IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

DOSING INFORMATION FOR RITUXAN+FC

The regimen that drives longer progression-free survival (PFS) in CLL compared with FC alone[1]

Indication

RITUXAN® (Rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

RITUXAN is not recommended for use in patients with severe, active infections.

Please see the back of this brochure for safety information, including **BOXED WARNINGS**.

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ESTABLISHED SAFETY PROFILE

THE MAJORITY OF PATIENTS COMPLETED THERAPY[1,2]

Cycle completion by R-FC–treated patients in the Phase III CLL8 and REACH trials

6 CYCLES OF THERAPY WERE ADMINISTERED TO MOST PATIENTS

- 75% of patients in the CLL8 trial received 6 cycles of therapy
- 66% of patients in the REACH trial received 6 cycles of therapy

In the first-line CLL8 trial

- Grade 3 and 4 adverse reactions occurred in 77% of R-FC–treated patients vs 62% of FC-treated patients[2]
  - — Safety data collection in CLL8 was limited to Grade 3 or 4, and serious adverse reactions[1]
- Grade 3 or 4 adverse reactions that occurred more frequently (≥2%) in patients treated with R-FC vs FC were neutropenia (30% vs 19%), febrile neutropenia (9% vs 6%), leukopenia (23% vs 12%), and pancytopenia (3% vs 1%)[1]
- Grade 3 or 4 infusion-related adverse reactions[§] occurred in 9% of patients treated with R-FC[1]
- Grade 3 or 4 infections observed during the trial were similar between treatment arms (18% R-FC vs 17% FC)[2]
- Grade 3 or 4 adverse reactions that occurred more frequently in R-FC–treated patients ≥70 years of age compared with R-FC–treated patients <70 years of age were neutropenia (44% vs 31%), febrile neutropenia (16% vs 6%), pancytopenia (7% vs 2%), and anemia (5% vs 2%)[1]

In the REACH trial of previously treated RITUXAN-naive patients

- The most common (≥25%) adverse reactions were neutropenia, nausea, and pyrexia[2]
- Grade 3 or 4 adverse reactions occurred in 80% of R-FC–treated patients vs 74% of FC-treated patients[2]
- Grade 3 or 4 adverse reactions that occurred more frequently (≥2%) in patients treated with R-FC vs FC were neutropenia (49% vs 44%), febrile neutropenia (15% vs 12%), thrombocytopenia (11% vs 9%), hypotension (2% vs 0%), and hepatitis B (2% vs <1%)[1]
- 59% of R-FC–treated patients experienced an infusion-related adverse reaction[§]; 7% of reactions were Grade 3 or 4[1]
- Grade 3 or 4 infections observed during the trial were similar between treatment arms (18% R-FC vs 19% FC)[2]
- Grade 3 or 4 adverse reactions that occurred more frequently in R-FC–treated patients ≥70 years of age compared with R-FC–treated patients <70 years of age were neutropenia (56% vs 39%), infections (30% vs 14%), anemia (21% vs 10%), thrombocytopenia (19% vs 8%), and pancytopenia (7% vs 2%)[1]

[§]Infusion-related adverse reactions were defined as any of the following adverse reactions occurring within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea.

RITUXAN—DOSING THAT DRIVES PATIENT OUTCOMES IN CLL

DOSING USED IN 2 LARGE RANDOMIZED TRIALS, INCLUDING MORE THAN 1,300 PATIENTS[1]

The R-FC regimen: Dosing in the first-line and previously treated* settings[1,2]

	Cycle 1	Cycles 2–6
R RITUXAN	**375 mg/m²** given on the **day prior** to the **first cycle** of FC	**500 mg/m²** given on **Day 1** of **subsequent cycles**
F Fludarabine	**25 mg/m²** given on Days 1–3 of **all cycles**	
C Cyclophosphamide	**250 mg/m²** given on Days 1–3 of **all cycles**	

Each cycle is 28 days in length.

*In the REACH trial, patients had received 1 prior therapy. Patients who had previously received RITUXAN, or both fludarabine and cyclophosphamide, either sequentially or in combination, were excluded from the trial, as were fludarabine-refractory patients; alkylator-refractory patients were permitted.[2]

Treatment considerations

- The CLL8 and REACH trials were not designed or powered to detect a significant difference in PFS by age category. However, exploratory analyses defined by age suggest no observed benefit with the addition of RITUXAN to FC chemotherapy in previously untreated CLL patients 70 years of age or older and in previously treated CLL patients 65 years of age or older[1]

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R-FC—MANAGEMENT STRATEGIES TO HELP PATIENTS STAY ON THERAPY

CHEMOTHERAPY DOSE MODIFICATIONS AS PER CLINICAL TRIALS[1,2]

FC dose modifications for myelosuppression

If patient experienced a Grade 3 or 4 cytopenia[†] • **Neutropenia** • **Anemia** • **Thrombocytopenia**	In both the CLL8 and REACH trials: • The next cycle of therapy was **delayed** for up to 2 weeks • The dose of FC was **reduced** by 25% for all subsequent cycles • The planned dose of RITUXAN was **maintained** at 500 mg/m^2
If patient experienced a second Grade 3 or 4 cytopenia[†]	In both the CLL8 and REACH trials: • The next cycle of therapy was **delayed** for up to 2 weeks • The dose of FC was **further reduced** by 25% for all subsequent cycles • The planned dose of RITUXAN was **maintained** at 500 mg/m^2
If patient continued to experience Grade 3 or 4 cytopenias[†] at time of next scheduled dose	In the CLL8 trial: • The next cycle of therapy was **delayed** for up to 2 weeks. If cytopenia did not resolve, therapy, including RITUXAN, was **discontinued** In the REACH trial: • Therapy, including RITUXAN, was **discontinued**

[†]Cytopenias were measured on Day 28 of each dosing cycle.

- In both trials, patients 70 years of age or older received a lower dose intensity of fludarabine and cyclophosphamide compared with younger patients, regardless of the addition of RITUXAN[1]
- In the CLL8 trial, the dose intensity of RITUXAN was similar in older and younger patients[1]
- In the REACH trial, older patients received a lower dose intensity of RITUXAN[1]

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SUPPORTIVE CARE WAS ADMINISTERED IN BOTH CLL8 AND REACH[2]

In the CLL8 trial of first-line CLL	In the REACH trial of previously treated RITUXAN-naive CLL
G-CSF was administered if a patient experienced Grade 3 or 4 neutropenia with fever or hypothermia.	G-CSF was administered at the investigator's discretion and also for all patients who experienced Grade 3 or 4 febrile neutropenia.

G-CSF=granulocyte colony–stimulating factor.

Premedication recommendations from the RITUXAN prescribing information[1]

- Patients should be premedicated with an antihistamine and acetaminophen prior to dosing
- A high number of circulating malignant cells (≥25,000/mm^3) or high tumor burden confers a greater risk of tumor lysis syndrome (TLS). Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS
- *Pneumocystis jiroveci* pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate

DOSE REDUCTIONS FOR PATIENTS WHO DEVELOPED IMPAIRED RENAL FUNCTION ON STUDY[2]

In the CLL8 trial of first-line CLL	In the REACH trial of previously treated RITUXAN-naive CLL
• CrCL 30–70 mL/min: Fludarabine dose was **reduced** by 20% and cyclophosphamide dose was **reduced** by 25% • CrCL <30 mL/min: **Discontinued** FC therapy	• CrCL 31–70 mL/min: Fludarabine dose was **reduced** by 25% for remainder of study‡ • CrCL ≤30 mL/min: Treatment was **delayed** for up to 2 weeks — If CrCL >30 mL/min, treatment was **restarted** at 75% of planned dose and patient was closely monitored — If CrCL ≤30 mL/min, treatment was permanently **discontinued**

‡The dose of fludarabine was not increased if renal function improved.

CrCL=creatinine clearance.

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Indication and Important Safety Information

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WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Infusion Reactions: RITUXAN administration can result in serious, including fatal, infusion reactions. Deaths within 24 hours of RITUXAN infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue RITUXAN infusion and provide medical treatment for Grade 3 or 4 infusion reactions.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) with RITUXAN monotherapy.

Severe Mucocutaneous Reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving RITUXAN.

Progressive Multifocal Leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving RITUXAN.

Warnings and Precautions

RITUXAN has also been associated with other serious and/or fatal adverse reactions. These include

- hepatitis B reactivation with fulminant hepatitis; hepatic failure resulting in death
- serious, including fatal, bacterial, fungal and new or reactivated viral infections
- cardiovascular events, including serious or life-threatening cardiac arrhythmias
- severe, including fatal, renal toxicity
- abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving RITUXAN in combination with chemotherapy

Additional Important Safety Information

- The most common adverse reactions of RITUXAN (incidence ≥25%) observed in clinical trials of patients with CLL were infusion reactions and neutropenia. Infusion-related adverse reactions occurring during or within 24 hours of the start of infusion included nausea, pyrexia, chills, hypotension, vomiting, and dyspnea. Most patients treated with R-FC experienced at least one Grade 3 or 4 adverse reaction. Grade 3 or 4 adverse reactions observed more frequently with R-FC compared with FC alone were neutropenia, leukopenia, febrile neutropenia, thrombocytopenia, infusion reactions, pancytopenia, hypotension, and hepatitis B
- In clinical trials, CLL patients 70 years of age or older who received R-FC had more Grade 3 and 4 adverse reactions compared with younger CLL patients who received the same treatment

For additional safety information, please see the accompanying full prescribing information, including **BOXED WARNINGS** and Medication Guide.

Attention Healthcare Provider: Provide Medication Guide to patient prior to RITUXAN infusion.

References: 1. RITUXAN® (Rituximab) full prescribing information, Genentech, Inc., 2010.
2. Data on file, Genentech, Inc.

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