



Submitted by:
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Date of Request: June 2, 2014

Dear NCCN Non-Hodgkin's Lymphoma Guidelines Panel Members:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Non-Hodgkin's Lymphoma (NHL) review recently published final data regarding the use of REVLIMID® (lenalidomide) in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP21) as first-line therapy in patients with diffuse large B-cell lymphoma (DLBCL). This is in follow-up to earlier data that had been submitted to the panel for their review and consideration the previous year. *Refer to the attached document DLBCL Celgene Submission 27June2013.*

Specific Changes: Recommend the use of lenalidomide in combination with R-CHOP21 as a suggested treatment regimen for DLBCL as first-line therapy. In addition, we respectfully request an update to the discussion surrounding first-line therapies for DLBCL to reflect the recently published results.

FDA Clearance: The FDA has not approved REVLIMID for the treatment of DLBCL. REVLIMID is indicated for the treatment of patients with (Revlimid Prescribing Information):

- Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib
- Multiple myeloma (MM), in combination with dexamethasone, in patients who have received at least one prior therapy
- Transfusion-dependent anemia due to low- or intermediate-1- risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities

Rationale: Two recently published Phase II studies of lenalidomide with R-CHOP21 (R2-CHOP21) in patients with newly-diagnosed DLBCL have demonstrated similar overall response rates (ORR) of $\geq 92\%$ as well as similar 2-year progression free survival (PFS) and overall survival (OS) regardless of cell of origin (non-germinal center B-cell [non-GCB] and germinal center B-cell [GCB]), suggesting that the R2-CHOP21 combination overcomes the negative impact of non-GCB phenotype on clinical outcome (Nowakowski 2014; Vitolo 2014).

The Phase II study of lenalidomide in combination with R-CHOP21 (R2-CHOP21) in newly-diagnosed patients with CD-20+, Stage II-IV DLBCL evaluated lenalidomide 25 mg/day on Days 1-10 of each 21-day cycle plus R-CHOP21 (day 1: rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m²; Days 1-5: prednisone 100 mg/m²) (Nowakowski 2014). Among 60 evaluable patients, ORR using positron emission tomography (PET) by standard criteria (Cheson et al. 2007) was 98%, consisting of 80% complete response (CR). PFS at 24 months was 59% (95% confidence interval [CI]: 48-74%) compared to 52% (95% CI: 43-64%) in a case-matched control group of 87 consecutive patients with DLBCL who received R-CHOP. OS at 24 months was 78% (95% CI: 68-90%) among patients treated with R2-CHOP21. The addition of lenalidomide to R-CHOP21 appeared to overcome the negative prognostic impact of non-GCB phenotype on PFS and OS. Patients treated with R2-CHOP21 with the non-GCB phenotype achieved a similar 2-year PFS compared to those with the GCB phenotype (60% [95% CI: 41-87%] vs. 59% [95% CI: 44-80%], respectively; $P=0.83$). However, patients with the non-GCB and GCB phenotypes treated with R-CHOP demonstrated significant differences in 2-year PFS (28% [95% CI: 15-51%] vs. 64% [95% CI: 53%-78%], respectively; $P<0.0001$). OS at 2 years with R2-CHOP was also similar between the non-GCB and GCB phenotypes (83% vs. 75%; $P=0.61$). In contrast, 2-year OS with R-CHOP significantly differed between the non-GCB and GCB phenotypes (46% vs. 78%; $P<0.001$). Grade 3/4 hematologic adverse events (AEs) in this study included:

thrombocytopenia (26.6%/17.2%), neutropenia (12.5%/75%), leukopenia (31.3%/48.4%) and anemia (15.6%/0%). Grade 3 febrile neutropenia occurred in 9.4% of patients. Grade 4 venous thrombosis, sepsis and intra-abdominal hemorrhage each developed in 1 (1.6%) patient. Death due to bowel perforation/sepsis occurred after 1 cycle in 1 patient with known gastrointestinal (GI) involvement by lymphoma.

The second study was a prospective, multicenter, dose-finding Phase I/II study of R2-CHOP21 in patients with previously untreated CD-20+, Stage II-IV DLBCL (REAL07) (Vitolo et al. 2014). During Phase II, elderly (aged 60-80 years) patients received lenalidomide at the maximum tolerated dose (MTD) of 15 mg daily on Days 1-14 along with R-CHOP21. ORR among the 49 enrolled patients was 92% (95% CI: 81-97%) after 6 cycles, consisting of 86% CR and 6% partial response (PR). The 2-year OS was 92% (95% CI: 79-97%) and 2-year PFS was 80% (95% CI: 64-89%) after a median follow-up of 28 months. A cell of origin analysis conducted on tissue samples from 32 patients showed similar baseline characteristics and clinical outcomes between GCB (n=16) and non-GCB (n=16) groups, respectively. ORR was 88% (81% CR) and 88% (88% CR); 2-year PFS was 71% (95% CI: 51-93%) and 81% (95% CI: 51-93%); and 2-year OS was 88% (95% CI: 59-97%) and 94% (95% CI: 63-99%). Grade 3/4 hematologic AEs included: leukopenia (22%/37%), neutropenia (14%/55%), thrombocytopenia (12%/18%), anemia (18%/2%) and febrile neutropenia (10%/0%). Grade 3 non-hematologic AEs included: neurologic and deep vein thrombosis (2 patients [4%] each) and cardiac, GI, renal, infection, constipation, skin rash and fatigue (1 patient [2%] each).

Please note that a copy of the Vitolo et al. e-publication is attached for your review. The Nowakowski et al. publication is currently *in press* and will be sent following its publication. In the meanwhile, attached for your review is a copy of the final data that Dr. Nowakowski presented on Saturday May 31st, 2014 at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO), which was held in Chicago, Illinois (Nowakowski et al. 2014).

Your consideration of this submission is greatly appreciated.

Sincerely,



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Kenneth Foon, MD
Vice President, Medical Affairs Global Disease Lead – Lymphoma and CLL

Cited References:

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2. Nowakowski G, LaPlant B, Macon WR, et al. Lenalidomide combined with R-CHOP (R2CHOP) overcomes negative prognostic impact of non-germinal center B-cell (non-GCB) phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase 2 study. *JCO*: in press.
3. Nowakowski G, LaPlant B, Macon WR, et al. Effect of lenalidomide combined with R-CHOP (R2CHOP) on negative prognostic impact of nongerminal center (non-GCB) phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase 2 study [oral]. *Oral presented at: 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) 2014*; May 30-June 3; Chicago, IL USA.
4. Revlimid (lenalidomide) Prescribing Information. Summit, NJ: Celgene Corporation.
5. Vitolo U, Chiappella A, Franceschetti S, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, Phase 2 trial [published online ahead of print, May 12, 2014]. *Lancet Oncology* 2014; doi:10.1016/S1470-2045(14)70191-3.
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