September 8, 2010

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Afinitor® (everolimus) in Neuroendocrine Tumors (NET)

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NCCN Guidelines Panel:	Neuroendocrine Tumors

To Whom It May Concern:

As the NCCN Neuroendocrine Tumors Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Neuroendocrine Tumors, v.2.2010 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with everolimus. This information is highlighted below:

- Data to support the use of everolimus in advanced pancreatic neuroendocrine tumors (NET) and carcinoid tumors

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Everolimus for the treatment of advanced pancreatic NET and carcinoid tumors
This request is for the Panel to consider amending the category recommendation of everolimus (currently 2B) in section "ISLT-5" of the Neuroendocrine Tumors Guidelines and the associated "NCCN Drugs and Biologics Compendium™" based on results from a phase III trial. In this randomized, placebo controlled, phase III trial, the use of everolimus (10 mg/day) (n=207) compared to placebo (n=203) for the treatment of patients with advanced low to intermediate grade pancreatic NET was evaluated (Yao et al. 2010). The median progression free survival (PFS) (primary endpoint) was 11.04 months in the everolimus arm compared with 4.60 months in the placebo arm (*P*<.001;HR=0.35). The most common treatment-related grade 3/4 adverse events with everolimus were anemia (6%), hyperglycemia (5%), stomatitis (5%), thrombocytopenia (4%), and diarrhea (3%). In addition, we would like the Panel to consider the addition of everolimus in combination with octreotide LAR in section "CARC-5" of the Guidelines and associated Compendium. In a randomized, double-blind, placebo controlled phase III trial, the use of everolimus (10 mg/day) in combination with octreotide LAR compared with placebo plus octreotide LAR in 429 patients with advanced (unresectable or metastatic) carcinoid tumor was studied (Novartis Data on File). The median PFS per adjudicated central radiology review was 16.43 months in the everolimus arm compared with 11.33 months in the placebo arm (*P*<.026; HR=.77). However, a predefined *P* value of 0.024 was not met. The most common grade 3/4 (≥10%) adverse events, irrespective of causality, reported with everolimus were diarrhea (13.5% grade 3), fatigue (10.7% grade 3/0.9% grade 4), and hypokalemia (10.7% grade 3/0.9% grade 4).

Specific changes recommended for the Guidelines & Compendium
Please amend the category recommendation for everolimus in the treatment of patients with advanced (unresectable or metastatic) pancreatic NET and add everolimus therapy as an option for patients with advanced carcinoid tumors.

FDA Status
Everolimus is not FDA-approved for the treatment of patients with advanced neuroendocrine tumors.

Rationale for recommended change
Efficacy and safety of everolimus has now been demonstrated in randomized, multi-center phase III trials in patients with advanced pancreatic NET and carcinoid tumors and in earlier phase II trials.

Literature support

1. Yao JC, Shah MH, Ito T, et al. Everolimus versus placebo in patients with advanced pancreatic neuroendocrine tumors (pNET) (RADIANT-3). Poster #O-0028 and oral presentation at the World Congress on Gastrointestinal Cancer (WCGI), Barcelona, Spain, June 30-July 1, 2010.

2. Novartis Data on File. RADIANT-2.

3. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol*.2008.26(26);4311-4318.

4. Yao JC, Lombard-Boha C, Baudin E. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol*.2010.28(1);69-76.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Neuroendocrine Tumors 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
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Enclosures: Copies of referenced primary literature