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 presented 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).

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 presented results.

FDA Clearance: The FDA has not approved REVLIMID for the treatment of DLBCL. REVLIMID is indicated for the treatment of (Revlimid Prescribing Information):
- Patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib
- Multiple myeloma, in combination with dexamethasone, in patients who have received at least one prior therapy
- Patients with 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 presented Phase II studies of lenalidomide with R-CHOP21 (R2-CHOP21) in patients with newly diagnosed DLBCL have demonstrated similar overall response rates (ORR) ≥92% (Nowakowski et al. 2013b; Chiappella et al. 2012).

The Phase II study of lenalidomide in combination with R-CHOP21 in newly diagnosed patients with CD-20+, Stage II-IV DLBCL presented at the 12th International Conference on Malignant Lymphoma (ICML) 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 et al. 2013b). Among 51 evaluable patients, ORR using PET by standard criteria (Cheson et al. 2007) was 100%, consisting of 73% complete response (CR) and 27% partial response (PR). Progression free survival (PFS) at 12 months was 69% (95% confidence interval [CI]: 58-82%) in comparison to 62% (95% CI: 53-73%) in a case-matched historical control group of 87
consecutive patients with DLBCL who received R-CHOP. The addition of lenalidomide to R-CHOP appeared to overcome the negative prognostic impact of non-germinal center B-cell (GCB) phenotype on PFS. Patients treated with R2-CHOP21 with the non-GCB subtype experienced a similar 18-month PFS compared to those with the GCB subtype (73% [95% CI: 55-97%] vs. 55% [95% CI: 37-83%], respectively; \( P=0.78 \)) (Nowakowski et al. 2013a). However, patients with non-GCB and GCB subtypes treated with R-CHOP demonstrated significant differences in 18-month PFS (32% [95% CI: 19-55%] vs. 70% [95% CI: 59-82%], respectively; \( P=0.002 \)). Grade 3/4 hematologic adverse events (AEs) in this study included: thrombocytopenia (30%/16%), neutropenia (12%/74%) and anemia (20%/0%). Grade 3 neutropenic fever occurred in 12% of patients and Grade 4 venous thrombosis was observed in 2% of patients (Nowakowski et al. 2013b).

The second study was a prospective, multicenter, dose-finding Phase I/II study of R2-CHOP21 in patients with previously untreated DLBCL (REAL07) (Chiappella et al. 2012). 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 was 92% after 6 cycles, consisting of 86% CR and 6% PR; the 2-year overall survival (OS) was 92% (95% CI: 79-97%) and 2-year PFS was 73% (95% CI: 57-84%) at a median follow-up of 22 months (range, 3-49 months). Grade 3/4 hematologic AEs included leukocytopenia (15%/13%), neutropenia (9%/22%), thrombocytopenia (6%/7%), anemia (4%/<0.5%) and febrile neutropenia (3%/1%); Grade 3 non-hematologic AEs included neurological (4%) and cardiac, gastrointestinal, renal, infection and deep vein thrombosis (DVT; 2% each).

Please note that a copy of the (Chiappella et al. 2012) presentation is enclosed for your review. A copy of the presentation from ICML (Nowakowski et al. 2013b) will be submitted separately as permission to distribute is obtained.

Your consideration of this submission is greatly appreciated.

Sincerely,

Anjali Shah, PharmD
Sr. Manager, Global Medical Information

Ken Foon, MD
Vice President, Global Medical Affairs Disease Lead

Encl. Chaippella et al. 2012; Revlimid Prescribing Information
Cited References:

   http://www.pubmed.gov/17242396


4. Nowakowski G, Reeder CB, Foran JM, et al. Combination of lenalidomide with rchop (R2chop) overcomes negative prognostic impact of non-Gcb phenotype in DLBCLA - A Phase 2 study [poster]. Poster presented at: 12th Triennial International Conference on Malignant Lymphoma (ICML). Lugano, Switzerland; Abstract #213: 2013b; June 19-22; Lugano, Switzerland.

   http://www.revlimid.com/