AUSTRALIAN PRODUCT INFORMATION
Gazyva® (obinutuzumab)

WARNING

Progressive Multifocal Leukoencephalopathy

Progressive Multifocal Leukoencephalopathy (PML) including fatal PML can occur in patients receiving Gazyva. Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If such symptoms occur, further administration of Gazyva should be immediately suspended until a diagnosis of PML has been excluded. If a diagnosis of PML is confirmed Gazyva must be permanently discontinued (see section 4.4 Special warnings and precautions).

1. NAME OF THE MEDICINE
Obinutuzumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial of 40 mL concentrate contains 1000 mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion

Clear, colourless to slightly brownish

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chronic Lymphocytic Leukaemia
Gazyva in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL).

Follicular Lymphoma
Gazyva in combination with chemotherapy followed by Gazyva maintenance is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.

Gazyva in combination with bendamustine, followed by Gazyva maintenance, is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Pre-treatment to reduce the risk of Cytokine Release Syndrome (CRS) induced by glofitamab
Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

General

Gazyva should be administered as an intravenous infusion through a dedicated line in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced physician. Gazyva infusions should not be administered as an intravenous push or bolus. Isotonic 0.9% sodium chloride solution should be used as the infusion vehicle (see section 6.6 Special precautions for disposal).

Prophylaxis and Premedication for Tumour Lysis Syndrome (TLS)

Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl < 70 mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to start of Gazyva infusion as per standard practice (see section 4.4 Special warnings and precautions for use). Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.

Prophylaxis and Premedication for Infusion Related Reactions (IRR)

Premedication to reduce the risk of IRRs (see section 4.4 Special warnings and precautions for use) is outlined in Table 1. Corticosteroid premedication is recommended for FL patients and mandatory for CLL patients for the first infusion and patients receiving Gazyva as a pre-treatment. Premedication for subsequent infusions and other premedication should be administered as described below. Patients with a high tumour burden and/or (i.e. high peripheral circulating lymphocyte count in CLL (> 25 x 10^9/L)) may be at increased risk of severe IRR.

Hypotension as a symptom of IRR may occur during Gazyva intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each infusion, and for the first hour after administration (see section 4.4 Special warnings and precautions for use).

Table 1 Premedication to be administered before Gazyva infusion to reduce the risk of infusion-related reactions

Indication/Day of Treatment/ Cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1 **CLL: Day 1*, Day 2** **FL: Day 1**	All patients	Intravenous corticosteroid[1,2]	Completed at least 1 hour prior to Gazyva infusion
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	
All subsequent infusions:	Patients with no IRR during the previous infusion	Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion

Indication/Day of Treatment/ Cycle	**Patients requiring premedication**	**Premedication**	**Administration**
CLL and FL	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	
	Patients with a Grade 3 IRR with the previous infusion OR patients with lymphocyte counts > 25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1,2]	Completed at least 1 hour prior to Gazyva infusion
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	
Pre-treatment to reduce the risk of CRS induced by glofitamab	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to Gazyva infusion.
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	

[*]If the 100 mg dose of Gazyva is administered without interruption or modification of the infusion rate the subsequent 900 mg dose may also be administered on the same day (see Table 5). In the event the 900 mg dose is given on the same day no additional premedication is required prior to commencement of the 900 mg dose.
[1] 20 mg IV dexamethasone or 80 mg IV methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions
[2] If a corticosteroid-containing chemotherapy regimen is administered on the same day as Gazyva the corticosteroid can be administered as an oral medication if given at least 60 minutes prior to Gazyva, in which case additional IV corticosteroid as premedication is not required.
[3] e.g. 1000 mg paracetamol
[4] H1 histamine receptor blockade

Standard Dosage

Chronic Lymphocytic Leukaemia (in combination with chlorambucil[*])

Cycle 1

The recommended dosage of Gazyva is 1000 mg administered over Day 1 and 2, and on Day 8 and Day 15 of the first 28 day treatment cycle as shown in Table 2.

Two infusion bags should be prepared; one for the first infusion of 100 mg and one for the second infusion of 900 mg. If the 100 mg dose is completed without modifications of the infusion rate or interruptions, the 900 mg dose can be administered on the same day (no dose delay necessary) provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg the 900 mg infusion must be administered the following day (see Table 2).

Cycles 2-6

The recommended dosage of Gazyva is 1000 mg administered on Day 1 for each 28 day treatment cycle as shown in Table 2.

Table 2 Dose and infusion rate of Gazyva for patients with CLL

Day of Treatment Cycle		**Dose of Gazyva**	**Rate of infusion** For management of IRRs that occur during infusion, refer to Table 5
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 or Day 1 (continued)	900 mg	If no IRR occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an IRR during the previous infusion, start administration at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	If no IRR occurred during the previous infusion where the final infusion rate was ≥ 100 mg/hr, 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 the patient experienced an IRR 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	1000 mg	
Cycles 2 – 6	Day 1	1000 mg	

[*] see section 5.1 Pharmacodynamic properties for information on chlorambucil dose.

Delayed or missed doses (CLL)

If a planned dose of Gazyva is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for Gazyva should be maintained between doses thereafter.

Follicular Lymphoma

The recommended dosage of Gazyva is 1000 mg administered intravenously according to Table 3.

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Previously Untreated Follicular Lymphoma

For patients with previously untreated follicular lymphoma, Gazyva should be administered with chemotherapy as follows:

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

Previously untreated patients who achieve a complete or partial response to Gazyva plus chemotherapy should continue to receive Gazyva (1000 mg) alone as maintenance therapy once every 2 months until disease progression or for up to 2 years.

Relapsed/refractory Follicular Lymphoma

For patients with follicular lymphoma who have relapsed after or who are refractory to rituximab or a rituximab-containing regimen, Gazyva should be administered in six 28-day cycles in combination with bendamustine**.

Relapsed/refractory patients who achieve complete or partial response or have stable disease should continue to receive Gazyva 1000 mg alone as maintenance therapy once every 2 months until disease progression or for up to 2 years.

Gazyva should be administered at the standard infusion rate in Cycle 1 (see Table 3). In patients who do not experience Grade ≥3 infusion related reactions (IRRs) during Cycle 1, Gazyva may be administered as a short (approximately 90 minutes) duration infusion (SDI) from Cycle 2 onwards (see Table 4).

Table 3 Dose and standard infusion rate of Gazyva for patients with FL

<table>
<tr><th colspan="2">Day of Treatment Cycle</th><th>Dose of Gazyva</th><th>Rate of infusion
For management of IRRs that occur during infusion, refer to Table 5</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>1000 mg</td><td>Administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.</td></tr>
<tr><td>Day 8</td><td>1000 mg</td><td rowspan="4">If no IRR or a Grade 1 IRR occurred during the previous infusion, where the final infusion rate was ≥100 mg/hr, 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 the patient experienced a Grade 2 IRR or higher during the previous infusion administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.</td></tr>
<tr><td>Day 15</td><td>1000 mg</td></tr>
<tr><td>Cycles 2-6 or 2-8</td><td>Day 1</td><td>1000 mg</td></tr>
<tr><td>Maintenance for FL patients</td><td>Every 2 months until progression or up to 2 years</td><td>1000 mg</td></tr>
</table>

** see section 5.1 Pharmacodynamic properties for information on bendamustine dose.

Table 4 Dose and short duration infusion (SDI) rate of Gazyva for patients with FL

Day of treatment cycle		**Dose of Gazyva**	**Rate of infusion** For management of IRRs that occur during infusion, refer to Table 5
Cycles 2–6 or 2-8	Day 1	1000 mg	If no IRR of Grade ≥3 occurred during Cycle 1: 100 mg/hr for 30 minutes, then 900 mg/hr for approximately 60 minutes. If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 IRR occurred during the previous SDI infusion, administer obinutuzumab at the standard infusion rate (see Table 3).
Maintenance	Every 2 months until progression or up to 2 years	1000 mg	

Delayed or missed doses (FL)
If a planned dose of Gazyva is missed, it should be administered as soon as possible; do not omit it or wait until the next planned dose.

If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15 requiring delay of treatment, these doses should be given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1.

During maintenance, maintain the original dosing schedule for subsequent doses.

Pre-treatment to reduce the risk of CRS induced by glofitamab

The recommended dose for pre-treatment is a single 1000 mg dose of Gazyva administered intravenously, 7 days prior to initiation of glofitamab. Refer to the glofitamab Product Information for more information.

Administer Gazyva at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Dosage modifications during treatment (all indications)
No dose reductions of Gazyva are recommended.

For management of symptomatic adverse events (including IRRs), see Table 5 below and section 4.4 Special warnings and precautions for use.

Table 5 Infusion Rate Modification Guidelines for Infusion Related Reactions (see section 4.4 Special warnings and precautions for use)

Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. **<u>For FL patients who experience Grade 3 IRRs during standard infusion;</u>** • Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred). • If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 2 and 3). • If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy. **<u>For FL patients who experience Grade 3 IRRs during SDI;</u>** • Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and not greater than 400 mg/hr. • If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion must be given at the standard rate. • If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy. **<u>For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days;</u>** • Upon resolution of symptoms, the Day 1 infusion rate may be increased back to 25 mg/hr after 60 minutes, but not increased further. • If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy. **<u>For patients receiving Gazyvva as a pre-treatment for glofitamab;</u>** • Upon resolution of symptoms, escalation may resume at increments of 50mg/hr every 30 minutes without exceeding 400mg/hr.
Grade 1-2 (mild and moderate)	Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion.

**

	If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 2, 3 and 4). **For patients receiving Gazyva as a pre-treatment for glofitamab;** • Upon resolution of symptoms, escalation may resume at increments of 50mg/hr every 30 minutes without exceeding 400mg/hr **For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days;** • Upon resolution of symptoms, the Day 1 infusion rate may be increased back up to 25 mg/hr after 60 minutes, but not increased further.

Special Populations

Children
The safety and efficacy of Gazyva in children below 18 years of age have not been established.

Elderly
No dose adjustment is required in elderly patients (see section 4.4 Special warnings and precautions for use).

Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Gazyva has not been studied in patients with a CrCl < 30mL/min (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Hepatic Impairment
The safety and efficacy of Gazyva in patients with hepatic impairment have not been established.

Method of Administration

Instructions for dilution

Gazyva should be prepared by a healthcare professional using aseptic technique. Use a sterile needle and syringe to prepare Gazyva.

For CLL cycles 2-6, all FL cycles and as a pre-treatment to reduce the risk of CRS induced by glofitamab
Withdraw the required amount of Gazyva liquid concentrate from the vial and dilute in a PVC or non-PVC polyolefin infusion bag containing the appropriate volume of sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Do not use dextrose-containing solutions or other diluents (see section 6.2 Incompatibilities).

For CLL cycle 1, Day 1 only: Preparation of infusion bags for dose administered over 2 days
The table below provides guidance on the volume of Gazyva liquid concentrate to be diluted and the volume of sterile 0.9% sodium chloride solution it is to be diluted in. Withdraw the required amount of Gazyva liquid concentrate from the vial and dilute in a PVC or non-PVC polyolefin infusion bag containing the appropriate volume of sterile, non-pyrogenic 0.9%

aqueous sodium chloride solution. Do not use dextrose-containing solutions or other diluents (see section 6.2 Incompatibilities).

To ensure differentiation of the two infusion bags for the initial 1000 mg dose, the recommendation is to utilise bags of different sizes to distinguish between the 100 mg dose for Cycle 1 Day 1 and the 900 mg dose for Cycle 1 Day 1 (continued) or Day 2. To prepare the 2 infusion bags, withdraw 40 mL of Gazyva liquid concentrate from the vial and dilute 4 mL into a 100 mL infusion bag and the remaining 36 mL into a 250 mL PVC or non-PVC polyolefin infusion bag containing sterile, non pyrogenic 0.9% aqueous sodium chloride solution. Clearly label each infusion bag.

Each bag should be gently inverted to mix the solution in order to avoid foaming.

Dose of Gazyva to be administered	Required amount of Gazyva liquid concentrate	Volume of PVC or non-PVC polyolefin infusion bag
100 mg	4 mL	100 mL
900 mg	36 mL	250 mL
1000 mg	40 mL	250 mL

Parenteral drug products should be inspected visually for particulates and discolouration prior to administration.

Gazyva is for single use in one patient only. Once the infusion is prepared it should be administered immediately (see section 6.4 Special precautions for storage).

4.3 CONTRAINDICATIONS

Gazyva is contraindicated in patients with a known hypersensitivity to obinutuzumab, murine proteins or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded in the patient medical record.

In study BO21223 of patients with previously untreated follicular lymphoma (FL), Gazyva plus chemotherapy compared with rituximab plus chemotherapy demonstrated a higher incidence of adverse events (AEs), in particular serious AEs, Grade 3-5 AEs and infections. Prescribers should consider this when choosing to prescribe Gazyva for patients with previously untreated FL, particularly for patients who are older age (65 years and over), or have reduced renal function.

Infusion Related Reactions (IRRs)

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyva were infusion related reactions (IRRs) which occurred predominantly during infusion of the first 1000 mg.

In CLL patients who received the combined measures for prevention of IRRs (corticosteroid; oral analgesic/anti-histamine (H1 histamine receptor blockade); omission of antihypertensive medication in the morning of the first infusion; Cycle 1 Day 1 dose administered over 1 or 2 days; see section 4.2 Dose and method of administration) decreased incidence of IRRs of all

Grades was observed. The incidence of IRRs was independent of the corticosteroid pre-medication given (prednisone/prednisolone or methylprednisolone/ dexamethasone). The incidence of Grade 3-4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented. Mitigation measures to reduce IRRs should be followed (see section 4.2 Dose and method of administration). The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of Gazyva (see section 4.8 Adverse Effects (Undesirable Effects)).

In the majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumour burden and/or high circulating lymphocyte count in CLL (> 25 x 10^9/L) may be at increased risk of severe IRR. See section 4.2 Dose and method of administration for information on prophylaxis and Table 5 for advice on how to manage IRRs based on Grade of reaction.

Patients should not receive further Gazyva infusions if they experience:

- acute life-threatening respiratory symptoms,
- other life-threatening anaphylactoid symptoms,
- a Grade 4 (i.e. life-threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion)

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during Gazyva intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyva infusion, and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Hypersensitivity reactions

Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness) have been reported in patients treated with Gazyva. If a hypersensitivity reaction is suspected during or after an infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped, appropriate treatment of the hypersensitivity reaction should be commenced, and Gazyva treatment permanently discontinued. Patients with known hypersensitivity to Gazyva must not be treated (see section 4.3 Contraindications). Hypersensitivity may be clinically difficult to distinguish from IRRs.

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to the foreign recognition of the humanised antibody in cynomolgus monkeys [C_{max} and $AUC_{0\text{-}168\ h}$ at steady state (Day 176) after weekly administration of 5, 25, and 50 mg/kg, were 377, 1,530, and 2,920 µg/mL and 39,800, 183,000, and 344,000 (µg•h)/mL, respectively]. Findings included acute anaphylactic or anaphylactoid reactions and an increased prevalence of systemic inflammation and infiltrates consistent with immune-complex mediated hypersensitivity reactions, such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation. These reactions led to unscheduled termination of 6/36

animals treated with Gazyva during dosing and recovery phases; these changes were partially reversible. No renal toxicity with a causal relationship to Gazyva has been observed in humans.

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) has been reported with Gazyva. Patients who are considered to be at risk of TLS [e.g. patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl < 70 mL/min)] should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to the infusion of Gazyva as described in section 4.2 Dose and method of administration. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines should also be followed, according to standard practice. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated (see section 4.4 Special warnings and precautions for use).

Neutropenia

Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with Gazyva. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. Concomitant infection should be treated as appropriate. Dose delays should be considered in case of severe or life threatening neutropenia. It is strongly recommended that patients with severe neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should also be considered. If treatment is necessary, it should be administered in accordance with local guidelines, and administration of granulocyte colony-stimulating factors (G-CSF) should be considered. Late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) may occur. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia.

Thrombocytopenia

Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with Gazyva. Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with Gazyva. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician.

Use of any concomitant therapies which could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Coagulation abnormalities including disseminated intravascular coagulation (DIC)

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Disseminated intravascular coagulation (DIC) has been reported in patients receiving obinutuzumab for treatment of follicular lymphoma and chronic lymphocytic leukaemia. In the majority of cases, the events have involved subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring within one to two weeks. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC have been identified (see section 4.8 Adverse Effects (Undesirable Effects)).

Worsening of Pre-existing Cardiac Conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyva (see section 4.8 Adverse Effects (Undesirable Effects)). These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

Infections

Gazyva should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyva in patients with a history of recurring or chronic infections. Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Gazyva therapy. Fatal infections have been reported. Patients with both CIRS > 6 and CrCl < 70 mL/min are more at risk of infections, including severe infections.

In the FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance. During the follow-up phase, Grade 3-5 infections are observed more in patients who received Gazyva plus bendamustine in the induction phase.

Hepatitis B 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 (see section 4.8 Adverse Effects (Undesirable Effects)). HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also 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 (i.e. HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti HBs] positive).

Screen all patients for HBV infection by measuring HBsAg and anti-HBc. The results of HBsAg and anti-HBc testing should be known in all patients 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 physicians 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 at least 12 months following treatment with Gazyva. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving Gazyva, immediately discontinue Gazyva and any concomitant chemotherapy, and institute appropriate treatment and refer the patient to a gastroenterologist. Resumption of Gazyva in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming Gazyva in patients who developed HBV reactivation.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Gazyva (see Boxed Warning and section 4.8 Adverse Effects (Undesirable Effects)). The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are non-specific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (CSF testing for JC viral DNA). Therapy with Gazyva should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunisation

The safety of immunisation with live or attenuated viral vaccines, during or following Gazyva therapy has not been studied. Vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery. Treatment with Gazyva following vaccination should only commence once protective antibody titres have been reached.

Exposure in utero to Gazyva and vaccination of infants with live virus vaccines

Due to the potential depletion of B cells in infants of mothers who have been exposed to Gazyva during pregnancy, the safety and timing of vaccinations with live virus vaccines should be discussed with the child’s healthcare provider. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infants’ B cell levels are within normal ranges (see section 4.6 Fertility, Pregnancy and Lactation).

Use in renal impairment

Chronic Lymphocytic Leukaemia

In the pivotal study in CLL, 27% (90 out of 336) of patients treated with Gazyva plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than those associated with CrCl ≥ 50 mL/min (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties). No significant differences in efficacy were observed between patients with CrCl < 50 mL/min and those with CrCl ≥ 50 mL/min. Patients with CrCl < 30 mL/min were excluded from the study (see section 5.1 Pharmacodynamic properties).

Non-Hodgkin Lymphoma (NHL)

In the pivotal studies in iNHL, 6.9% of patients (14 of 204) in study GAO4753g and 5% of patients (35 of 698) in study BO21223 had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events, grade 3 to 5 adverse events and adverse events leading to treatment withdrawal (patients in Study BO21223 only) than those associated with CrCl ≥ 50 mL/min (see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties). Patients with CrCl < 40 mL/min were excluded from the studies (see section 5.1 Pharmacodynamic properties).

Use in hepatic impairment

The safety and efficacy of Gazyva in patients with hepatic impairment have not been established.

Paediatric use

The safety and efficacy of Gazyva in children below 18 years of age have not been established.

Use in the elderly

Chronic Lymphocytic Leukaemia

In the pivotal study in CLL, 46% (156 out of 336) of patients treated with Gazyva plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than patients < 75 years of age. No significant differences in efficacy were observed between patients ≥ 75 years of age and those < 75 years of age (see section 5.1 Pharmacodynamic properties).

Non-Hodgkin Lymphoma

In the pivotal studies in iNHL, patients ≥ 65 years of age experienced more serious adverse events and adverse events leading to withdrawal or death than patients < 65 years of age. No clinically meaningful differences in efficacy were observed. Table 6 outlines treatment-related AEs by age group for patients enrolled in study BO21223.

Table 6 Gazyva treatment-related Adverse Events by age group in patients receiving Gazyva plus chemotherapy vs rituximab plus chemotherapy followed by Gazyva or rituximab maintenance in study BO21223

	Rituximab plus chemotherapy		**Gazyva plus chemotherapy**	
Number of patients	<65 n=467	>=65 n=225	<65 n=465	>=65 n=233
Serious AEs	36.8%	50.7%	42.6%	62.2%
AEs leading to withdrawal from any treatment	13.9%	18.2%	13.1%	26.2%
AEs leading to death	2.4%	7.1%	2.6%	10.3%

Effect on laboratory tests

See section 4.4 Special warnings and precautions.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug-drug interaction studies have been performed, although limited drug interaction sub-studies have been undertaken for Gazyva with bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), FC (fludarabine,

cyclophosphamide) and chlorambucil. Co-administration with Gazyva had no effect on the pharmacokinetics of bendamustine, FC or the individual components of CHOP; in addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of Gazyva. A risk for interactions with concomitantly used medicinal products cannot be excluded.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific studies in animals have been performed to evaluate the effect of Gazyva on fertility. No adverse effects on male and female reproductive organs were observed in repeat dose toxicity studies in cynomolgus monkeys at up to 100 mg/kg/day for 3 months (8 times the clinical exposure based on AUC at the clinical dose of 1000 mg/kg, 3 doses per 28 day cycle) and 50 mg/kg/day for 6 months (6 times the clinical exposure based on AUC).

Use in pregnancy – Category C

Gazyva should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Women of child-bearing potential should use effective contraception while receiving Gazyva and for 18 months following treatment with Gazyva (see section 5.2 Pharmacokinetic properties). Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infants' B-cell levels are within normal ranges.

No studies in pregnant women have been performed. A reproduction study in pregnant cynomolgus monkeys showed no evidence of teratogenic effects. However, weekly obinutuzumab dosing from post-coitum day 20 to delivery resulted in complete depletion of B-lymphocytes, opportunistic infections and immune-complex mediated hypersensitivity reactions in infants at weekly intravenous obinutuzumab doses of 25 and 50 mg/kg (2-5 times the clinical exposure based on C_{max} and AUC). Offspring exposures on day 28 postpartum (mean C_{max} 80-240 µg/mL, in the range of concentrations in maternal serum) and very low concentrations in milk (less than 0.5% of the corresponding maternal serum levels) suggest in utero exposure. B-cell counts returned to normal levels in the infants, and immunologic function was restored within 6 months of birth. Furthermore, the serum concentrations of Gazyva in offspring were similar to those in the mothers on day 28 post-partum, whereas concentrations in milk on the same day were very low, suggesting that Gazyva crosses the placenta.

Use in lactation

As human IgG is secreted in human milk and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue breast-feeding during Gazyva therapy and for 18 months after the last dose of Gazyva (see section 5.2 Pharmacokinetic properties). Animal studies have shown excretion of Gazyva in breast milk (see section 4.6 Fertility, pregnancy and lactation).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Gazyva on the ability to drive and to use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Chronic Lymphocytic Leukaemia

The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up from the pivotal clinical trial, BO21004/CLL11, in which Gazyva was given in combination with chlorambucil compared to chlorambucil alone (Stage 1) or rituximab plus chlorambucil (Stage 2). In patients treated with Gazyva in combination with chlorambucil, 81% received all 6 treatment cycles compared to 89% of patients in the rituximab plus chlorambucil arm and 67% of patients in the chlorambucil alone arm.

Tables 7 and 8 summarise the ADRs that occurred at a higher incidence (difference of ≥2%) in patients receiving Gazyva plus chlorambucil as compared to chlorambucil alone or rituximab plus chlorambucil, respectively.

Table 7 Adverse Reactions reported with a higher incidence (difference of ≥ 2% compared to chlorambucil alone [Stage 1]) in patients receiving Gazyva plus chlorambucil *

ADR (MedDRA) System Organ Class	**All Grades %**		**Grades 3-5† %**	
	chlorambucil n=116	Gazyva + chlorambucil n=241	chlorambucil n=116	Gazyva + chlorambucil n=241
Injury, Poisoning and Procedural Complications				
Infusion related reactions	N/A	68.9	N/A	21.2
Blood and lymphatic system disorders				
Neutropenia	18.1	40.7	15.5	34.9
Thrombocytopenia	7.8	15.4	4.3	11.2
Anaemia	10.3	12.4	4.3	4.6
Leucopenia	0	7.1	0	5.4
Infections and Infestations				
Urinary tract infection	2.6	6.2	< 1	1.7
Oral herpes	< 1	3.7	0	0
Rhinitis‡	< 1	2.1	0	0
Pharyngitis	0	2.1	0	0
General disorders and administration site conditions				
Pyrexia	6.9	10.4	0	< 1
Respiratory, thoracic and mediastinal disorders				
Cough	6.9	9.5	< 1	0
Metabolism and nutrition disorders				
Tumour lysis syndrome	< 1	4.1	0	1.7
Hyperuricaemia	0	3.3	0	< 1
Musculoskeletal and connective tissue disorders				
Arthralgia	2.6	4.6	< 1	< 1
Back pain	1.7	5.0	0	< 1
Musculoskeletal chest pain	0	2.5	0	< 1
Vascular disorders				
Hypertension	1.7	3.7	1.7	1.7
Investigations				

ADR (MedDRA) System Organ Class	All Grades %		Grades 3-5† %	
	chlorambucil n=116	Gazyva + chlorambucil n=241	chlorambucil n=116	Gazyva + chlorambucil n=241
White blood cell count decreased‡	< 1	2.1	0	2.1
Neutrophil count decreased	0	2.1	0	2.1
Weight increased	0	2.1	0	0
Cardiac disorders				
Atrial fibrillation	0	2.1	0	< 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Squamous cell carcinoma of skin	0	2.1	0	1.2
Gastrointestinal disorders				
Diarrhoea‡	11.2	10.4	< 1	2.5
Skin and subcutaneous tissue disorders				
Alopecia	0	2.1	0	0

* In all Grades or Grade 3-5
† No Grade 5 adverse reactions have been observed with a difference of ≥ 2% between the treatment arms
‡ With Stage 1 update and Stage 2 data, this event was no longer reported with a difference of ≥ 2% between the treatment arms

Table 8 Adverse Reactions reported with a higher incidence (difference of ≥ 2%) in patients receiving Gazyva plus chlorambucil vs rituximab plus chlorambucil (Stage 2)*

ADR (MedDRA) System Organ Class	All Grades %		Grades 3-5† %	
	rituximab + chlorambucil n=321	Gazyva + chlorambucil n=336	rituximab + chlorambucil n=321	Gazyva + chlorambucil n=336
Injury, Poisoning and Procedural Complications				
Infusion related reactions	37.7	65.8	3.7	19.9
Blood and lymphatic system disorders				
Neutropenia	32.1	38.1	28.3	33.0
Thrombocytopenia	6.5	14.3	3.1	10.4
Leucopenia	1.9	6.3	< 1	4.5
Gastrointestinal disorders				
Diarrhoea	7.5	10.1	0	2.1
Constipation	5.0	8.3	0	0
Infections and Infestations				
Nasopharyngitis	3.1	5.7	0	< 1
Urinary tract infection	1.6	5.4	< 1	1.5
Musculoskeletal and connective tissue disorders				
Back pain	2.8	4.8	< 1	< 1
Arthralgia	2.5	4.8	0	< 1
Metabolism and nutrition disorders				
Tumour lysis syndrome	0	4.2	0	1.8

* In all Grades or Grade 3-5
† No Grade 5 adverse reactions have been observed with a difference of ≥ 2% between the treatment arms

Non-Hodgkin Lymphoma

In patients with FL, the profile of adverse drug reactions (ADRs) was consistent with the overall iNHL population.

ADRs described in this section were identified during induction, maintenance and follow-up in 2 pivotal studies that investigated Gazyva in combination with bendamustine, CHOP, or CVP followed by Gazyva maintenance therapy in:

- Patients with previously untreated iNHL (study BO21223, n=1390; 692 patients in the rituximab plus chemotherapy arm, and 698 patients in the Gazyva plus chemotherapy arm), of whom 86% had FL. Of these patients, 92.7% who were treated with Gazyva plus chemotherapy (induction) received all 6 or 8 treatment cycles (depending on the chemotherapy) of Gazyva.

- Patients with relapsed/refractory iNHL (study GAO4753g, n=407; 203 patients in the bendamustine arm, and 204 in the Gazyva plus bendamustine arm), of whom 81% had FL. Of these patients, 79.4% who were treated with Gazyva plus bendamustine received all 6 treatment cycles of Gazyva.

The adverse drug reactions (ADRs) described in Table 9 this section (based on a safety population of 407 patients with indolent NHL) were identified during induction, maintenance, and follow-up from study GAO4753g, in which Gazyva was given in combination with bendamustine during induction (G+B), and as Gazyva monotherapy in maintenance and compared to bendamustine during induction alone (B). In patients treated with G+B, 79.4% received all 6 treatment cycles of Gazyva and 75.6% received all 6 cycles of B compared to 66.7% of patients in the B arm.

Table 9 summarises the ADRs that occurred at a higher incidence (difference of ≥ 2%) in patients receiving G+B during induction followed by Gazyva maintenance as compared to B during induction alone.

Table 9 Adverse Reactions reported with a higher incidence (difference of ≥ 2%) in patients receiving Gazyva plus bendamustine (induction) followed by Gazyva maintenance vs bendamustine (induction) alone

ADR (MedDRA[a]) System Organ Class	**All Grades %**		**Grades 3-5[†] %**	
	bendamustine n=203	**Gazyva + bendamustine* n=204**	**bendamustine n=203**	**Gazyva + bendamustine* n=204**
Injury, Poisoning and Procedural Complications				
Infusion related reactions[‡]	62.6	66.7	5.4	11.3
Blood and Lymphatic System Disorders				
Neutropenia	29.6	37.3	27.1	34.8
Febrile Neutropenia	3.4	6.4	3.4	5.9
Gastrointestinal Disorders				
Constipation	16.3	18.1	0	0
Dyspepsia	3.0	5.4	0	0

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ADR (MedDRA[a]) System Organ Class	**All Grades %**		**Grades 3-5[†] %**	
	bendamustine n=203	**Gazyva + bendamustine* n=204**	**bendamustine n=203**	**Gazyva + bendamustine* n=204**
Haemorrhoids	0	2.5	0	0
General Disorders And Administration Site Conditions				
Fatigue	27.6	30.9	2.5	2.5
Pyrexia	14.8	19.1	0	1.0
Asthenia	9.4	11.8	0	1.0
Chest Pain	2.5	5.4	0.5	0
Infections And Infestations				
Upper Respiratory Tract Infection	8.9	13.7	0.5	2.0
Sinusitis	5.4	12.3	0.5	1.0
Urinary Tract Infection	5.9	11.8	0	2.9
Nasopharyngitis	3.9	10.8	0	0
Pharyngitis	1.0	3.9	0	0
Lung Infection	1.0	4.4	0.5	2.5
Influenza	0	3.9	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	5.4	11.8	0	0
Pain In Extremity	4.9	10.8	0	1.0
Bone Pain	1.5	3.4	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal Cell Carcinoma	0.5	2.9	0.5	1.0
Psychiatric Disorders				
Depression	1.5	4.4	0	0
Renal and Urinary Disorders				
Dysuria	1.0	2.5	0	0.5
Urinary incontinence	0.5	2.9	0	0.5
Respiratory, Thoracic and Mediastinal Disorders				
Cough	19.7	31.4	0	0
Nasal Congestion	2.5	8.3	0	0
Rhinorrhoea	1.5	5.4	0	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	5.6	8.8	0	0
Eczema	0.5	2.9	0	0

*followed by Gazyva maintenance

[a]MedDRA coded adverse reactions as reported by investigators (excluding IRRs).

[†] No Grade 5 adverse reactions have been observed with a difference of ≥ 2% between the treatment arms

‡ defined as any related adverse event that occurred during or within 24 hours of infusion

In study GAO4753g, patients in the B arm received 6 months of induction treatment only, whereas after the induction period, patients in the G+B arm continued on with Gazyva maintenance treatment. During the maintenance period with Gazyva, the most common adverse reactions were cough (20.3%), neutropenia (12.7%), upper respiratory tract infections (12.0%), diarrhoea (10.1%), bronchitis (9.5%), sinusitis (9.5%), nausea (8.9%), fatigue (8.9%), IRRs (8.2%), urinary tract infections (7.0%), nasopharyngitis (7.0%), pyrexia (7.0%), arthralgia (6.3%), vomiting (5.7%), rash (5.7%), pneumonia (5.1%), dyspnoea (5.1%) and pain in extremity (5.1%). The most common grade 3-5 adverse reactions were neutropenia (10.8%), febrile neutropenia (1.9%) and anaemia, thrombocytopenia, pneumonia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1.3%).

The adverse drug reactions (ADRs) described in Table 10 (based on a safety population of 1390 patients with indolent NHL) were identified during induction, maintenance and follow-up from study BO21223, in which patients were treated with either Gazyva or rituximab in combination with chemotherapy followed by Gazyva or rituximab monotherapy in responding patients, every 2 months until disease progression or for a maximum of 2 years. During combination therapy with chemotherapy, 93% of patients received all treatment cycles of Gazyva and 92% of patients received all treatment cycles of rituximab. Of the responding patients who commenced monotherapy with Gazyva or rituximab, 77% and 73% completed the full course, respectively.

Table 10 summarises the ADRs that occurred at a higher incidence (difference of ≥ 2%) in patients receiving Gazyva plus chemotherapy during induction followed by Gazyva maintenance as compared to rituximab plus chemotherapy during induction followed by rituximab maintenance in study BO21223.

Table 10 Adverse Reactions reported with a higher incidence (difference of ≥ 2%) in patients receiving Gazyva plus chemotherapy vs rituximab plus chemotherapy

ADR (MedDRA[a]) System Organ Class	**All Grades %**		**Grades 3-5[†] %**	
	rituximab + chemo n=692	**Gazyva + chemo n=698**	**rituximab + chemo n=692**	**Gazyva + chemo n=698**
Injury, Poisoning and Procedural Complications				
Infusion related reactions[‡]	60.1	71.6	8.5	12.3
Blood and Lymphatic System Disorders				
Neutropenia	44.9	50.3	39.6	46.4
Thrombocytopenia	7.5	12.3	2.7	6.3
Gastrointestinal Disorders				
Nausea	37.9	33.8	0.9	1.0
Constipation	29.2	32.2	0.4	0.3
Diarrhoea	23.4	27.8	1.4	1.9
Dyspepsia	5.9	8.5	0	0

ADR (MedDRA[a]) System Organ Class	**All Grades %**		**Grades 3-5[†] %**	
	rituximab + chemo n=692	**Gazyva + chemo n=698**	**rituximab + chemo n=692**	**Gazyva + chemo n=698**
General Disorders And Administration Site Conditions				
Pain	5.1	2.9	0.4	0
Infections And Infestations				
Upper Respiratory Tract Infection	19.1	21.5	0.7	0.9
Pneumonia	7.5	10.2	4.2	5.4
Herpes Zoster	6.9	10.6	0.9	1.3
Sinusitis	6.6	9.3	0.4	0.3
Rhinitis	4.8	8.0	0	0.3
Pharyngitis	2.2	4.3	0	0
Metabolism And Nutrition Disorders				
Hypokalaemia	3.9	6.4	0.9	0.7
Musculoskeletal and Connective Tissue Disorders				
Back pain	16.2	13.0	0.6	0.4
Psychiatric Disorders				
Insomnia	11.3	14.3	0.3	0.1
Anxiety	3.8	6.2	0.1	0.1
Nervous System Disorders				
Headache	14.5	16.8	0.1	0.1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	24.9	30.2	0.1	0.1
Oropharyngeal pain	7.4	9.5	0.1	0.1
Skin and Subcutaneous Tissue Disorders				
Alopecia	10.4	12.6	0.1	0
Pruritus	8.1	10.6	0	0.1

[†] No Grade 5 adverse reactions have been observed with a difference of ≥ 2% between the treatment arms
[‡] defined as any related adverse event that occurred during or within 24 hours of infusion

During the monotherapy period with Gazyva, the most common adverse events (incidence ≥ 5%) in patients with previously untreated iNHL were cough (20%), neutropenia (19%), upper respiratory tract infection (14%), viral upper respiratory tract infection (15%), diarrhoea (12%), arthralgia (9%), fatigue (9%), sinusitis (9%), infusion reactions (8%), pneumonia (8%), herpes zoster (8%), lower respiratory tract infection (7%), pyrexia (6%), back pain (6%), headache (6%), urinary tract infection (6%), nausea (6%), bronchitis (5%) and vomiting (5%). The most common Grade 3-4 adverse events (incidence ≥ 1%) during the monotherapy period were neutropenia (17%), pneumonia (3%, with 2 deaths due to pneumonia reported in the Gazyva treatment arm) and febrile neutropenia (2%).

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Hypogammaglobulinemia: uncommon

Further information on selected adverse reactions

Infusion related reactions

Most frequently reported (≥ 5%) symptoms associated with an IRR were nausea, vomiting, diarrhoea, headache, dizziness, fatigue, chills, pyrexia, hypotension, flushing, hypertension, tachycardia, dyspnoea, and chest discomfort. Respiratory symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and cardiac symptoms such as atrial fibrillation have also been reported (see section 4.4 Special warnings and precautions).

In study BO21223 the most frequent symptoms of IRRs (> 5% occurrence in the G-chemo arm) were as follows (percentages expressed as R-chemo vs. G-chemo): nausea (20.3% vs. 25.7%), chills (7.0% vs. 15.6%), pyrexia (5.5% vs. 14.3%), chest discomfort (3.4% vs. 5.0%) vomiting (8.0% vs. 11.1%), fatigue (6.9% vs. 7.2%), dyspnoea (4.7% vs. 7.6%), throat irritation (5.4% vs. 3.5%), headache (4.4% vs. 8.7%), flushing (3.7% vs. 5.4%), hypotension (1.7% vs. 5.0%), pruritus (6.0% vs. 4.0%), rash (5.9% vs. 4.2%) and constipation (3.0% vs. 5.4%).

Chronic Lymphocytic Leukaemia

The incidence of IRRs was 65% with the infusion of the first 1000 mg of Gazyva (20% of patients experiencing a Grade 3-4 IRR). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyva. The incidence of IRR with subsequent infusions was 3% with the second 1000 mg dose and 1% thereafter. No Grade 3-5 IRR were reported beyond the first 1000 mg infusions of Cycle 1.

In patients who received the recommended measures for prevention of IRRs as described in section 4.2 Dose and method of administration, a decreased incidence of all Grades IRRs was observed. The incidence of Grade 3-4 IRRs (which are based on a relatively low number of patients) were similar before and after mitigation measures were implemented.

Non-Hodgkin Lymphoma

In Cycle 1, the overall incidence of IRRs was higher in patients receiving Gazyva plus chemotherapy compared to patients in the comparator arm. In patients receiving Gazyva plus chemotherapy, the incidence of IRRs was highest on Day 1 and gradually decreased with subsequent infusions. This decreasing trend continued during maintenance therapy with Gazyva.

Overall, 3% of patients experienced an IRR leading to discontinuation of Gazyva.

Short Duration Infusion in patients with Follicular Lymphoma

Study MO40597/GAZELLE was designed to characterise the safety profile of short duration Gazyva infusions (approximately 90 minutes) from Cycle 2 in patients with previously untreated FL.

In study MO40597 a greater proportion of patients experienced any grade IRRs at Cycle 2 compared to the proportion who experienced IRRs after standard infusion at Cycle 2 in study BO21223 (10/99 [10.1%] vs. 23/529 [4.3%] respectively; IRRs attributed by the investigator to any component of study therapy). No patients experienced Grade ≥ 3 IRRs after SDI at Cycle 2 in study MO40597; 3/529 (0.6%) experienced Grade ≥ 3 IRRs at Cycle 2 in study BO21223. IRR symptoms and signs were similar in both studies. Infusion related reactions observed in study MO40597/GAZELLE are summarised in Table 11.

Table 11 Study MO40597/GAZELLE Short-Duration Infusion: Infusion Related Reactions[a] by Cycle (Safety-Evaluable Population)

CTCAE Grade	C1 Overall (standard infusion)	C1[b] by day				C2[c]	C3	C4	C5	C6	C7	Over all induction cycles
		Day 1	Day 2[d]	Day 8	Day 15							
All Grade	65/113 (57.5%)	57/113 (50.4%)	4/51 (7.8%)	6/112 (5.4%)	5/111 (4.5%)	13/110 (11.8%)	9/108 (8.3%)	7/108 (6.5%)	6/107 (5.6%)	5/105 (4.8%)	2/55 (3.6%)	71/113 (62.8%)
Grade ≥3	6/113 (5.3%)	5/113 (4.4%)	1/51 (2.0%)	0	0	0	0	0	1/107 (0.9%)	0	0	7/113 (6.2%)

C=cycle; CTCAE = Common Terminology Criteria for Adverse Events; IRR=infusion related reaction

[a] Infusion related reaction defined as any event that occurred during or within 24 hours from the end of study treatment infusion that were judged by the investigator to be related to any components of therapy.

[b] C1 comprised three infusions at the standard infusion rate, administered at weekly intervals

[c] Patients received short-duration infusion from C2 onward. The denominator at C2 and subsequent cycles represents the number of patients who received SDI at that cycle.

[d] Patients treated with bendamustine on Cycle 1 Day 2.

Neutropenia and infections

Chronic Lymphocytic Leukaemia

The incidence of neutropenia was higher in the Gazyva plus chlorambucil arm compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte colony-stimulating factors. The incidence of infection was 38% in the Gazyva plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms). Cases of prolonged neutropenia (2% in the Gazyva plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyva plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see section 4.4 Special warnings and precautions).

Non-Hodgkin Lymphoma

In the Gazyva plus chemotherapy arm, the incidence of neutropenia was higher relative to the comparator arm with an increased risk during the induction period. The incidence of prolonged neutropenia and late onset neutropenia in the Gazyva plus chemotherapy arm were 3% and 7%, respectively. The incidence of infection was 81% in the Gazyva plus chemotherapy arm (with Grade 3-5 events reported in 22% of patients and fatal events reported in 2% of patients). The incidence of infection was 72% in the rituximab plus chemotherapy arm (with Grade 3-5 events reported in 17% of patients and fatal events reported in 1% of patients). Patients who received G-CSF prophylaxis had a lower rate of Grade 3-5 infections (see section 4.4 Special warnings and precautions).

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597, assessing the safety of SDI, neutropenia was reported as an adverse event in a higher proportion of patients compared to study BO21223 in which patients received standard duration infusion (69/113 [61.1%] vs. 247/595 [41.5%] respectively, throughout

induction). The median and range of neutrophil count values were similar in both studies at each time point. Febrile neutropenia was reported in a similar proportion of patients in study MO40597 and study BO21223 (6/113 [5.3%] vs. 31/595 [5.2%] respectively). Infection was reported less frequently in study MO40597 than in study BO21223 (45/113 [39.8%] vs. 284/595 [47.7%] respectively).

Thrombocytopenia and haemorrhagic events

Chronic Lymphocytic Leukaemia

The incidence of thrombocytopenia was higher in the Gazyva plus chlorambucil arm compared to the rituximab plus chlorambucil arm especially during the first cycle. Four percent of patients treated with Gazyva plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyva infusion) (see section 4.4 Special warnings and precautions). The overall incidence of haemorrhagic events was similar in the Gazyva treated arm and in the rituximab treated arm. The number of fatal haemorrhagic events was balanced between the treatment arms; however all of the events in patients treated with Gazyva were reported in Cycle 1. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Non-Hodgkin Lymphoma

Thrombocytopenia occurred more frequently during Cycle 1 in the Gazyva plus chemotherapy arm. Thrombocytopenia occurring during or 24 hours from end of infusion (acute thrombocytopenia) was more frequently observed in patients treated with Gazyva plus chemotherapy than in the relevant comparator arm. The incidence of haemorrhagic AEs was similar across all treatment arms. Haemorrhagic events and Grade 3-5 haemorrhagic events occurred in 12% and 4% of patients, respectively. While fatal haemorrhagic events occurred in less than 1% of patients, none of these fatal AEs occurred in Cycle 1.

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597, assessing the safety of SDI, thrombocytopenia was reported as an adverse event in a higher proportion of patients compared to study BO21223 in which patients received standard duration infusion (21/113 [18.6%] vs. 63/595 [10.6%] respectively, throughout induction). The median and range of platelet count values were similar in both studies at each time point. No thrombocytopenia events reported in study MO40597 were associated with bleeding.

Coagulation abnormalities including disseminated intravascular coagulation (DIC)

DIC has been reported in patients receiving obinutuzumab for treatment of follicular lymphoma and chronic lymphocytic leukemia. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC have been identified. Three patients were reported with DIC (one serious, two non-serious) among a total of 1837 obinutuzumab-treated patients in four major company-sponsored controlled trials in Non-Hodgkin's Lymphoma. All events occurred in the obinutuzumab treatment groups; no cases were reported in the comparator groups. All events occurred within 1-2 days after the first infusion. All patients continued treatment (see section 4.4 Special warnings and precautions for use).

Progressive multifocal leukoencephalopathy (PML)

PML has been reported in patients treated with Gazyva (see Boxed Warning and section 4.4 Special warnings and precautions).

Hepatitis B Reactivation
Cases of hepatitis B reactivation have been reported in patients treated with Gazyva (see section 4.4 Special warnings and precautions).

Worsening of Pre-existing Cardiac Conditions
Cases of fatal cardiac events have been reported in patients treated with Gazyva (see section 4.4 Special warnings and precautions).

Gastro-Intestinal Perforation
Cases of gastro-intestinal perforation have been reported in patients receiving Gazyva, mainly in NHL.

Malignancies
There is an increased incidence of second malignancies in patients with CLL. Data from the pivotal study in CLL does not demonstrate an increased risk of second malignancies following Gazyva therapy.

Laboratory Abnormalities
Transient elevation in liver enzymes (AST, ALT, ALP) has been observed shortly after the first infusion of Gazyva.

For additional information see section 4.8 Adverse Effects (Undesirable Effects).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems .

4.9 OVERDOSE
No experience with overdosage is available from human clinical trials. In clinical trials with Gazyva, doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent. Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. Patients should be closely monitored with regular blood cell counts, and for increased risk of infections, while B cell-depleted.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FA03

Mechanism of Action
Obinutuzumab specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre B and mature B lymphocytes. CD20 is not expressed on haemopoietic stem cells, pro B cells, or normal plasma cells. Glycoengineering

of the Fc part of obinutuzumab results in higher affinity for FcϒRIII receptors on immune effector cells such as natural killer (NK) cells and macrophages and monocytes as compared to non-glycoengineered antibodies.

In nonclinical studies, obinutuzumab induces direct cell death and mediates antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcϒRIII positive immune effector cells. In addition, obinutuzumab mediates a low degree of complement dependent cytotoxicity (CDC). In animal models, obinutuzumab mediates potent B cell depletion and anti-tumour efficacy. Compared to Type I CD20 antibodies, obinutuzumab, a Type II antibody, is characterised by a direct cell death induction with a concomitant reduction in CDC. Compared to non-glycoengineered CD20 antibodies, obinutuzumab is characterised by greater ADCC and phagocytosis (ADCP) as a consequence of the glycoengineering, but *in vivo* studies in xenograft tumour models in SCID mice showed no difference in tumour growth inhibition between obinutuzumab and non-glycoengineered wild type obinutuzumab.

Pre-treatment with obinutuzumab to deplete peripheral blood and lymphoid tissue B cells was shown to attenuate glofitamab-induced cytokine release and related adverse effects in cynomolgus monkeys and tumour-bearing humanised mice.

In the pivotal clinical trial in patients with CLL BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with Gazyva were B cell depleted (defined as CD19+ B-cell counts $< 0.07 \times 10^9$/L) at the end of treatment period and remained depleted during the first 6 months of follow up. Recovery of B cells was observed within 12 to 18 months of follow up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease.

Clinical trials

Chronic Lymphocytic Leukaemia (CLL)

A phase III, international, multicentre, open-label, randomised, two-stage, three arm study (BO21004/CLL11) investigating the safety and efficacy profile of Gazyva plus chlorambucil compared to rituximab plus chlorambucil or chlorambucil alone was conducted in patients with previously untreated CLL with comorbidities.

Prior to enrolment, patients had to have documented CD20+ CLL, and one or both of the following measures of coexisting medical conditions: comorbidity score [total Cumulative Illness Rating Scale (CIRS)] of greater than 6 or reduced renal function as measured by CrCl < 70 mL/min. Patients with inadequate liver function (NCICTC Grade 3 liver function tests (AST, ALT > 5 x ULN for > 2 weeks; bilirubin > 3 x ULN) and renal function (CrCl < 30 mL/min) were excluded.

A total of 781 patients were randomised 2:2:1 to receive Gazyva plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1 compared Gazyva plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared Gazyva plus chlorambucil to rituximab plus chlorambucil in 663 patients. Efficacy results are summarised in Table 12 and in Figures 1-3.

In the majority of patients, Gazyva was given intravenously as a 1000 mg initial dose administered on Day 1, Day 8 and Day 15 of the first treatment cycle. In order to reduce the rate of infusion related reactions in patients, an amendment was implemented and 140

patients received the first Gazyva dose administered over 2 days (Day 1 (100mg) and Day 2 (900mg), see section 4.2 Dose and method of administration). For each subsequent treatment cycle (Cycles 2 to 6), patients received Gazyva 1000 mg on Day 1 only. Chlorambucil was given orally at 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (1 to 6).

The demographics data and baseline characteristics were well balanced between the treatment groups. The majority of patients enrolled were Caucasian (95%) and male (61%). The median age was 73 years, with 44% being 75 years or older. At baseline, 22% of patients had Binet Stage A, 42% had Binet Stage B and 36% had Binet Stage C. The median comorbidity score was 8 and 76% of the patients enrolled had a comorbidity score above 6. The median estimated CrCl was 62 mL/min and 66% of all patients had a CrCl < 70 mL/min. Forty-two percent of patients enrolled had both a CrCl <70 ml/min and a comorbidity score of >6. Thirty-four percent of patients were enrolled on comorbidity score alone, and 23% of patients were enrolled with only impaired renal function.

The most frequently reported coexisting medical conditions (using a cut off of 30% or higher) in the MedDRA body systems are: Vascular disorders 73%, Cardiac disorders 46%, Gastrointestinal disorders 38%, Metabolism and Nutrition disorders 40%, Renal and Urinary disorders 38%, musculoskeletal and connective tissue disorders 33%.

The primary endpoint of the study was investigator assessed progression-free survival (PFS-INV). In addition, an independent review committee (IRC) assessed all patients for progression and IRC assessed PFS (PFS-IRC) was evaluated.

Key secondary efficacy endpoints were end of treatment response, molecular remission at end of treatment (minimal residual disease status) and time to event endpoints (event-free survival, new anti-leukemic therapy). Overall survival for Stage 1 is presented in Figure 2. Overall survival for Stage 2 will continue to be followed and is not yet mature.

Table 12 Summary of efficacy from BO21004 (CLL11) study

	Stage 1		**Stage 2**	
	Chlorambucil n=118	**Gazyva + Chlorambucil n=238**	**Rituximab + Chlorambucil n=330**	**Gazyva + Chlorambucil n=333**
	22.8 months median observation time		**18.7 months median observation time**	
Investigator-assessed PFS (PFS-INV)*				
Number (%) of patients with event	96 (81.4%)	93 (39.1%)	199 (60.3%)	104 (31.2%)
Median time to event (months)	11.1	26.7	15.2	26.7
HR (95% Cl)	0.18 [0.13; 0.24]		0.39 [0.31; 0.49]	
p-value (Log-Rank test, stratified[†])	< 0.0001		< 0.0001	
IRC-assessed PFS (PFS-IRC)*				

	Stage 1		**Stage 2**	
	Chlorambucil n=118	**Gazyva + Chlorambucil n=238**	**Rituximab + Chlorambucil n=330**	**Gazyva + Chlorambucil n=333**
	22.8 months median observation time		**18.7 months median observation time**	
Number (%) of patients with event	90 (76.3%)	89 (37.4%)	183 (55.5%)	103 (30.9%)
Median time to event (months)	11.2	27.2	14.9	26.7
HR (95% Cl)	0.19 [0.14; 0.27]		0.42 [0.33; 0.54]	
p-value (Log-Rank test, stratified[†])	< 0.0001		< 0.0001	
End of Treatment Response				
No. of patients included in the analysis	118	238	329	333
Responders (%)	37 (31.4 %)	184 (77.3%)	214 (65.0%)	261 (78.4%)
Non-responders (%)	81 (68.6%)	54 (22.7%)	115 (35.0%)	72 (21.6%)
Difference in response (95% Cl)	45.95 [35.6; 56.3]		13.33 [6.4; 20.3]	
p-value (Chi-squared Test)	< 0.0001		< 0.0001	
No. of complete responders[‡] (%)	0 (0.0%)	53 (22.3%)	23 (7.0%)	69 (20.7%)
Molecular Remission at end of treatment[§]				
No. of patients included in the analysis	90	168	244	239
MRD negative[¶] (%)	0 (0%)	45 (26.8%)	6 (2.5%)	61 (25.5%)
MRD positive[\\] (%)	90 (100%)	123 (73.2%)	238 (97.5%)	178 (74.5%)
Difference in MRD (95% Cl)	26.79 [19.5; 34.1]		23.06 [17.0; 29.1]	
Event Free Survival				
No. (%) of patients with event	103 (87.3%)	104 (43.7%)	208 (63.0%)	118 (35.4%)
Median time to event (months)	10.8	26.1	14.3	26.1
HR (95% Cl)	0.19 [0.14; 0.25]		0.43 [0.34; 0.54]	
p-value (Log-Rank test, stratified[†])	<0.0001		< 0.0001	
Time to new anti-leukaemic therapy				
No. (%) of patients with event	65 (55.1%)	51 (21.4%)	86 (26.1%)	55 (16.5%)
Median time to event (months)	14.8	-	30.8	-
HR (95% Cl)	0.24 [0.16; 0.35]		0.59 [0.42; 0.82]	
p-value (Log-Rank test, stratified[†])	<0.0001		< 0.0018	
Overall Survival				
No. (%) of patients with event	24 (20.3%)	22 (9.2%)	41 (12.4%)	28 (8.4%)

AusPAR – Gazyva - obinutuzumab (rch) - Roche Products Pty Ltd - PM-2022-03031-1-6 Date of finalisation: December 2024. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi>

	Stage 1		**Stage 2**	
	Chlorambucil n=118	**Gazyva + Chlorambucil n=238**	**Rituximab + Chlorambucil n=330**	**Gazyva + Chlorambucil n=333**
	22.8 months median observation time		**18.7 months median observation time**	
Median time to event (months)	NR	NR	NR**	NR**
HR (95% Cl)	0.41 [0.23; 0.74]		0.66 [0.41; 1.06]**	
p-value (Log-Rank test, stratified†)	0.0022		0.0849**	

IRC: Independent Review Committee; PFS: progression-free survival; HR: hazard ratio; CI: confidence intervals; MRD: minimal residual disease; NR: not reached
* Defined as the time from randomisation to the first occurrence of progression, relapse or death from any cause as assessed by the investigator
** Data not yet mature
† stratified by Binet stage at baseline
‡ includes 11 patients in the GClb arm with a complete response with incomplete marrow recovery
§ blood and bone marrow combined
¶ Minimal Residual Disease (MRD) negativity is defined as <1 CLL cell in 10,000 leucocytes
\\ includes MRD positive patients and patients who progressed or died before the end of treatment

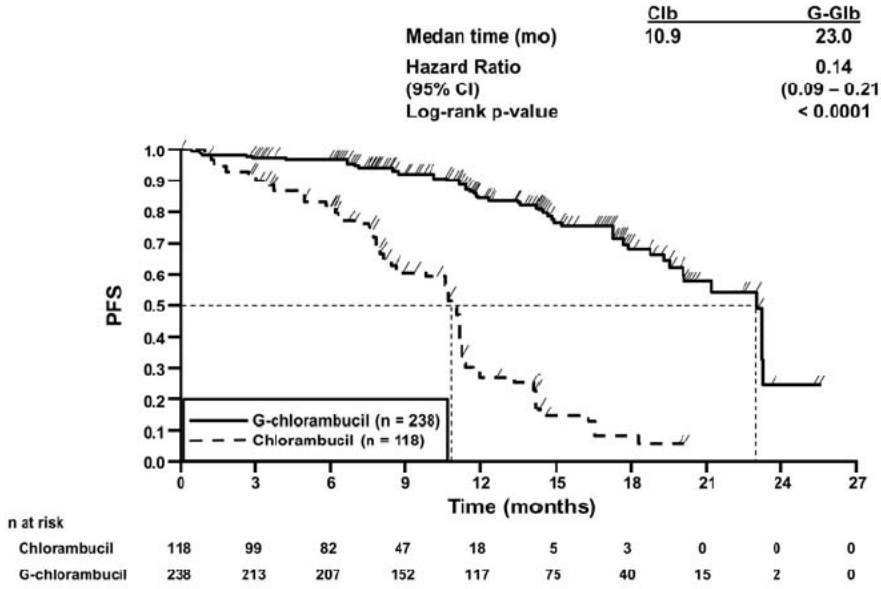
Results of the PFS subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in the Gazyva plus chlorambucil (GClb) arm compared to the rituximab plus chlorambucil (RClb) arm and the chlorambucil (Clb) alone arm in all subgroups. The hazard ratios ranged from 0.08 to 0.42 for GClb vs Clb and 0.28 to 0.71 for GClb vs RClb.

Patient Reported Outcomes

In the QLQC30 and QLQ-CLL-16 questionnaires conducted during the treatment period, no substantial difference in any of the subscales was observed. Data during follow up, especially for the chlorambucil alone arm, is limited. However, no notable differences in quality of life during follow up have been identified to date.

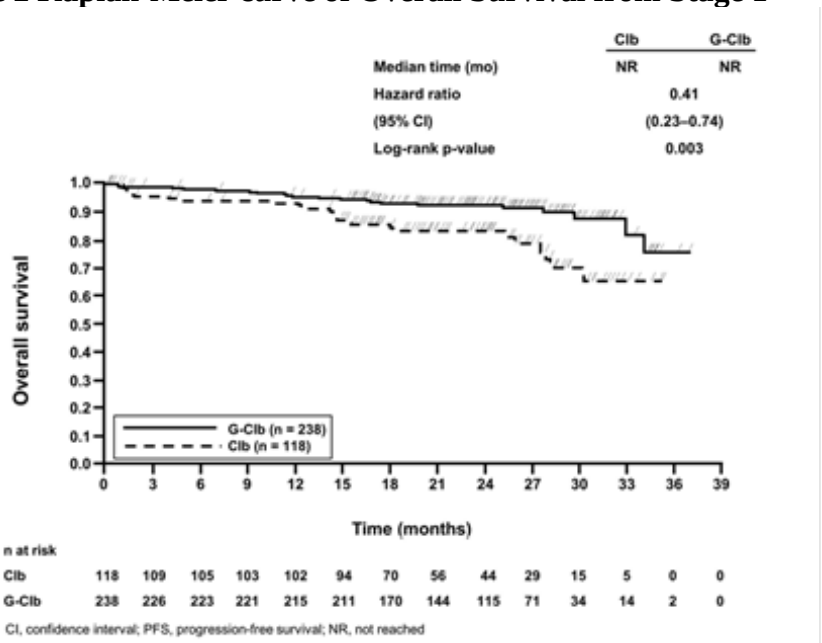
Health-related quality of life assessments, specific to fatigue through treatment period, show no statistically significant difference suggesting that the addition of Gazyva to chlorambucil regimen does not increase the experience of fatigue for patients.

Figure 1 Kaplan-Meier curve of Investigator-assessed PFS from Stage 1



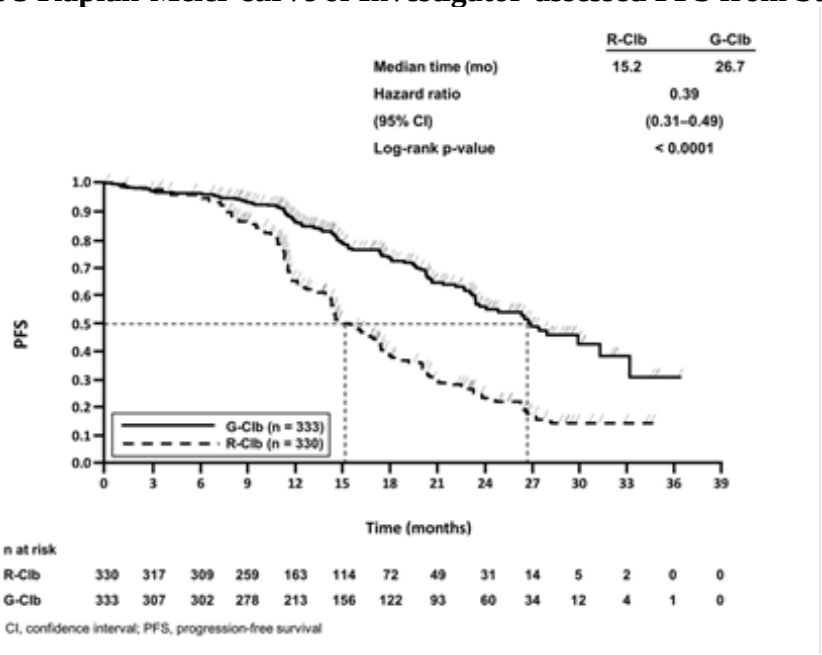
CI, confidence interval; PFS, progression-free survival.

Figure 2 Kaplan-Meier curve of Overall Survival from Stage 1



CI, confidence interval; PFS, progression-free survival; NR, not reached

Figure 3 Kaplan-Meier curve of Investigator-assessed PFS from Stage 2



Non-Hodgkin Lymphoma (Follicular Lymphoma)

Previously Untreated Follicular Lymphoma
In a multicentre phase III, open-label, randomised study (BO21223/GALLIUM), 1401 previously untreated patients with either stage II (bulky)/III/IV follicular lymphoma (FL) (n=1202) or marginal zone lymphoma (MZL) (n=199) were randomised. Of the 199 patients randomised to the MZL cohort, 4 presented with a non-MZL histology. Patients were randomised 1:1 to receive either Gazyva or rituximab in combination with chemotherapy (CHOP, CVP, or bendamustine) followed by Gazyva or rituximab maintenance in patients who achieved a complete or partial response. The remainder of the study description focuses on the FL population.

The demographic data and baseline characteristics of the FL population were well balanced. The median age was 59 years, the majority of patients were Caucasian (81%), and female (53%). Seventy-nine percent of patients had a FLIPI score of ≥ 2. Seven percent had Stage II (bulky) disease, 35% had Stage III disease and 57% had Stage IV disease. Fifty-seven percent received bendamustine, 33% received CHOP, and 10% received CVP chemotherapy. Forty-four percent had bulky disease (> 7 cm), 34% had at least one B-symptom at baseline and 97% had an ECOG performance status of 0-1 at baseline.

Gazyva (1000 mg) was administered intravenously prior to chemotherapy as described in section 4.2 Dose and method of administration – Follicular Lymphoma. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m^2/day when given in combination with Gazyva. Standard dosing of CHOP (n=6 cycles) and CVP (n=8 cycles) was given. Following Cycles 6-8, when Gazyva was given in combination with chemotherapy, Gazyva maintenance therapy was given every 2 months for 2 years for responding patients or until disease progression.

Efficacy results are summarised in Table 13. Kaplan-Meier curves for PFS are shown in Figure 4.

Table 13 Summary of efficacy in FL patients from BO21223 (GALLIUM) study

	Rituximab + chemotherapy followed by rituximab maintenance n=601	**Gazyva + chemotherapy followed by Gazyva maintenance n=601**
	Median observation time 34 months	**Median observation time 35 months**
Primary Endpoint		
Investigator-assessed PFS[§] (PFS-INV)		
Number (%) of patients with event	144 (24.0%)	101 (16.8%)
HR [95% CI]	0.66 [0.51, 0.85]	
p-value (Log-Rank test, stratified*)	0.0012	
2 year PFS estimate [95% CI]	80.9 [77.4, 84.0]	87.7 [84.6, 90.1]
3 year PFS estimate [95% CI]	73.3 [68.8, 77.2]	80.0 [75.9, 83.6]
Key Endpoints		
IRC-assessed PFS[§] (PFS-IRC)		
Number (%) of patients with event	125 (20.8%)	93 (15.5%)
HR [95% CI]	0.71 [0.54, 0.93]	
p-value (Log-Rank test, stratified*)	0.0138	
2 year PFS estimate [95% CI]	82.0 [78.5, 85.0]	87.2 [84.1, 89.7]
3 year PFS estimate [95% CI]	77.9 [73.8, 81.4]	81.9 [77.9, 85.2]
Time to next anti-lymphoma therapy		
Number (%) of patients with event	111 (18.5%)	80 (13.3%)
HR [95% CI]	0.68 [0.51, 0.91]	
p-value (Log-Rank test, stratified*)	0.0094	
Overall Survival		
Number (%) of patients with event	46 (7.7%)	35 (5.8%)
HR [95% CI]	0.75 [0.49, 1.17][¶]	
p-value (Log-Rank test, stratified*)	0.21[¶]	
Overall Response Rate at End of Induction[‡] (INV-assessed, CT)**		
Responders (%) (CR, PR)	522 (86.9%)	532 (88.5%)
Difference in response rate (%) [95% CI]	1.7% [-2.1%, 5.5%]	

AusPAR – Gazyva - obinutuzumab (rch) - Roche Products Pty Ltd - PM-2022-03031-1-6 Date of finalisation: December 2024. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi>

	Rituximab + chemotherapy followed by rituximab maintenance n=601	**Gazyva + chemotherapy followed by Gazyva maintenance n=601**
p-value (Cochran-Mantel-Haenszel test)	0.33	
Complete Response (CR)	143 (23.8%)	117 (19.5%)
95% CI Clopper-Pearson	[20.4%, 27.4%]	[16.4%, 22.9%]
Partial Response (PR)	379 (63.1%)	415 (69.1%)
95% CI Clopper-Pearson	[59.1%, 66.9%]	[65.2%, 72.7%]
Conversion Rate from End Of Induction		
Patients in PR at end of induction	222	271
Conversion from PR to CR	97 (43.7%)	134 (49.4%)
Difference in rate (%) [95% CI]	5.7% [-3.1, 14.6%]	
Overall Response Rate at End of Maintenance		
Patients assessed at end of maintenance	533	525
Responders (%) (CR, PR)	341 (64.0%)	371 (70.7%)
Difference in response rate (%) [95% CI]	6.7% [1.0%, 12.4%]	
p-value (Cochran-Mantel-Haenszel test)	0.0197	
Complete response (CR)	195 (36.6%)	205 (39.0%)
95% CI Clopper-Pearson	[32.5%, 40.8%]	[34.9%, 43.4%]
Partial response (PR)	146 (27.4%)	166 (31.6%)
95% CI Clopper-Pearson	[23.7%, 31.4%]	[27.7%, 35.8%]

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Interval, NR = Not Reached

* Stratification factors were chemotherapy regimen, FLIPI risk group for follicular lymphoma, geographic region)

¶ Data Not Yet Mature. Median was not reached at time of analysis

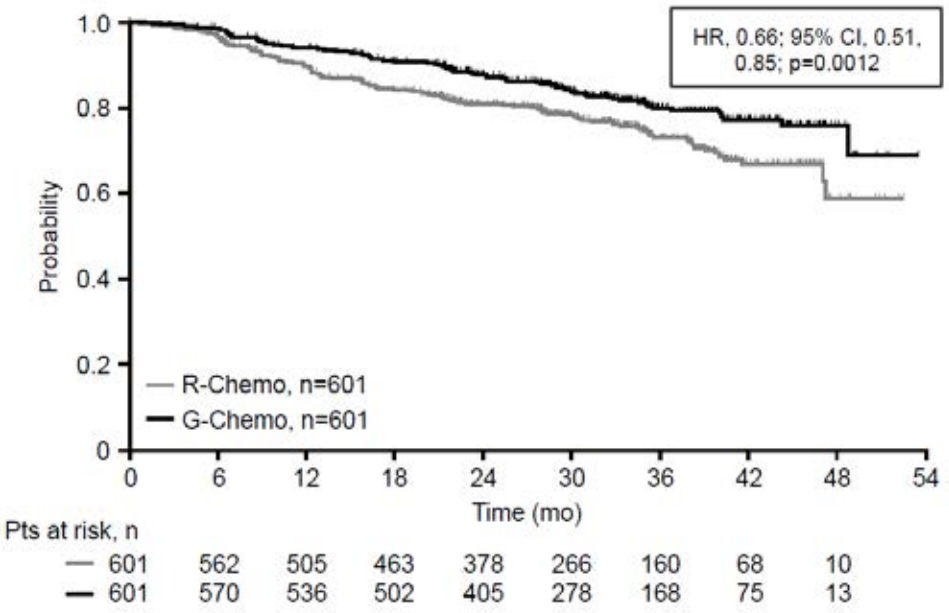
‡ End of Induction = end of Induction phase, does not include monotherapy maintenance

**Assessed as per modified Cheson 2007 criteria

§ Significance level at this efficacy interim analysis: 0.012

Response rates at the end of induction assessed by positron emission tomography (PET) were available for 297 of 601 patients in the Gazyva plus chemotherapy arm and 298 of 601 patients in the rituximab plus chemotherapy arm of the study. Complete response rates at end of induction as assessed by PET were 62.3% in the Gazyva plus chemotherapy arm and 56.7% in the rituximab plus chemotherapy arm. Overall response rates were similar in the two arms, with a difference of 4.3% in favour of the Gazyva plus chemotherapy arm (85.9% for G-chemo vs 81.5% for R-chemo). The differences were 4.3% (OR, 95% CI [-1.8,10.4], p=0.19) and 5.6% (CR, 95% CI [-2.5,13.6], p=0.28).

Figure 4 Kaplan-Meier estimates of INV-assessed progression-free survival in FL patients



R-Chemo: rituximab plus chemotherapy; G-Chemo: Gazyva plus chemotherapy; HR: hazard ratio; CI: confidence interval

Results of subgroup analyses

Results of subgroup analyses were, in general, consistent with the results seen in the FL population, supporting the robustness of the overall result. The subgroups evaluated included IPI, FLIPI, Chemo Regimen, Bulky Disease, B Symptoms at Baseline, Ann Arbor Stage and ECOG at Baseline.

Relapsed/Refractory Follicular Lymphoma

In a phase III, open-label, multicentre, randomised study (GAO4753g/GADOLIN), 396 patients with indolent NHL (iNHL), who had no response or who progressed during or up to 6 months after treatment, with rituximab or a rituximab-containing regimen, were evaluated. Patients were randomised 1:1 to receive either bendamustine (B) alone (n=202) or Gazyva in combination with bendamustine (G+B) (n=194) for 6 cycles, each of 28 days duration. Patients in the G+B arm who did not have disease progression [i.e. patients with a complete response (CR), partial response (PR) or stable disease (SD)] at the end of induction continued receiving Gazyva maintenance until disease progression or for up to two years (whichever occurred first).

The demographic data and baseline characteristics were well balanced [median age was 63 years; the majority of patients were Caucasian (88%) and male (58%)]. The median time from initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10); 44% of patients had received 1 prior therapy and 34% of patients had received 2 prior therapies. The majority of the patients had follicular lymphoma (FL) (81.1%). Of the non-follicular patients, 11.6% had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL).

Gazyva was given intravenously as a 1000 mg dose on Days 1, 8 and 15 of Cycle 1, on Day 1 of Cycles 2-6, and in patients who did not have disease progression, every 2 months for up to 2 years or until disease progression. Bendamustine was given intravenously on Days 1 and 2

for all treatment cycles (Cycles 1-6) at 90 mg/m^2/day when given in combination with Gazyva or 120 mg/m^2/day when given alone.

The primary analysis demonstrated a statistically significant and clinically meaningful 52% reduction in the risk of disease progression (PD) or death, based on IRC assessment, in patients with FL receiving G+B followed by G maintenance vs B alone (stratified log-rank test p value <=0.0001). IRC-assessed response rates at the end of induction treatment and IRC-assessed best overall response within 12 months of start of treatment were similar in the two treatment arms.

The majority of the patients in study GAO4753g had FL (81.1%). Efficacy results from the primary analysis in the FL population are shown in Table 14 and Figures 5 and 6. 11.6% of the patients had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL). In the non-FL population, the HR for IRC-assessed PFS was 0.94 [95% CI: 0.49, 1.90]. No definitive conclusions could be drawn on efficacy in the MZL and SLL sub-populations.

At final analysis, the median observation time was 45.9 months (range: 0-100.9 months) for FL patients in the B arm and 57.3 months (range: 0.4-97.6 months) for patients in the G+B arm, representing an additional 25.6 months and 35.2 months of median follow-up in B and G+B arms, respectively, since the primary analysis. Only Investigator (INV) assessed endpoints were reported at final analysis since IRC assessments did not continue. Overall, the efficacy results were consistent with what was observed in the primary analysis. The overall survival (OS) in patients with FL was stable with longer follow-up (see Figure 6); the HR for risk of death was 0.71 (95%CI: 0.51, 0.98).

Table 14 Summary of primary efficacy analysis in FL patients from GAO4753g (GADOLIN) study

	Bendamustine n=166	**G+B followed by Gazyva maintenance n=155**
	Median observation time 20 months	**Median observation time 22 months**
Primary Endpoint in FL population		
IRC-assessed PFS (PFS-IRC)		
Number (%) of patients with event	90 (54.2%)	54 (34.8%)
Median duration of PFS (months)	13.8	NR
HR [95% CI]	0.48 [0.34, 0.68]	
p-value (Log-Rank test, stratified*)	<0.0001	
Secondary Endpoints		
Investigator-assessed PFS (PFS-INV)		
Number (%) of patients with event	102 (61.4%)	62 (40.0%)
Median duration of PFS (months)	13.7	29.2
HR [95% CI]	0.48 [0.35, 0.67]	
p-value (Log-Rank test, stratified*)	<0.0001	

	Bendamustine n=166	**G+B followed by Gazyva maintenance n=155**
Best Overall Response (BOR) (IRC-assessed)§		
No. of patients included in the analysis	161	153
Responders (%) (CR, PR)	124 (77.0%)	122 (79.7%)
Difference in response rate (%) [95% CI]	2.72 [-6.74, 12.18]	
p-value (Cochran-Mantel-Haenszel test)	0.6142¶	
Duration of response (IRC-assessed)		
No. of patients included in the analysis	127	122
No. (%) of patients with event	74 (58.3%)	36 (29.5%)
Median duration of response (months)	11.9	NR
HR [95% CI]	0.36 [0.24, 0.54]	
Overall Survival		
No. (%) of patients with event	36 (21.7%)	25 (16.1%)
Median time to event (months)	NR¶	NR¶
HR [95% CI]	0.71 [0.43, 1.19] ¶	
p-value (Log-Rank test, stratified*)	0.1976¶†	
Overall Response Rate at End of Induction‡ **(IRC-assessed)**		
Patients assessed at end of treatment	155	149
Responders (%) (CR, PR)	97 (62.6%)	105 (70.5%)
Difference in response rate (%) [95% CI]	7.89 [-3.05, 18.83]	
p-value (Cochran-Mantel-Haenszel test)	0.1713	
Complete response (CR)	21 (13.5%)	14 (9.4%)
Partial response (PR)	76 (49.0%)	91 (61.1%)
Stable disease (SD)	15 (9.7%)	12 (8.1%)
Progressive disease (PD)	15 (9.7%)	15 (10.1%)
Unable to evaluate (UE)	4 (2.6%)	3 (2.0%)
Missing (NA)	24 (15.5%)	14 (9.4%)

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, NR = Not Reached

* Stratification factors were iNHL subtype (follicular vs. non-follicular: not used in analysis of patients with FL), refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs. > 2)

§ Best response within 12 months of start of treatment

¶ Data Not Yet Mature

‡ End of Induction = end of Induction phase, does not include monotherapy maintenance

Figure 5 Kaplan-Meier curve of IRC-assessed PFS in FL patients from GAO4753g (GADOLIN) study

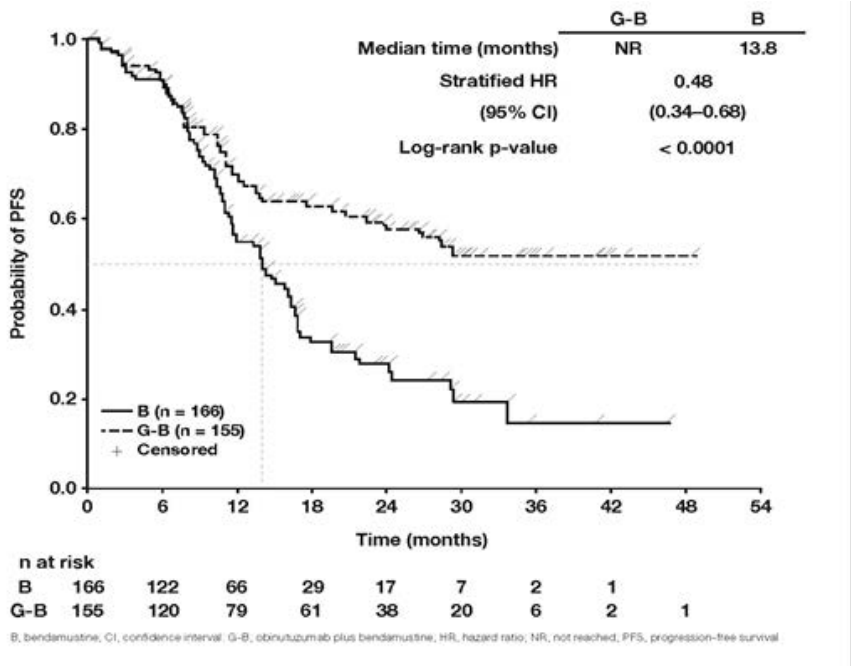
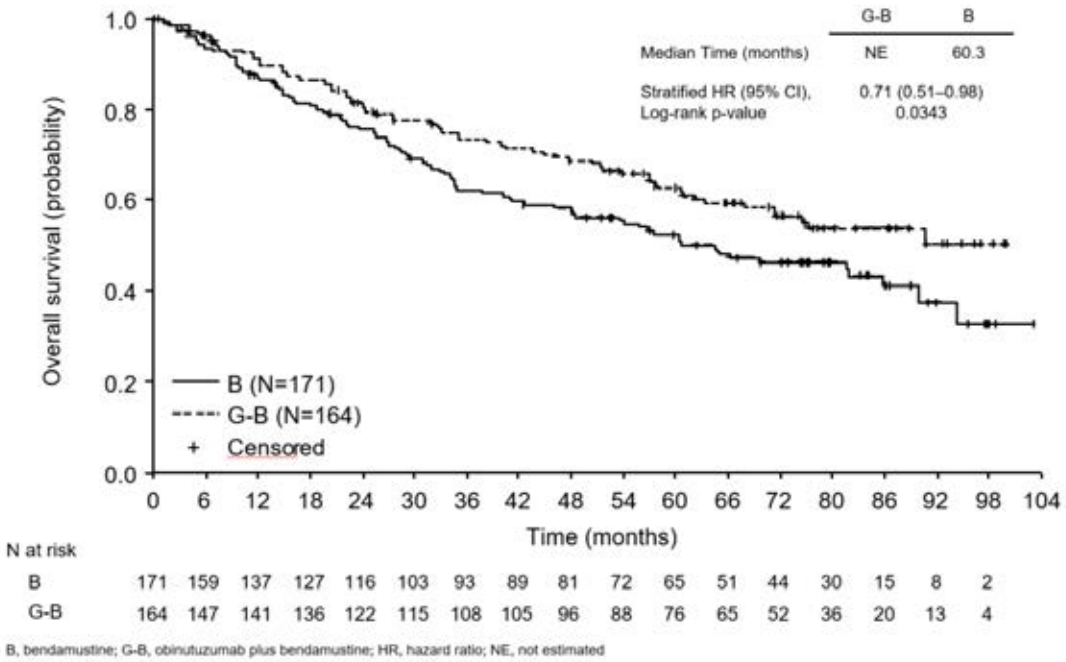


Figure 6 Kaplan-Meier curve of Overall Survival in FL patients at final analysis from GAO4753g (GADOLIN) study



Results of subgroup analyses

Results of subgroup analyses were in general consistent with the results seen in the overall FL population, supporting the robustness of the overall result.

Short Duration Infusion Study (MO40597/GAZELLE)

The safety of short (approximately 90 minutes) duration infusion (SDI) of obinutuzumab administered in combination with CHOP, CVP or bendamustine chemotherapy was evaluated in a multicentre, open-label, single arm study in 113 patients with previously untreated advanced follicular lymphoma (Study MO40597/GAZELLE).

Patients received the first cycle of obinutuzumab at the standard infusion rate on Day 1, 8, and 15 of Cycle 1. Patients who did not experience any Grade ≥3 IRRs during the first cycle received SDI from Cycle 2 onwards.

The primary endpoint of the study was the proportion of patients who experienced a Grade ≥3 IRR associated with SDI during Cycle 2, among those who had previously received 3 administrations of obinutuzumab at the standard infusion rate during Cycle 1 without experiencing a Grade ≥3 IRR.

No Grade ≥3 IRRs were observed among patients receiving SDI at Cycle 2. After Cycle 2 only one patient experienced a Grade 3 IRR (hypertension at Cycle 5). See Section 4.8 Adverse Effects (Undesirable Effects).

Patient Reported Outcomes

Previously Untreated Follicular Lymphoma

Based on the FACT-Lym questionnaire collected during treatment and follow-up periods, both arms experienced clinically meaningful improvements in lymphoma-related symptoms as defined by a ≥ 3 point increase from baseline in the Lymphoma subscale, a ≥ 6 point increase from baseline in the FACT Lym TOI and a ≥ 7 point increase from baseline in the FACT Lym Total score. EQ-5D utility scores were similar at baseline, during treatment and follow-up. No meaningful differences were seen between the arms in health-related quality of life (HRQoL) or health status measures.

Relapsed/refractory Follicular Lymphoma

Based on the FACT-Lym questionnaire and EQ-5D index scale collected during the treatment and follow-up periods, HRQoL was generally maintained in the pivotal study with no meaningful difference between the arms. However, the addition of Gazyva to bendamustine delayed the time to worsening of quality of life as measured by the FACT-Lym TOI score (HR=0.83; 95% CI: 0.60, 1.13).

Pre-treatment to reduce the risk of CRS induced by glofitamab

Gazyva was used as a pre-treatment to reduce the risk of CRS induced by glofitamab in study NP30179, a Phase I/II, multicentre, open-label, dose-escalation study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of glofitamab as a single agent following pre-treatment with a fixed dose of Gazyva. All patients dosed with glofitamab monotherapy received Gazyva by intravenous infusion 1000 mg 7 days prior to the first dose glofitamab. Pre-treatment with obinutuzumab 1000 mg was well tolerated in study NP30179. In the overall safety population (n = 424), 67.5% of patients (286/424) had B-cell counts < 70 cells/µL at study entry. Following Gazyva and prior to glofitamab administration, almost all patients had B-cell counts < 70 cells/µL (97.5% [314/322] at Cycle 1, Day 7 [C1D7], 95%

[40/42] at C1D8), reflecting the depletion of peripheral B cells with Gazyva. No new safety concerns were identified. Refer to the glofitamab Product Information for more information.

Immunogenicity

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, assay robustness to quantities of Gazyva/antibody in circulation, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Gazyva with the incidence of antibodies to other products may be misleading.

Patients in the pivotal CLL trial, BO21004/CLL11, were tested at multiple time-points for anti therapeutic antibodies (ATA) to Gazyva. In Gazyva treated patients, 8 out of 140 in the randomised phase and 2 out 6 in the run-in phase tested positive for ATA at 12 months of follow-up. Of these patients, none experienced either anaphylactic or hypersensitivity reactions that were considered related to ATA, nor was clinical response affected.

No post-baseline Human Anti-Human Antibody (HAHA) were observed in patients with iNHL treated in study GAO4753g/GADOLIN. In study BO21223/GALLIUM, 1/565 patient (0.2% of patients with a post-baseline assessment) developed HAHA at induction completion. While the clinical significance of HAHA is not known, a potential correlation between HAHA and clinical course cannot be ruled out.

5.2 PHARMACOKINETIC PROPERTIES

A population pharmacokinetic (PK) model was developed to analyse the PK data in 469 patients with indolent non-Hodgkin lymphoma (iNHL), 342 patients with chronic lymphocytic leukaemia (CLL), and 130 patients with diffuse large B-cell lymphoma who received Gazyva in phase I, phase II and phase III studies. From the population PK model, after the Cycle 6 Day 1 infusion in CLL patients, the C_{max} value was 465.7 µg/mL and $AUC_{(T)}$ value was 8,961 µg*d/mL. In iNHL patients the estimated median C_{max} value was 539.3 µg/mL and $AUC_{(T)}$ value was 10,956 µg*d/mL.

Absorption

Obinutuzumab is administered intravenously. There have been no clinical studies performed with other routes of administration.

Distribution

Following intravenous administration, the volume of distribution of the central compartment (2.72 L), approximates serum volume, which indicates distribution is largely restricted to plasma and interstitial fluid.

Metabolism

The metabolism of obinutuzumab has not been directly studied. Antibodies are mostly cleared by catabolism.

Excretion

The clearance of obinutuzumab was approximately 0.11 L/day in CLL patients and 0.08 L/day in iNHL patients with a median elimination t½ 26.4 days in CLL patients and 36.8 days in iNHL patients.

Obinutuzumab elimination comprises two parallel pathways which describe clearance, a linear clearance pathway and a non-linear clearance pathway which changes as a function of

time. During initial treatment, the non-linear time-varying clearance pathway is dominant and is consequently the major clearance pathway. As treatment continues, the impact of this pathway diminishes and the linear clearance pathway predominates. This is indicative of target mediated drug disposition (TMDD), where the initial abundance of CD20 cells causes rapid removal of obinutuzumab from the circulation. However, once the majority of CD20 cells are bound with obinutuzumab, the impact of TMDD on PK is minimised.

Pharmacokinetics in special populations

In the population PK analyses, gender was found to be a covariate which explains some of the inter-patient variability, with an 18% greater steady state clearance (CLss) and a 19% greater volume of distribution (V) in males. However, results from the population analyses have shown that the differences in exposure between genders are not clinically important (with an estimated median AUC and C_{max} in CLL patients of 11,282 µg*d/mL and 578.9 µg/mL in females and 8,451 µg*d/mL and 432.5 µg/mL in males, respectively at Cycle 6, and AUC and C_{max} in iNHL patients of 13,172 µg*d/mL and 635.7 µg/mL in females and 9,769 µg*d/mL and 481.3 µg/mL in males, respectively), indicating that there is no need to dose adjust based on gender.

Elderly Patients

The population pharmacokinetic analysis of obinutuzumab showed that age did not affect the pharmacokinetics of obinutuzumab. No significant difference was observed in the pharmacokinetics of obinutuzumab among patients < 65 years (n=454), patients between 65-75 years (n=317) and patients > 75 years (n=190).

Paediatric Patients

No studies have been conducted to investigate the pharmacokinetics of obinutuzumab in children.

Renal impairment

The population pharmacokinetic analysis of obinutuzumab showed that creatinine clearance does not affect the pharmacokinetics of obinutuzumab. Pharmacokinetics of obinutuzumab in patients with mild creatinine clearance (CrCl 50 to 89 mL/min, n=464) or moderate (CrCl 30 to 49 mL/min, n=106) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=383). PK data in patients with severe renal impairment (CrCl 15-29 mL/min) is limited (n=8), therefore no dosage recommendations can be made.

Hepatic impairment

No formal PK study has been conducted and no population PK data was collected in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been performed to establish the mutagenic potential of Gazyva.

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Gazyva.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Poloxamer 188

6.2 INCOMPATIBILITIES

No incompatibilities between Gazyva and polyvinyl chloride, polyethylene, polypropylene or polyolefine bags, polyvinyl chloride, polyurethane, or polyethylene infusion sets, as well as optional inline filters with product contact surfaces of polyethersulfon, a 3-way stopcock infusion aid made from polycarbonate, and catheters made from polyetherurethane have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of Gazyva with 0.9% sodium chloride.

Diluted product should not be shaken or frozen. Do not use other diluents such as dextrose (5%) solution to dilute Gazyva since their use has not been tested.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Gazyva does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

Diluted solution

Physical and chemical stability of the prepared infusion solution of Gazyva has been demonstrated for 24 hours at 2°C - 8°C followed by 24 hours at ambient temperature (≤ 30°C) followed by an infusion taking no longer than 24 hours. To reduce microbiological hazard, the prepared infusion solution should be used immediately. If storage is necessary, hold at 2°C - 8°C for not more than 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vial in a refrigerator at 2°C - 8°C. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

For storage conditions after dilution of the medicine, see section 6.3 Shelf Life.

6.5 NATURE AND CONTENTS OF CONTAINER

Gazyva 40 mL concentrate solution for infusion (25mg/mL) in a sterile, preservative free, non-pyrogenic 50 mL vial (clear Type I glass).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

Gazyva (obinutuzumab) is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype.

CAS number

CAS: 949142-50-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

15 May 2014

10. DATE OF REVISION OF THE TEXT

29 October 2024

Summary table of changes

Section Changed	Summary of new information
4.8	Addition of adverse reaction hypogammaglobulinaemia