

October 20, 2015

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Afinitor® (everolimus) in advanced, non-functional Neuroendocrine Tumors (NET) of gastrointestinal (GI) or lung origin

Name: Neilda Baron, MD
Company/Organization: Novartis Pharmaceuticals Corporation
Address: One Health Plaza, Building 345
East Hanover, NJ 07936
Phone: 862-778-5494
Email: neilda.baron@novartis.com
Date of request: October 20, 2015
NCCN Guidelines Panel: Neuroendocrine Tumors

To Whom It May Concern:

As the NCCN NET Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Neuroendocrine Tumors and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with everolimus. This information is highlighted below:

- Data to support use of everolimus in the treatment of advanced, NET of GI or lung origin

* * * * *

Everolimus for the treatment of advanced, non-functional NET of GI or lung origin

This request is for the Panel to consider amending the category recommendation of everolimus (currently category 3) in section CARC-6 of the Neuroendocrine Tumors Guidelines and the associated NCCN Drugs and Biologics Compendium™ based on results from the RADIANT-4 study. The RADIANT-4 study was a prospective, randomized, double-blind, multicenter, Phase III study investigating the efficacy of everolimus (RAD001) 10 mg daily plus best supportive care (BSC) versus placebo plus BSC in the treatment of patients with advanced, non-functional NET GI or lung origin (N=302). The primary objective was to determine the effect on progression-free survival (PFS) with everolimus plus BSC compared to placebo plus BSC. Secondary objectives were overall survival (OS), overall response rate (ORR), disease control rate (DCR), health-related quality of life based on the functional assessment of cancer therapy - general total score, change in value from baseline in chromogranin A and neuron-specific enolase, time to deterioration for World Health Organization (WHO) PS, and safety and tolerability. Patients with history of or active symptoms of carcinoid syndrome were excluded.^{1,2}

Crossover to open label everolimus after progression was not allowed prior to the primary analysis. Treatment was continued until discontinuation due to death, loss to follow-up, disease progression, or other reasons other than disease progression. Patients were stratified by prior somatostatin analog (SSA) use, tumor origin and WHO PS. Median PFS by central review was 11.0 months (95% CI, 9.2–13.3) in everolimus arm and 3.9 months (95% CI, 3.6–7.4) in placebo arm (HR, 0.48; 95% CI, 0.35–0.67; $P < 0.001$). Subgroup analyses of PFS by prior SSA use, tumor origin and WHO PS were consistent with the primary efficacy analysis. ORR (complete response [CR] and partial responses [PR]) was seen in 4 patients (2%) on everolimus and 1 patient (1%) on placebo. DCR (CR, PR and stable disease [SD]) was seen in 169 patients (82.4%) treated with everolimus vs 63 patients (64.9%) on placebo. Disease progression (DP) occurred in 19 patients (9.3%) in the everolimus arm vs 26 patients (26.8%) in the placebo arm. Tumor response was not evaluable in 17 patients (8.3%) treated with everolimus and 8 patients (8.2%) on placebo. An interim OS analysis showed an HR of 0.64 (95% CI, 0.40–1.05; $P = 0.037$) in favor of everolimus however the difference in OS does not achieve statistical significance (threshold P value for significance, 0.000213).^{1,2}

The most common drug related adverse events (AEs) included stomatitis, diarrhea, fatigue, infections, rash and peripheral edema. Most frequent Grade 3/4 AEs with everolimus vs. placebo included diarrhea (7% vs 2%), stomatitis (9% vs 0), abdominal pain (5% in each), and anemia (5% vs 2%). Most common reasons for treatment discontinuation in patients treated with everolimus vs. placebo were DP (37% vs 72%), AE (29% vs 7%), withdrawal of consent (7% vs 5%), and death (2% vs. 1%).²

Although results of the RADIANT-2 study, a Phase III, prospective, double-blind, randomized, placebo-controlled, multicenter study in patients with advanced low- or intermediate-grade functional NET comparing everolimus and octreotide LAR to placebo and octreotide LAR were not statistically significant (HR = 0.77; 95% CI: 0.59, 1.00; $P=.026$), the RADIANT-4 study has shown efficacy in patients with advanced, non-functional NET of GI or lung origin.^{2,3}

Specific changes recommended for the Guidelines & Compendium

Please amend the category recommendation for everolimus for the treatment of patients with advanced, non-functional NET of GI or lung origin.

FDA Status

Everolimus is approved for the treatment of adults with progressive neuroendocrine tumors of pancreatic origin that are unresectable, locally advanced or metastatic. Everolimus is not indicated for the treatment of patients with functional carcinoid tumors. Everolimus is not FDA-approved for the treatment of patients with advanced, non-functional NET of GI or lung origin.

Rationale for recommended change

The results of the RADIANT-4 study, a prospective, randomized, double-blind, multicenter, Phase III study have shown the efficacy and safety of everolimus in the treatment of advanced, non-functional NET of GI or lung origin.

Literature support

1. Yao JC, Buzzoni R, Carnaghi C, et al. Baseline demographics of the randomized, placebo-controlled, double-blind, Phase III RADIANT-4 study of everolimus in nonfunctional gastrointestinal or lung neuroendocrine tumors. In: Proceedings from the ASCO Gastrointestinal Cancers Symposium; January 15 - January 17, 2015; San Francisco, CA. Abstract 276.
2. Yao J , Fazio N, Singh S, et al. Everolimus in advanced, nonfunctional, neuroendocrine tumors of lung or gastrointestinal origin: efficacy and safety results from the placebo-controlled, double-blind, multicenter, phase 3 RADIANT-4 study. Oral presentation at: European Multidisciplinary Cancer Congress (ECCO ESMO ESTRO); September 25 - September 29, 2015; Vienna, Austria.
3. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011; 378 (9808): 2005 - 2012.

* * * * *

We appreciate the opportunity to provide this additional information for consideration by the NCCN NET Cancer 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