

February 24, 2014

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Farydak® (panobinostat) in Hodgkin's Lymphoma

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NCCN Guidelines Panel: Hodgkin's Lymphoma

To Whom It May Concern:

As the NCCN Panel reviews the NCCN Clinical Practice Guidelines in Hodgkin's Lymphoma (HL), and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with panobinostat. This information is highlighted below:

- Data to support the use of panobinostat in hodgkin's lymphoma (HL)

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Panobinostat for the treatment of hodgkin's lymphoma

This request is for the NCCN Panel to consider the addition of panobinostat use of panobinostat hodgkin's lymphoma based on results of a Phase II, single-agent, open-label study of panobinostat in heavily pre-treated patients with relapsed/refractory classical HL after autologous hematopoietic stem cell transplant (AHSCT). This international trial with Simon optimal 2-stage design enrolled 129 eligible patients who received oral panobinostat 40 mg three times a week (Monday, Wednesday, Friday) in 21-day treatment cycles. Dose delay and modification were allowed for management of adverse events. Response assessments were made after every two cycles by computed tomography (CT) or magnetic resonance imaging (MRI) scans according to modified Cheson criteria. The primary study objective was objective response rate (ORR) by investigator. Secondary objectives were response by central review, time to response (TTR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety and tolerability. As of June 11, 2010, in the final efficacy analysis of 129 evaluable patients, the primary endpoint of ORR was met ($P < .001$). Median time to response by investigator was 10 weeks (range, 4-51). A reduction in measurable tumor size was observed in 74% of patients. Median DOR was 6.9 months and the median PFS was >6 months. At the time of final analysis, median OS was not reached; estimated OS at 1 year is 78%. Median TTR was not reached at time of final analysis. Response rates in patient subsets (poor prognostic groups; 22.4%-33.0%) were comparable to the full analysis set (N=129; 27%).¹

The most common Grade 1/2 non-hematological adverse events (AEs) were diarrhea, nausea, fatigue, vomiting, decreased appetite, dysgeusia, constipation, asthenia and hypothyroidism. Serious grade 3/4 hematological AEs of $\geq 10\%$ included thrombocytopenia (79%), anemia (21%), neutropenia (21%) and leukopenia (5%). Thrombocytopenia was managed long term and was reversible with dose interruption or modification. There were no significant QTc interval events. A total of three deaths occurred within 28 days of stopping therapy; none were considered drug-related.¹ Farydak can cause serious side effects, including severe diarrhea which occurred in 25% of FARYDAK-treated patients, and Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes.²

Specific changes recommended for the Guidelines & Compendium

Please add panobinostat for the treatment of hodgkin's lymphoma.

FDA Status

FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.²

Rationale for recommended change

Efficacy and safety of panobinostat in hodgkin's lymphoma has been assessed a Phase II, single-agent, open-label study of panobinostat in heavily pre-treated patients with relapsed/refractory classical HL after AHSCT.¹

Literature support

1. Younes A, Sureda A, Ben-Yehuda D et al. Panobinostat in Patients with Relapsed/Refractory Hodgkin's Lymphoma After Autologous Stem-Cell Transplantation: Results of a Phase II Study. *Journal of Clinical Oncology*. 2012; 30(18); 2197-2203.
2. Farydak [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; 2015.

We appreciate the opportunity to provide this additional information for consideration by the NCCN Hodgkin's Lymphoma Panel. If you have any questions or require additional information, please do not hesitate to contact me at 862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time and consideration.

Sincerely,



Neilda Baron, MD
Executive Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Copies of referenced primary literature; Author disclosures included within references