Submitted by:
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Celgene Corporation
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Date of Request: May 28, 2019

Dear NCCN B-Cell Lymphomas Guidelines Panel Members:

On behalf of Celgene Corporation, we respectfully request the NCCN Guidelines Panel for B-Cell Lymphomas review the enclosed information based on the recently approved indications for REVLIMID® (lenalidomide) in combination with a rituximab product, for the treatment of adult patients with previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL).

Specific Changes:
We respectfully request updating the recommendation for the lenalidomide + rituximab combination to a Category 1, Preferred regimen for second-line and subsequent therapy in follicular lymphoma as a follow-up to previous data submissions made by Celgene Corporation on March 22, 2019 and December 3, 2018.

FDA Status:
On May 28, 2019 the US Food and Drug Administration (FDA) granted approval for the use of REVLIMID® in combination with a rituximab product for patients with previously treated FL and MZL. These new indications are as follows:

REVLIMID® in combination with a rituximab product, is indicated for the treatment of adult patients with previously treated follicular lymphoma[1]

REVLIMID® in combination with a rituximab product, is indicated for the treatment of adult patients with previously treated marginal zone lymphoma[1]

Please see the enclosed full Prescribing Information.

Rationale for Proposed Change:
The March 22, 2019 and December 3, 2018 submissions were based on the results of a phase III clinical study evaluating the efficacy and safety of REVLIMID® and rituximab compared to rituximab-placebo (control) in patients with relapsed/refractory follicular or marginal zone lymphoma (AUGMENT)[2] and included the full publication and oral presentation of the data, respectively.

Additionally, select data from the MAGNIFY study included in the updated full Prescribing Information that were not included in the previous submissions are below.

> MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of REVLIMID and rituximab. MAGNIFY included patients diagnosed with Grade 1, 2,3a, 3b follicular (including transformed), marginal zone, or mantle cell lymphoma Stage I to IV who were previously treated for their lymphoma, had been refractory or had a relapse after their last treatment, had at least one measurable nodal or extranodal lesion by CT or MRI scan, and had adequate

bone marrow, liver, and renal function. Patients refractory to rituximab were also included. The information from the subjects who received at least 1 dose of initial therapy in the first 12 induction cycles (n=222) in the MAGNIFY trial was included in the evaluation of the efficacy of REVLIMID/rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma. In MAGNIFY, REVLIMID 20 mg was given on Days 1-21 of repeated 28-day cycles for up to 12 cycles or until unacceptable toxicity, progression, or withdrawal of consent. The dose of rituximab was 375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15, and 22) and on Day 1 of every other 28-day cycle (Cycles 3,5,7,9, and 11) up to 12 cycles therapy. All dosage calculations for rituximab were based on the patient BSA and actual weight. Dose adjustments were allowed based on clinical and laboratory findings.

The overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median duration of response was not reached with a median follow-up time of 7.9 months [95% CI: 4.6, 9.2]. The overall response by investigator assessment was 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma. Median duration of response was not reached with a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

The safety of REVLIMID/ rituximab was evaluated in 398 patients with either previously treated follicular lymphoma or marginal zone lymphoma in two clinical trials; AUGMENT (N=176) and MAGNIFY (N=222). Subjects were 18 years or older in age, had an ECOG PS ≤2, ANC ≥1,000 cells/mm^3 and platelets≥ 75,000/mm^3 (unless secondary to bone marrow involvement by lymphoma), hemoglobin ≥8g/dL, AST and ALT ≤ 3x ULN (unless documented liver involvement with lymphoma, and creatinine clearance of ≥ 30mL/min. Subjects with active HIV, hepatitis B or C were not eligible.

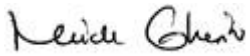
Fatal adverse reactions occurred in 6 patients (1.5%) receiving REVLIMID/rituximab. Fatal adverse reactions (1 each) included cardio-respiratory arrest, arrhythmia, cardiopulmonary failure, multiple organ dysfunction syndrome, sepsis, and acute kidney injury. Serious adverse reactions occurred in 26% of patients receiving REVLIMID/rituximab on AUGMENT and 29% on MAGNIFY. The most frequent serious adverse reaction that occurred in ≥ 2.5% of patients in the REVLIMID/rituximab arm was febrile neutropenia (3%). Permanent discontinuation of REVLIMID or rituximab due to an adverse reaction occurred in 14.6% of patients in the REVLIMID/rituximab arm. The most common adverse reaction (in at least 1%) requiring permanent discontinuation of REVLIMID or rituximab was neutropenia (4.8%).

The most common adverse reactions occurring in at least 20% of subjects were; neutropenia 48%, fatigue 37%, diarrhea 32%, constipation 27%, nausea 21%, and cough 20%.

Copies of the phase III AUGMENT publication and the updated REVLIMID® Prescribing Information are enclosed for your review. Your consideration of this submission is greatly appreciated.

Sincerely,

Christopher Papa, PharmD, RPh
Senior Manager, Global Medical Information



Mecide Gharibo, MD
Senior Director, US Medical Affairs, Lymphoma

REFERENCES

1. Celgene Corporation. Revlimid (lenalidomide) [Package Insert]. Summit, NJ: Celgene Corporation.
2. Leonard et al. 2019. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol*. 2019. doi:10.1200/JCO.19

Submitted by:
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Date of Request: March 22, 2019

Dear NCCN B-Cell Lymphoma Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for B-Cell Lymphoma review the enclosed data regarding the use of REVLIMID® (lenalidomide) in combination with rituximab in patients with relapsed/refractory follicular or marginal zone lymphoma. This data, recently published in the Journal of Clinical Oncology, is being sent for the panel's consideration as a follow-up to the REVLIMID submission made by Celgene Corporation on December 3, 2018.

Specific Changes:
We respectfully request updating the recommendation for the lenalidomide + rituximab combination to a Category 1, preferred regimen for second-line and subsequent therapy in follicular lymphoma.

FDA Status:
REVLIMID is not approved for the treatment of follicular or marginal zone lymphoma. Please see the enclosed full Prescribing Information.

Rationale:
The December 3, 2018 submission was based on the results of a phase III clinical study evaluating the efficacy and safety of lenalidomide plus rituximab (R^2) compared to rituximab-placebo (control) in patients with relapsed/refractory follicular or marginal zone lymphoma and included the oral presentation of data from that study. The attached full publication and supplementary appendix include additional safety and efficacy endpoint results from the phase III study that were not included in the previously submitted oral presentation.

Your consideration of this submission is greatly appreciated.

Sincerely,

Arpit Shah, PharmD
Sr. Manager, Global Medical Information

Kenneth Foon, MD
Vice President, Global Medical Affairs, Lymphoma

Reference List:

1. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma [epub ahead of print]. *J Clin Oncol*. 2019: JCO1900010.

Submitted by:
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Sr. Manager, Global Medical Information
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86 Morris Ave
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Phone: 908-679-7870
Email: arpshah@celgene.com
Date of Request: December 3, 2018

Dear NCCN B-Cell Lymphoma Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for B-Cell Lymphoma review the enclosed, recently presented data regarding the use of REVLIMID® (lenalidomide) in combination with rituximab in patients with relapsed/refractory follicular or marginal zone lymphoma.

Specific Changes:
We respectfully request updating the recommendation for the lenalidomide + rituximab combination to a Category 1, preferred regimen for second-line and subsequent therapy in follicular lymphoma.

FDA Status:
REVLIMID is not approved for the treatment of follicular or marginal zone lymphoma. Please see the enclosed full Prescribing Information.

Rationale:
In support of the proposed change, results from the phase III clinical study (AUGMENT) evaluating the efficacy and safety of lenalidomide plus rituximab (R^2) compared to rituximab-placebo (control) in patients with relapsed/refractory follicular or marginal zone lymphoma (n=358) are enclosed for your review. In the R^2 arm, patients received oral REVLIMID 20 mg daily on Days 1-21 every 28 days for 12 cycles and intravenous rituximab 375 mg/m^2 weekly in Cycle 1 and Day 1 of Cycles 2-5. Patients in the control arm received rituximab and placebo on the same schedule.

The study met its primary endpoint of progression-free survival (PFS) at median follow-up of 28.3 months (HR [95% CI]: 0.46 [0.34-0.62]; P<0.0001). Median PFS was 39.4 months and 14.1 months for R^2 and control arms, respectively. Overall response rate was observed in 78% and 53% of patients (P<0.0001) for R^2 and control, respectively.

Complete response was observed in 34% of patients treated with R^2 vs 18% of patients in the control arm (*P*=0.001). Grade 3/4 treatment-emergent adverse events (TEAEs) were reported in 69% and 32% of patients in the R^2 and control arms, respectively. More frequent Grade 3/4 TEAEs in the R^2 vs control arms were attributable to increased neutropenia (50% and 13%) and leukopenia (7% and 2%), respectively. Grade 5 TEAEs were reported in 2 patients in each arm. At the time of analysis, 16 and 26 deaths were reported in the R^2 and control arms, respectively.

A copy of the phase III data presentation and the REVLIMID Prescribing Information are enclosed for your review. Your consideration of this submission is greatly appreciated.

Sincerely,

Arpit Shah, PharmD
Sr. Manager, Global Medical Information

Kenneth Foon, MD
Vice President, Global Medical Affairs, Lymphoma

Reference List:

1. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma [Oral]. Presented at: 60th Annual Meeting & Exposition of the American Society of Hematology (ASH); December 1-4, 2018; San Diego, CA, USA.