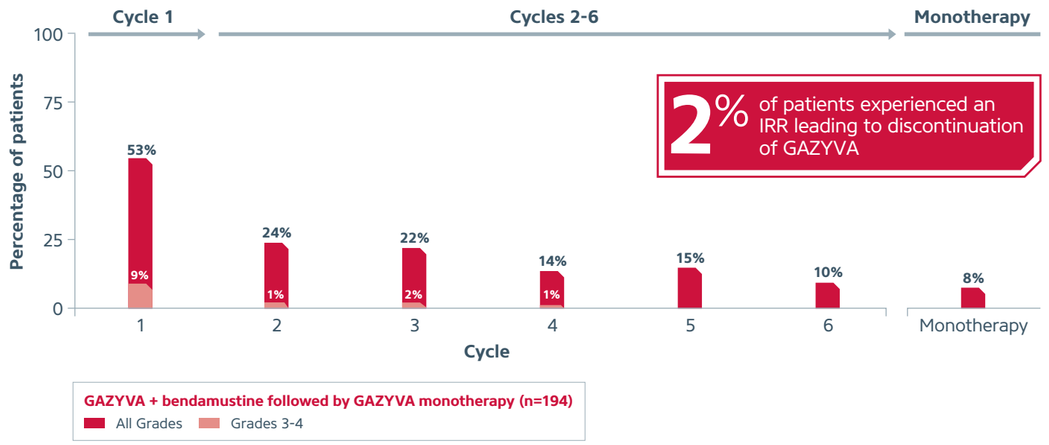
IRRs with GAZYVA may be severe and life threatening, and can occur at any time[1]

- 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, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills

Incidence of IRRs in the GALLIUM Trial: Previously Untreated NHL[1,18]



Incidence of IRRs in the GADOLIN Trial: Relapsed or Refractory NHL[1,18,‖]



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

†Grade 3-4 IRRs in treatment Cycles 3-8 and during Monotherapy were ≤1% for both GAZYVA and rituximab product arms.

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

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

‖Patients relapsed or were refractory to a rituximab product-containing regimen.

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Select Important Safety Information

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

Relapsed/Refractory NHL

- The GADOLIN study evaluated safety in 407 patients with relapsed or refractory NHL, including FL (81%), small lymphocytic lymphoma (SLL) and marginal zone lymphoma (MZL) (a disease for which GAZYVA is not indicated), who did not respond to or progressed within 6 months of treatment with rituximab product or a rituximab product-containing regimen. In patients with follicular lymphoma, the profile of adverse reactions was consistent with the overall NHL population
- Serious adverse reactions occurred in 45% of the GAZYVA arm and 37% of the bendamustine-only arm. Fatal adverse reactions within 90 days of treatment occurred in 3.4% and 2.5%, respectively. Throughout follow-up, fatal adverse reactions occurred in 10% of GAZYVA recipients and in 7.4% of recipients of bendamustine alone, with infection and second primary malignancies being the leading causes
- The most common adverse reactions (incidence ≥20%) in GAZYVA recipients included infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain
- During GAZYVA monotherapy (160 patients), adverse reactions in ≥10% of patients included upper and lower respiratory tract infections, cough, neutropenia, musculoskeletal pain, fatigue, diarrhea, rash, and urinary tract infection
- In the GAZYVA monotherapy phase, new or worsening Grade 3 or 4 abnormalities included neutropenia in 25% of patients (Grade 4, 10%) and lymphopenia in 23% (Grade 4, 5%)

Select Important Safety Information

Additional Important Safety Information (cont'd)

Previously Untreated NHL

- A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1385 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.

CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; CI, confidence interval; CLL, chronic lymphocytic leukemia; CVP, cyclophosphamide, vincristine sulfate, and prednisone; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; PFS, progression-free survival; PS, Performance Status; SLL, small lymphocytic lymphoma.

References: 1. GAZYVA® (obinutuzumab) full Prescribing Information. South San Francisco, CA: Genentech, Inc.; 2020. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Horsham, PA: Janssen Biotech, Inc.; 2019. **3.** VENCLEXTA® (venetoclax tablets) Prescribing Information. North Chicago, IL: AbbVie Inc.; 2019. **4.** CALQUENCE® (acalabrutinib) Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **5.** Mössner E, Brünker P, Moser S, et al. *Blood*. 2010;115(22):4393-4402. **6.** Herter S, Herting F, Mundigl O, et al. *Mol Cancer Ther.* 2013;12(10):2031-2042. **7.** Klein C, Lammens A, Schäfer W, et al. *mAbs*. 2013;5(1):22-33. **8.** Honeychurch J, Alduaij W, Azizyan M, et al. *Blood*. 2012;119(15):3523-3533. **9.** Nastoupil L, Sinha R, Hirschey A, et al. *Community Oncol.* 2012;9(11):S53-S60. **10.** Pavanello F, Steffanoni S, Ghielmini M, et al. *Mediterr J Hematol Infect Dis*. 2016;8(1):e2016062. **11.** Casulo C, Byrtek M, Dawson KL, et al. *J Clin Oncol*. 2015;33(23):2516-2522. **12.** Solal-Celigny P, Roy P, Colombat P, et al. *Blood*. 2004;104:1258-1265. **13.** Meignan M, Cottereau AS, Versari A, et al. *J Clin Oncol*. 2016;34:3618-3626. **14.** Pastore A, Jurinovic V, Kridel R, et al. *Lancet Oncol*. 2015;16:1111-1122. **15.** Jurinovic V, Kridel R, Staiger AM, et al. *Blood*. 2016;128:1112-1120. **16.** Huet S, Tesson B, Jais JP, et al. *Lancet Oncol*. 2018;19:549-561. **17.** Luminari S, Merli F. *Eur J Oncol*. 2018;23:19. **18.** Data on file. Genentech, Inc. **19.** Seymour JF, Marcus R, Davies A, et al. *Haematologica*. 2019;104(6):1202-1208. doi:10.3324/haematol.2018.209015.

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

A Commitment to Innovation. A Continuum of Approvals Across FL & CLL.

It's Time to Rethink GAZYVA

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 bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen
- 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 as well as accompanying full Prescribing Information, including BOXED WARNINGS.

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