



June 20, 2016

Submission Request  
National Comprehensive Cancer Network

**RE: Evidence in Support of Stomatitis Safety Profile with Afinitor® (everolimus) in Metastatic HR+/HER2- Breast Cancer**

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NCCN Guidelines Panel: Breast Cancer

To Whom It May Concern:

As the NCCN Breast Cancer Panel reviews the Breast Cancer NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines) for Breast Cancer v.3.2016 and the associated Evidence Blocks™, please find data relating to Afinitor® (everolimus) enclosed for your consideration:

- Data in support of the stomatitis safety profile with everolimus for patients with metastatic HR+/HER2- breast cancer

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**Everolimus in the treatment of metastatic HR+/HER2- breast cancer**

This request is for the Panel to consider the submitted data when assessing the overall safety of the regimen of everolimus + exemestane in patients with metastatic HR+/HER2- breast cancer within the NCCN Guidelines and Evidence Blocks.

During the Phase II, open-label, multicenter stomatitis prevention study, (N=92; 86 evaluable) postmenopausal patients with locally advanced or metastatic HR+/HER2- breast cancer receiving everolimus 10 mg + exemestane 25 mg used concomitant alcohol-free 0.5mg/5ml dexamethasone oral solution from the time of treatment initiation. Patients were instructed to swish for 2 minutes and spit the dexamethasone oral solution four times daily for, for 8 weeks. Patients could continue dexamethasone mouthwash regimen for a total of 32 weeks at clinician's discretion. Patients reported dietary intake and level of oral pain on a Visual Analog Scale (range, 0 [most favorable] to 10 [least favorable]). The primary endpoint was the incidence of Grade  $\geq 2$  stomatitis at 8 weeks compared to BOLERO-2 historical controls (refer to enclosed publication).<sup>1,2</sup> Secondary endpoints included: average daily use of dexamethasone solution at 8 weeks, dose intensity of treatment drugs at 8 weeks, incidence of all-Grade stomatitis at 8 weeks and time to resolution Grade  $\leq 1$ , patient reported dietary intake and oral pain and pharmacokinetics.<sup>2</sup>

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The incidence of Grade  $\geq 2$  stomatitis at 8 weeks was 2.4% (n=2, 95%CI: 0.29-8.24) compared with 33% reported from the historical control from BOLERO-2 ( $P < 0.001$ ). All-Grade stomatitis at 8 weeks occurred in 21.2% (n=18, 95% CI: 13.06-31.39) of patients versus 67% in BOLERO-2. Normal diet was reported in 88% of patients at 8 weeks and the mean oral pain score was  $< 1$  at all visits (range, 0.1-0.6).<sup>2</sup>

The most commonly reported ( $\geq 5\%$ ) all-Grade adverse events, regardless of causality, were stomatitis (27.2%), fatigue (17.4%), nausea (15.2%) and hyperglycemia (15.2%). The incidence of SAEs regardless of causality was 21.7%. Dyspnea (Grade 3 [1.1%]; Grade 4 [2.2%]), pneumonia (Grade 3 [2.2%]), pyrexia (Grades 3 and 4 [1.1% each]), and respiratory failure (Grades 3 and 4 [1.1% each]) were the most frequently reported SAEs.<sup>2</sup>

**Specific changes recommended for the Guidelines and Evidence Blocks** Please consider the data related to the stomatitis safety profile, including patient-reported outcomes, with concomitant dexamethasone oral solution and everolimus + exemestane when assessing the overall safety of everolimus in the treatment of metastatic HR+/HER2- breast cancer.

#### **FDA Status**

Everolimus is approved for the treatment of postmenopausal women with advanced HR+, HER2- breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

#### **Rationale for recommended change**

The stomatitis safety profile of everolimus + exemestane has been evaluated in patients receiving concomitant dexamethasone oral solution; these results should be taken into consideration when assessing the overall safety of everolimus within the NCCN Guidelines and Evidence Blocks for breast cancer.

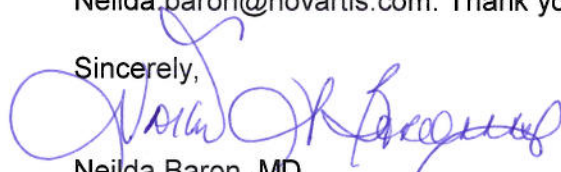
#### **Literature support**

1. Baselga et al. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *NEJM* 2012; 366 (6): 520-529.
2. Rugo et al. Prevention of Everolimus/Exemestane Stomatitis in Postmenopausal Women with Hormone Receptor-Positive Metastatic Breast Cancer Using a Dexamethasone-Based Mouthwash: Results of the SWISH Trial. Poster presented at: American Society of Clinical Oncology; June 3-7, 2016; Chicago, IL. Poster 525.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Breast 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](mailto:Neilda.baron@novartis.com). Thank you for your time and consideration.

Sincerely,



Neilda Baron, MD  
Executive Director, Medical Information Oncology  
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Enclosure: Copy of referenced primary literature  
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