NOVARTIS
ONCOLOGY

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Submission Request
National Comprehensive Cancer Network

**RE: Clinical Evidence in Support of Everolimus in Combination with Trastuzumab and Vinorelbine in HER2+ Locally Advanced or Metastatic Breast Cancer**


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| Date of request: | June 26, 2013 |
| 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.3.2013 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 combination with trastuzumab and vinorelbine in HER2+ locally advanced or metastatic breast cancer

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**Everolimus in combination with trastuzumab and vinorelbine for the treatment of HER2+ locally advanced or metastatic breast cancer**

This request is for the Panel to consider the addition of everolimus in section "BINV-21" and "BINV-O" of the Breast Cancer Guidelines and the associated "NCCN Drugs and Biologics Compendium™" based on results from a Phase III trial. BOLERO-3 (Breast cancer trials of OraL EveROlimus-3) is a Phase III, multicenter, randomized, double-blind, placebo-controlled study that evaluated treatment with everolimus in combination with vinorelbine and trastuzumab versus treatment with placebo plus vinorelbine and trastuzumab in patients with HER2+ locally advanced or metastatic breast cancer. Patients had to have been previously treated with a taxane and demonstrated resistance to trastuzumab.[1] Patients were randomized to vinorelbine 25 mg/m$^2$ administered intravenously weekly, trastuzumab 2 mg/kg administered intravenously weekly plus either everolimus 5 mg orally daily (n=284), or placebo (n=285). If necessary, each patient received a loading dose of trastuzumab of 4 mg/kg on day one of cycle 1. Treatment was continued until disease progression or the development of unacceptable toxicity. Patients were stratified based on prior lapatinib use.[1]

The addition of everolimus led to a significant improvement in median progression-free survival (PFS) based on local review. The median PFS was 7.00 months in the everolimus-containing arm versus 5.78 months in the placebo-containing arm (HR=0.78 [95% CI, 0.65-0.95], *P*=.0067). An improvement in PFS was also observed across subgroups defined by demographic characteristics (e.g., age, region), prior therapy (e.g., lapatinib, adjuvant/neoadjuvant trastuzumab), and disease characteristics (e.g., hormone receptor status, visceral involvement). Overall response rate (ORR) and clinical benefit rate (CBR) was slightly higher in the everolimus-containing arm, however the differences were not statistically significant.[1]

At the time of the data analysis on March 15, 2013, 220 deaths had occurred; 36.3% in the everolimus-containing arm and 41.1% in the placebo-containing arm. Statistical significance was not reached at the interim overall survival analysis. A final overall survival analysis will be conducted after 384 events have occurred. On-treatment deaths and deaths due to an adverse event were balanced between treatment arms (2.5% per arm and 0.7% per arm, respectively). The most common all-grade adverse reactions (incidence ≥30%) were neutropenia, stomatitis, anemia, fatigue, pyrexia, diarrhea, nausea, decreased appetite and constipation.[1]

**Specific changes recommended for the Guidelines & Compendium**
Please add everolimus in combination with vinorelbine and trastuzumab as an option in the treatment of patients with HER2+ locally advanced or metastatic breast cancer who are resistant to trastuzumab.

**FDA Status**
Everolimus is not FDA-approved for the treatment of patients with HER2+ advanced breast cancer.

**Rationale for recommended change**
Efficacy and safety of everolimus in combination with vinorelbine and trastuzumab has been demonstrated in Phase III and Phase I trials for the treatment of locally advanced or metastatic breast cancer patients who are resistant to trastuzumab; these results provide evidence to support the hypothesis that inhibition of the PI3K/Akt/mTOR pathway with everolimus might be a reasonable approach to overcome resistance and restore sensitivity to trastuzumab-based therapy.[1-3]

**Literature support**


1. O'Regan R, Ozguroglu M, Andre F, et al. Phase 3, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3). Oral Presentation at American Society of Clinical Oncology- 49th Annual Meeting; May 31-June 4, 2013; Chicago IL. Abstract# 505.

2. Morrow PK, Wulf GM, Ensor J, et al. Phase I/II study of trastuzumab in combination with everolimus (RAD001) in patients with HER2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy. J Clin Oncol. 2011 Aug 10;29(23):3126-32. doi: 10.1200/JCO.2010.32.2321.

3. Jerusalem G, Fasolo A, Dieras V et al. Phase I trial of oral mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine in pre-treated patients with HER2-overexpressing metastatic breast cancer. Breast Cancer Res Treat. 2011 Jan;125(2):447-55. doi: 10.1007/s10549-010-1260-x.


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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