December 13, 2012

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Afinitor® (everolimus) in Non-Clear Cell Renal Cell Carcinoma (RCC)

Name:	Neilda Baron, MD
Company/Organization:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza, Building 432, 5th floor East Hanover, NJ 07936
Phone:	862-778-5494
Email:	neilda.baron@novartis.com
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NCCN Guidelines Panel:	Kidney Cancer

To Whom It May Concern:

As the NCCN Kidney Cancer Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Kidney Cancers, v.2.2012 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to the use of everolimus for the treatment of patients with non-clear cell renal cell carcinoma. This information is highlighted below:

- Data to support the use of everolimus in patients with non-clear cell renal cell carcinoma.

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Everolimus for the treatment of Non-Clear Cell Renal Cell Carcinoma

This request is for the Panel to consider the addition of Afinitor® (everolimus) for the treatment of non-clear cell renal cell carcinoma (RCC) in the Kidney Cancer Guidelines and associated "NCCN Drugs and Biologics Compendium™". Results from Phase II trials and a subgroup analysis of an expanded access program evaluated the efficacy and safety of everolimus in patients with metastatic RCC of non-clear cell histology.[1-4] Based on results from a subgroup analysis of a global, open-label, RAD001 Expanded Access Clinical Trial (REACT) that evaluated the long-term efficacy and safety of everolimus 10 mg once daily in patients with non-clear cell metastatic RCC who had received prior VEGFr-TKI (sunitinib and sorafenib) therapy, responses to everolimus treated patients with non-clear cell RCC (n=75) were 1.3% partial response and 49.3% stable disease, compared with 1.7% and 51.6%, respectively, for the total study population. The median everolimus treatment duration in the non-clear cell subgroup was 12.1 weeks (range: 0.9-49.0 weeks), compared with 14.0 weeks (range: 0.1 - 83.7 weeks) for the total study population.[1] The most commonly reported Grade 3 and 4 adverse events (AEs), respectively, in the non-clear cell RCC subgroup included: anemia (9.3% and 8.0%), pleural effusion (9.3% and 0%), dyspnea (8.0% and 2.7%), fatigue (8.0% and 0%), asthenia (4.0% and 1.3%), stomatitis (4.0% and 0%), and pneumonitis (4.0% and 0%).[1] In a Phase II study, 49 patients with non-clear cell RCC who had previously received a VEGFr-TKI (sunitinib and sorafenib) were administered everolimus 10 mg orally daily until disease progression or unacceptable toxicity.[2-3] The histology of enrolled patients included papillary (n=29), chromophobe (n=8), collecting duct (n=2), sarcomatoid (n=4), and unclassified (n=6).[3] The median progression-free survival was 5.2 months. The objective response rate was 10.2% with all patients having a partial response. Twenty five patients (51%) had stable disease; 16 patients (32.7%) progressed despite everolimus

administration. Adverse events greater than Grade 3 included anemia (10.2%), hyperglycemia (8.2%), infection (6.1%), and pneumonitis (4.1 %).[3] Interim results from RAPTOR (RAD001 in Advanced Papillary Tumor Program in Europe), an ongoing, Phase II trial evaluating the efficacy and safety of everolimus 10 mg once daily in previously untreated adult patients with type I or type II advanced papillary RCC demonstrated that everolimus provides a clinical benefit.[4] Of the 71 eligible patients confirmed with papillary renal cancer, 55% were progression-free at 6 months. The median progression-free survival as assessed by the investigator was 7.3 months (95% CI, 5.6-15.2). Safety and progression-free survival of patients still on treatment as assessed by independent radiology review is ongoing. The most common reasons for discontinuation of therapy included disease progression (39.1%), adverse events (16.3%), and death (9.8%). The mean duration of everolimus exposure was 139.3 days ±113.4 and the median relative dose intensity was 100%. A change in dose was required in 45.7% of patients, most often due to an adverse event (41.3%).[4]

Specific changes recommended for the Guidelines & Compendium
Please add the use of everolimus in the treatment of patients with non-clear cell renal cell carcinoma.

FDA Status
Everolimus is not FDA-approved for the treatment of patients with non-clear cell renal cell carcinoma.

Rationale for recommended change
Efficacy and safety of everolimus has now been demonstrated in multiple clinical trials in patients with non-clear cell renal cell carcinoma.

Literature Support

1. Blank C, Bono P, Larkin J, et al. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy: subgroup analysis of REACT. Poster presented at: 2012 Genitourinary Cancers Symposium; February 2¿4, 2012; San Francisco, California, USA.
2. Koh Y, Kim JY, Lim HY, et al. Phase II trial of everolimus for the treatment of non-clear cell renal cell carcinoma. Poster Presentation at American Society of Clinical Oncology - 48th Annual Meeting;June 1-5, 2012;Chicago, IL. Poster 4544.
3. Koh Y, Kim JY, Lim HY, et al. Phase II trial of RAD001 in renal cell carcinoma patients with non-clear cell histology. *J Clin Oncol*. 2012;30(Suppl). Abstract 4544.
4. Escudier B, Bracarda S, Maroto JP, et al. Open-label phase II trial of first-line everolimus monotherapy in patients with advanced papillary renal cell carcinoma: RAPTOR interim analysis. Poster Presentation at European Society of Medical Oncology 37th Congress - ESMO2012; September 28-October 2, 2012; Vienna Austria. Abstract 789PD.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Kidney Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
Senior Director & Head, Medical Information Oncology
Novartis Pharmaceuticals Corporation

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