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Submission Request
National Comprehensive Cancer Network

RE: Updated Clinical Evidence in Support of Afinitor® (everolimus) in Advanced Breast Cancer

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NCCN Guidelines Panel:	Breast Cancer

To Whom It May Concern:

As an addendum to the submissions dated October 10, 2011, December 12, 2011 and June 8, 2012 as the NCCN Breast Cancer Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer, v.3.2014 and the associated Drugs and Biologics Compendium™, we have enclosed more recent data relating to treatment with everolimus. This information is highlighted below:

- Updated overall survival results supporting the use of everolimus in advanced breast cancer

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Everolimus for the treatment of advanced breast cancer
This request is to provide updated information related to the BOLERO-2 (Breast cancer trials of OraL EveROlimus-2) trial as the Panel reviews the Breast Cancer Guidelines and the associated "NCCN Drugs and Biologics Compendium™". BOLERO-2 is a Phase III, multicenter, randomized, double-blind, placebo-controlled study that evaluated treatment with everolimus in combination with exemestane versus treatment with exemestane plus placebo in postmenopausal women with hormone receptor-positive, HER2-negative, locally-advanced or metastatic breast cancer, who are refractory to letrozole or anastrozole.[1] Patients were randomized in a two to one ratio to receive either everolimus orally (10 mg daily) (n = 485) or placebo (n = 239) in combination with exemestane orally (25 mg daily). The primary endpoint was progression-free survival (PFS).[1]

In the final PFS analysis, based on 510 events at a median follow-up of 18 months, the median PFS by local investigators was 7.8 months for combination therapy versus 3.2 months with exemestane only (HR = 0.45 [95% CI: 0.38, 0.54]; *P*<.0001). Assessment by central review was 11.0 months vs. 4.1 months, respectively (HR = 0.38 [95% CI: 0.31, 0.48]; *P*<.0001). PFS benefit with combination therapy vs. monotherapy was evident in all pre-specified subgroup analyses. Objective response and clinical benefit rates for the everolimus + exemestane vs. placebo + exemestane arms were 12.6% vs. 1.7% (*P*<.0001) and 51.3% vs. 26.4% (*P*<.0001), respectively.[2]

In the final analysis of a secondary endpoint, overall survival (OS), at a median follow-up of 39 months (cut-off date of October 3, 2013), a total of 410 deaths had occurred and treatment was ongoing in 13 patients. There was a 4.4-month prolongation in median OS with everolimus + exemestane (31.0 months vs. 26.6 months with placebo + exemestane; HR = 0.89 [95% CI:

0.73, 1.10]; *P*=0.14); the stratified log-rank test at one-sided 2.5% level of significance for the difference in median OS between treatment arms was not statistically significant. The types of anticancer therapies that were given following study treatment were balanced across arms, with the exception of 10% more patients in the placebo + exemestane arm receiving chemotherapy (63% placebo arm vs. 53% everolimus arm). No new safety concerns were identified.[3]

Specific changes recommended for the Guidelines & Compendium
Please update the section on Endocrine Therapy for Stage IV or Recurrent Metastatic Disease to reflect the BOLERO-2 secondary endpoint of final OS data.

FDA Status
Everolimus is approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.

Rationale for recommended change
Efficacy and safety of everolimus in combination with an aromatase inhibitor have been demonstrated in Phase III and Phase II trials for the treatment of postmenopausal, hormone receptor-positive women with advanced breast cancer who are refractory to endocrine therapy.[1-7]

Literature support

1. Baselga J, Campone M, Piccart M, et al. Everolimus for postmenopausal hormone receptor-positive advanced breast cancer. *N Engl J Med.* 2012;366(6):520-529. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1109653

2. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther.* 2013;30(10):870-884.

3. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (BC): overall survival results from BOLERO-2. *Eur J Cancer.* 2014;50(suppl 3):S1. 1LBA.

4. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO Study. *J Clin Oncol.* 2012;30(22):2718-2724.

5. Pritchard KI, Burris HA, Ito Y, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. *Clin Breast Cancer.* 2013;13(6):421-432.e8.

6. Gnant M, Baselga J, Rugo HS, et al. Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2. *J Natl Cancer Inst.* 2013;105(9):654-663.

7. Campone M, Bachelot T, Gnant M, et al. Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: subgroup analysis from the BOLERO-2 study. *Eur J Cancer.* 2013;49(12):2621-2632.

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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 862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time and consideration.

Sincerely,

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