R^2 REVLIMID/RITUXIMAB

AT NEXT RELAPSE IN FL OR MZL,

TAKE PATIENTS FURTHER WITH R^2 VS RITUXIMAB ALONE

REVLIMID® (lenalidomide) in combination with a rituximab product is indicated for the treatment of adult patients with previously treated follicular lymphoma (FL)

REVLIMID in combination with a rituximab product is indicated for the treatment of adult patients with previously treated marginal zone lymphoma (MZL)

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials

REVLIMID is only available through a restricted distribution program, Lenalidomide REMS

Revlimid® (lenalidomide) capsules
2.5 · 5 · 10 · 15 · 20 · 25 mg

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the Lenalidomide REMS program.

Information about the Lenalidomide REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous and Arterial Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

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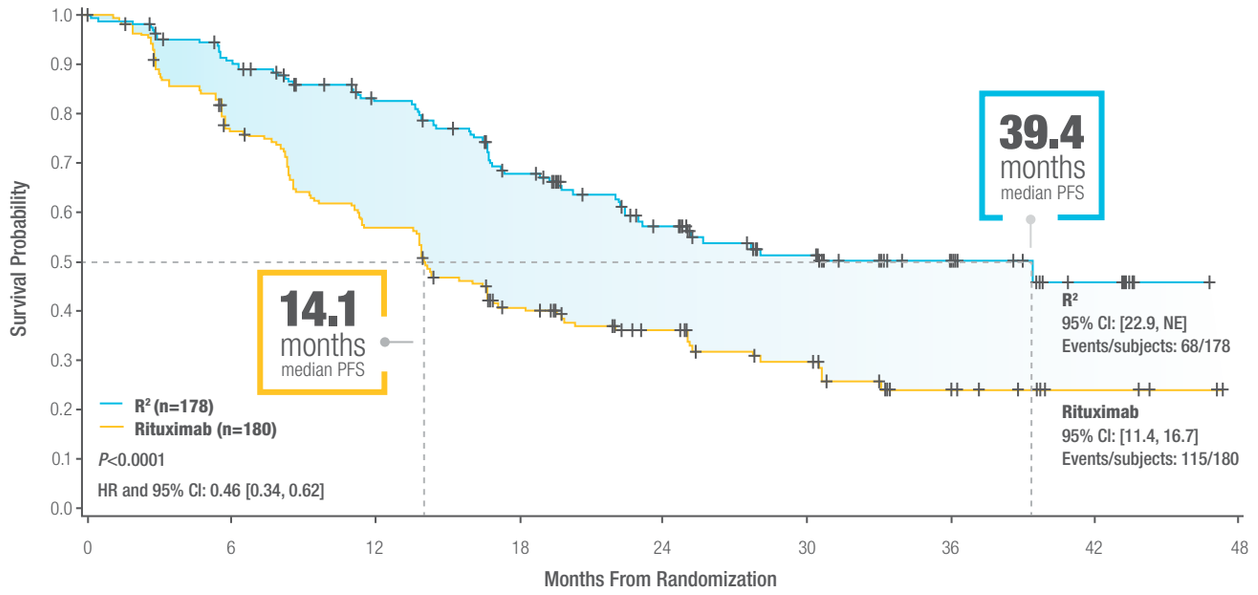
ITT Population (N=358)

R² SIGNIFICANTLY DELAYED THE RETURN OF RELAPSE VS RITUXIMAB ALONE[1]



Number of Subjects at Risk

R²	178	148	124	91	59	39	20	7	0
Rituximab	180	132	92	58	40	26	10	4	0

IN THE FL SUBGROUP (n=295), THE MEDIAN PFS WAS 39.4 MONTHS (95% CI: [23.1, NE]) IN THE R² ARM AND 13.9 MONTHS (95% CI: [11.2, 16.0]) WITH RITUXIMAB (HR AND 95% CI: 0.40 [0.29, 0.56])[2]

- **ANALYSIS LIMITATIONS**: PFS in the FL subgroup is exploratory in nature and data should not be interpreted to determine a treatment difference between arms due to a higher possibility of a false positive

PIVOTAL TRIAL DESIGN

- AUGMENT, a Phase III, multicenter, randomized trial of lenalidomide plus rituximab (R²) versus rituximab plus placebo, was conducted in 358 patients with previously treated Grade 1-3a FL (n=295) or MZL (n=63). Patients had been refractory or relapsed, not rituximab-refractory, and had adequate bone marrow, liver, and renal function. The ITT population included all patients randomized to the R² (n=178) and rituximab plus placebo (n=180) arms[1,3]
- At baseline, patients had a median age of 63 years (range, 26-88) and had received a median of 1 prior line of systemic therapy (range, 1-12). Seventy-three percent (73%) of patients had Ann Arbor Stage III-IV disease[1,3]
- The primary endpoint for the trial was PFS, defined as the time from date of randomization to first documentation of disease progression (by independent review committee using 2007 IWGRC without PET) or death due to any cause, whichever occurred first. Median follow-up time was 28.3 months (0.1, 51.3 months) in the ITT population[2]
- The starting dose of REVLIMID® (lenalidomide) was 20 mg orally on Days 1-21 of repeating 28-day cycles for 12 cycles or until unacceptable toxicity. The dose of rituximab was 375 mg/m² on Days 1, 8, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2-5 every 28 days[1]

CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; ITT, intent to treat; IWGRC, International Working Group Response Criteria; MZL, marginal zone lymphoma; NE, non-estimable; PET, positron emission tomographic imaging; PFS, progression-free survival.

IMPORTANT SAFETY INFORMATION (CONTINUED)

CONTRAINDICATIONS

Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (eg, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

Please see full Prescribing Information, including Boxed WARNINGS for REVLIMID, and Important Safety Information continued on next page. Please see the rituximab full Prescribing Information for Important Safety Information at www.rituxan.com.

Safety Population (N=356)

MANAGEABLE SAFETY PROFILE

MEDIAN TREATMENT DURATION WITH R² WAS 11.2 MONTHS²

- 71% of patients receiving R² completed all 12 cycles of treatment vs 62% receiving rituximab/placebo²
  - **Dose reduction (at least 1):** 36.4% of patients receiving R² vs 7.2% receiving rituximab/placebo²
  - **Dose interruption (at least 1):** 79.5% of patients receiving R² vs 54.4% receiving rituximab/placebo²

ALL GRADE ARs (≥20% OF PATIENTS)[1]

Body System Adverse Reaction[a]	All Adverse Reactions[b]		Grade 3/4 Adverse Reactions[c]	
	R² (n=176)	Rituximab (n=180)	R² (n=176)	Rituximab (n=180)
Neutropenia[d,e,f]	58%	22%	50%	13%
Diarrhea[e,f]	31%	23%	2.8%	0%
Constipation	26%	14%	0%	0%
Cough[g]	24%	19%	<1%	0%
Fatigue	22%	18%	1.1%	<1%
Rash[e,h]	22%	8%	2.8%	1.1%
Pyrexia[d,e]	21%	15%	<1%	1.7%
Leukopenia[e,f]	20%	9%	7%	1.7%
Pruritus[e,i]	20%	5%	1.1%	0%

ADR, adverse drug reaction; AR, adverse reaction; PT, preferred term; TEAE, treatment-emergent adverse event.

- Grade 3/4 neutropenia was reported in 50% of patients in the R² arm and 13% of patients in the rituximab arm[1]
  - All incidences of Grade 3/4 neutropenia in the R² arm recovered to Grade 1 or less, with a median time of 9 days²
- Patients receiving R² had an incidence of febrile neutropenia of 3% vs <1% with rituximab[1]

Note: ARs are coded to body system/AR using MedDRA 21. A patient with multiple occurrences of an AR is counted only once under the applicable body system/AR.
[a]ARs for combined ADR terms (based on relevant TEAE PTs [per MedDRA version 21.0]):
[b]All treatment-emergent ARs in at least 5% of patients in the REVLIMID + rituximab group and at least 1% higher frequency (%) than the rituximab + placebo group (control arm).
[c]All grade 3 or 4 treatment-emergent ARs in at least 1% of patients in the REVLIMID + rituximab group and at least 1% higher frequency (%) than the rituximab + placebo group (control arm).
[d]All serious treatment-emergent ARs in at least 1% of patients in the REVLIMID + rituximab group and at least 1% higher frequency (%) than the rituximab + placebo group (control arm).
[e]Serious ADR reported.
[f]ARs in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases).
[g]"Cough" combined AR term includes the following PTs: cough and productive cough.
[h]"Rash" combined AR term includes the following PTs: rash maculo-papular, rash erythematous, rash macular, rash papular, rash pruritic, and rash generalized.
[i]"Pruritus" combined AR term includes the following PTs: pruritus, pruritus generalized, rash pruritic, and pruritus allergic.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: See Boxed WARNINGS

- Females of Reproductive Potential: **See Boxed WARNINGS.**
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

Lenalidomide REMS Program: See Boxed WARNINGS: Prescribers and pharmacies must be certified with the Lenalidomide REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

Hematologic Toxicity: REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. Patients may require a dose interruption and/or dose reduction. Monitor complete blood counts (CBC) in patients taking REVLIMID for FL or MZL weekly for the first 3 weeks of Cycle 1 (28 days), every 2 weeks during Cycles 2-4, and then monthly thereafter.

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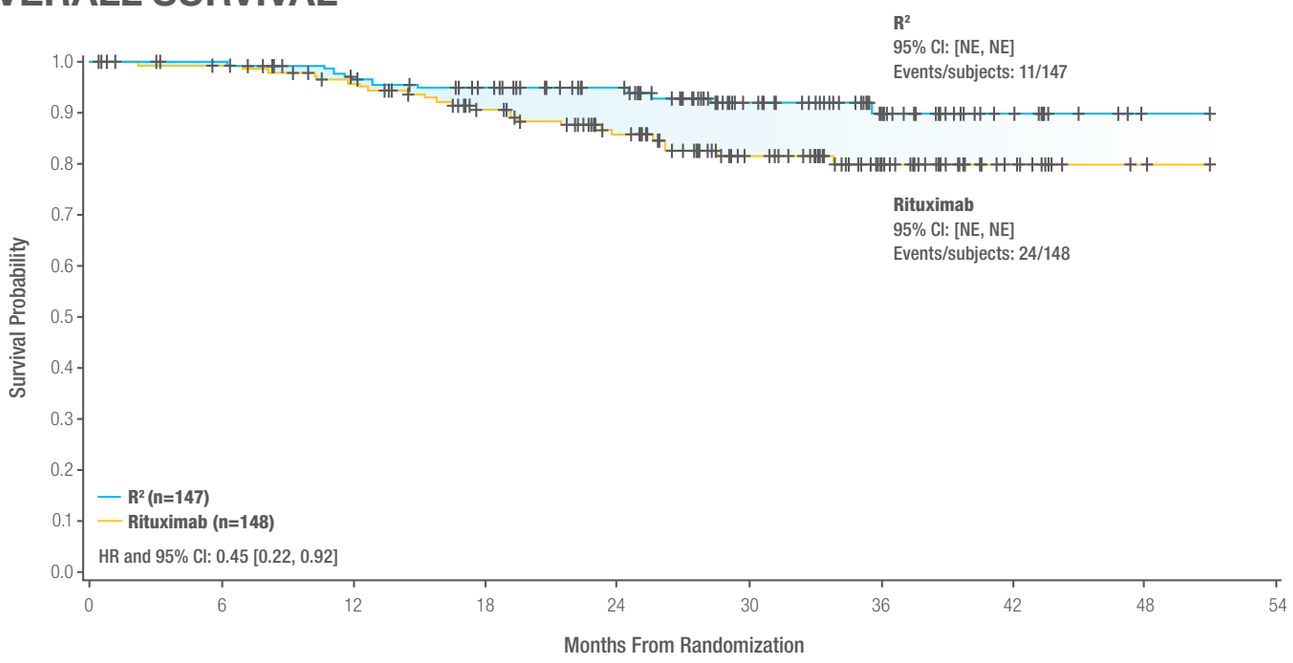
Follicular Lymphoma Population (n=295)

OVERALL SURVIVAL[2]*



Number of Subjects at Risk

R²	147	142	130	121	105	70	39	13	1	0
Rituximab	148	145	137	117	94	64	35	12	2	0

- Median OS has not been reached†
- **ANALYSIS LIMITATIONS:** OS was a secondary endpoint. These FL subgroup data are exploratory in nature and should not be interpreted to determine a treatment difference between arms due to a higher possibility of a false positive

OVERALL RESPONSE RATE AND DURATION OF RESPONSE

- **ORR:** 80.3% of patients receiving R² and 55.4% of patients receiving rituximab achieved a response[2‡]
  - **CRR:** 34.7% of patients receiving R² and 19.6% of patients receiving rituximab achieved a CR[2]
- **DOR:** Median DOR to R² was 36.6 months and 15.5 months with rituximab[2§]
- **ANALYSIS LIMITATIONS:** ORR and DOR were secondary endpoints. These FL subgroup data are exploratory in nature and should not be interpreted to determine a treatment difference between arms due to a higher possibility of a false positive

CI, confidence interval; CR, complete response; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; HR, hazard ratio; IRC, independent review committee; ITT, intent to treat; NE, non-estimable; ORR, overall response rate; OS, overall survival; PR, partial response.
*OS was calculated as the time from randomization to death from any cause.[2]
†Median follow-up time was 28.3 months (0.1, 51.3 months) in the ITT population.[2]
‡ORR was measured by objective response (by IRC) and included patients achieving a CR or PR.[2]
§DOR was defined as the time from initial response (at least PR) until documented progressive disease or death.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Venous and Arterial Thromboembolism: See Boxed WARNINGS: Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVLIMID. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (eg, hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended and the regimen should be based on the patient's underlying risks. Erythropoietin-stimulating agents (ESAs) and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision.

Increased Mortality in Patients With CLL: In a clinical trial in the first-line treatment of patients with CLL, single-agent REVLIMID therapy increased the risk of death as compared to single-agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in the REVLIMID arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Please see full Prescribing Information, including Boxed WARNINGS for REVLIMID, and Important Safety Information continued on next page. Please see the rituximab full Prescribing Information for Important Safety Information at www.rituxan.com.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Second Primary Malignancies (SPM): In clinical trials in patients with MM receiving REVLIMID and in patients with FL or MZL receiving REVLIMID + rituximab therapy, an increase of hematologic plus solid tumor SPM, notably AML, have been observed. In patients with MM, MDS was also observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment.

Increased Mortality With Pembrolizumab: In clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with MM with a PD–1- or PD–L1-blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Severe Cutaneous Reactions: Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

Tumor Lysis Syndrome (TLS): Fatal instances of TLS have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

Tumor Flare Reaction (TFR): TFR has occurred during investigational use of REVLIMID for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL or MZL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion.

Impaired Stem Cell Mobilization: A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

Thyroid Disorders: Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before starting REVLIMID treatment and during therapy.

Early Mortality in Patients With MCL: In another MCL study, there was an increase in early deaths (within 20 weeks); 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline ($\geq 10 \times 10^9$/L).

Hypersensitivity: Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for angioedema and anaphylaxis.

ADVERSE REACTIONS

Follicular Lymphoma/Marginal Zone Lymphoma

- Fatal adverse reactions occurred in 6 patients (1.5%) receiving REVLIMID + rituximab across both trials. Fatal adverse reactions (1 each) included: cardio-respiratory arrest, arrhythmia, cardiopulmonary failure, multiple organ dysfunction syndrome, sepsis, and acute kidney injury. The most frequent serious adverse reaction that occurred in the REVLIMID + rituximab arm was febrile neutropenia (3.0%).
- Grade 3 and 4 adverse reactions reported in ≥5% of patients treated in the FL/MZL trial with REVLIMID + rituximab were: neutropenia (50%) and leukopenia (7%).
- Adverse reactions reported in ≥15% of patients with FL/MZL treated with REVLIMID + rituximab were: neutropenia (58%), diarrhea (31%), constipation (26%), cough (24%), fatigue (22%), rash (22%), pyrexia (21%), leukopenia (20%), pruritus (20%), upper respiratory tract infections (18%), abdominal pain (18%), anemia (16%), headache (15%), thrombocytopenia (15%).

DRUG INTERACTIONS

Periodically monitor digoxin plasma levels due to increased C_{max} and AUC with concomitant REVLIMID therapy. Patients taking concomitant therapies such as ESAs or estrogen-containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

USE IN SPECIFIC POPULATIONS

- **PREGNANCY: See Boxed WARNINGS:** If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Please see full Prescribing Information, including Boxed WARNINGS for REVLIMID, and Important Safety Information continued on next page. Please see the rituximab full Prescribing Information for Important Safety Information at www.rituxan.com.

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R² REVLIMID/RITUXIMAB

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Lenalidomide (REVLIMID) + rituximab is a preferred treatment option (Category 2A) recommended in the NCCN Guidelines® for second-line and subsequent therapy for patients with Grade 1-2 FL and nodal or extra nodal MZL[4]

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

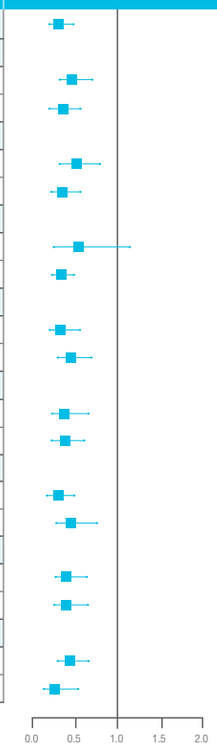
BASELINE CHARACTERISTICS OF AUGMENT PATIENT POPULATION (N=358)

- **Median age:** 63 years (range: 26-88)[1,3]
- **Ann Arbor Stage III-IV at enrollment:** 73%[2]
- **FL grade at diagnosis:** Grade 1 (31%), Grade 2 (38%), Grade 3a (13%)[2]
- **FLIPI high-risk:** 34%[2]
- **High tumor burden (GELF criteria):** 51%[1]
- **Bulky disease*:** 26%[2]
- **ECOG PS:** 0 (68%), 1 (31%), 2 (1%)[1]

Follicular Lymphoma Population (n=295)

PROGRESSION-FREE SURVIVAL ACROSS PRE-SPECIFIED SUBGROUPS[2]

Subgroup	R²	Rituximab	HR [95% CI]
Overall	56/147	99/148	0.40 [0.29, 0.56]
Age			
<65 years	37/86	60/94	0.47 [0.31, 0.71]
≥65 years	19/61	39/54	0.32 [0.18, 0.55]
Sex			
Male	28/61	55/80	0.50 [0.32, 0.79]
Female	28/86	44/68	0.35 [0.22, 0.57]
Ann Arbor stage at enrollment			
I-II	11/34	22/42	0.56 [0.27, 1.15]
III-IV	45/113	77/106	0.35 [0.24, 0.51]
FLIPI			
≥3	22/54	35/46	0.33 [0.19, 0.56]
<3	34/91	63/101	0.45 [0.30, 0.69]
Number of prior systemic anti-lymphoma regimens			
1	26/78	48/79	0.41 [0.25, 0.66]
>1	30/69	51/69	0.40 [0.25, 0.63]
High tumor burden (GELF)			
Yes	32/77	50/68	0.32 [0.20, 0.51]
No	24/70	49/80	0.45 [0.27, 0.73]
Time since last anti-lymphoma therapy			
≤2 years	32/77	54/78	0.41 [0.27, 0.64]
>2 years	24/70	45/70	0.39 [0.24, 0.65]
Prior rituximab-containing chemotherapy regimen			
Yes	43/108	74/108	0.45 [0.31, 0.66]
No	13/39	25/40	0.28 [0.14, 0.56]



- **ANALYSIS LIMITATIONS:** Data from selected FL subgroups of the PFS population are presented here. These analyses are exploratory in nature and data should not be interpreted to determine a treatment difference between arms due to a higher possibility of a false positive.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomas Folliculaires; PFS, progression-free survival.
*Defined as at least 1 lesion ≥7 cm or at least 3 lesions ≥3 cm.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

- **LACTATION:** There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID® (lenalidomide) on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.
- **RENAL IMPAIRMENT:** Adjust the starting dose of REVLIMID based on creatinine clearance value and for patients on dialysis.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, for REVLIMID.
Please see the rituximab full Prescribing Information for Important Safety Information at www.rituxan.com.

References: 1. REVLIMID [package insert]. Summit, NJ: Celgene Corp; 2021. **2.** Data on file. Celgene Corporation. **3.** Leonard JP, et al. *J Clin Oncol*. 2019;37(14):1188-1199. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V.5.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 22, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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