

October 10, 2011

Submission Request
National Comprehensive Cancer Network

RE: 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 the NCCN Breast Cancer Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer, v.2.2011 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 breast cancer

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Everolimus for the treatment of advanced breast cancer

This request is for the Panel to consider the addition of everolimus in section “BINV-18, 19 and/or 20” of the Breast Cancer Guidelines and the associated “NCCN Drugs and Biologics Compendium™” based on results from a Phase III and supportive Phase II trial. BOLERO-2 (Breast cancer trials of Oral Everolimus-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 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). At a pre-planned analysis, the trial met its primary endpoint of PFS showing treatment with everolimus improved median PFS to 6.9 months compared to 2.8 months (hazard ratio [HR] 0.43 [95% confidence interval (CI): 0.35 to 0.54]; P=1.4 x 10⁻¹⁵) by local investigator assessment. This significant improvement was consistent across all subgroups including sensitivity to primary hormonal therapy, presence of visceral disease, and prior use of chemotherapy. Median PFS by central radiology review was 10.6 months for the everolimus arm compared with 4.1 months for the placebo arm (HR 0.36 95% CI: 0.27 to 0.47; P=3.3 x 10⁻¹⁵). The most common grade 3/4 adverse events in the everolimus arm included: stomatitis (8%, 0%), fatigue (3%, <1%), dyspnea (4%, 0%), anemia (5%, <1%), hyperglycemia (4%, <1%), elevated AST (3%, <1%), and pneumonitis (3%, 0%).¹

TAMRAD is a Phase II randomized trial evaluating the efficacy of everolimus (RAD) and tamoxifen (TAM) combination therapy in hormone receptor positive/HER2 negative metastatic breast cancer patients (N=111) pre-treated with an aromatase inhibitor.² The combination of everolimus and tamoxifen contributed to a higher clinical benefit rate, longer median time to disease progression, and longer overall survival compared to tamoxifen alone. Adverse events

observed in the combination arm were consistent with those previously reported with everolimus in cancer patients.²

Specific changes recommended for the Guidelines & Compendium

Please add everolimus in combination with an aromatase inhibitor (AI) as an option in the treatment of postmenopausal, hormone receptor positive women with advanced breast cancer who are refractory to prior endocrine therapy.

FDA Status

Everolimus is not FDA-approved for the treatment of patients with advanced breast cancer.

Rationale for recommended change

Efficacy and safety of everolimus in combination with an AI has 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; these results provide evidence to support the hypothesis that hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells and that treatment with mTOR inhibitors including rapamycin analogs reverses this resistance.¹⁻³

Literature support

1. Baselga J, Campone M, Sahmoud T, et al. Everolimus in combination with exemestane for postmenopausal women with advanced breast cancer who are refractory to letrozole or anastrozole: results of the BOLERO-2 phase III trial. Oral Presentation at European Society for Medical Oncology 36th Congress - ECCO 16 and ESMO 36; September 23-27, 2011; Stockholm, Sweden.
2. Bourcier C, Ray-Coquard I, Provencal J, et al. Exploratory subgroup analysis of the TAMRAD phase 2 GINECO trial evaluating tamoxifen (TAM) plus everolimus (RAD) vs TAM alone in patients with hormone-receptor-positive, HER2-negative metastatic breast cancer (mBC) with prior exposure to aromatase inhibitors (AIs): implication for research strategies. Oral Presentation at European Society for Medical Oncology 36th Congress - ECCO 16 and ESMO 36; September 23-27, 2011; Stockholm, Sweden.
3. Miller TW, Hennessy BT, Gonzalez-Angulo AM, et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. *J Clin Invest.* 2010; 120(7):2406-2413.

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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