

October 16, 2015

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Everolimus in Combination with Sorafenib in Metastatic Differentiated Thyroid Cancer

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Date of request: October 16, 2015
NCCN Guidelines Panel: Thyroid Carcinoma

To Whom It May Concern:

As the NCCN Thyroid Carcinoma Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Thyroid Carcinoma, v.2.2015 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 sorafenib in metastatic differentiated thyroid cancer

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Everolimus in combination with sorafenib for the treatment of metastatic differentiated thyroid cancer (DTC)

This request is for the Panel to consider the addition of everolimus in combination with sorafenib in Thyroid Carcinoma Guidelines and the associated “NCCN Drugs and Biologics Compendium™” based on the results from Phase II trials.^{3,4} Everolimus monotherapy was evaluated in two open-label, Phase II trials in patients with either locally advanced or metastatic radioactive iodine refractory (RAIR) thyroid cancer (TC) of all histologic subtypes.^{1,2} Patients received everolimus 10 mg/day until acceptable toxicity or disease progression.^{1,2} In the first study the primary endpoint was disease control rate (DCR) (defined as partial response (PR) + stable disease (SD) ≥ 12 weeks).¹ Additional endpoints included progression free survival (PFS), overall survival (OS), duration of response and safety. Twenty four of forty patients (60%) had DTC (papillary, follicular). The primary endpoint (DCR) in the overall patient population was observed in 31 out of 38 evaluable (81%) patients. Partial response (PR) was observed in two (5%) patients and SD in 29 (76%). At a median follow up duration of 11 months (range 1-24) the median PFS of patients with DTC was 43 weeks.¹ In the second monotherapy study the primary end point was PFS. Thirty one patients with DTC were evaluable. Median PFS in the DTC cohort was 16 months (95% CI: 10-NR). Disease stability for six and 12 months or more was achieved in 18/31 and 10/31 patients with DTC respectively. One patient with DTC achieved a PR. One year survival in DTC cohort was 76%.²

Everolimus combination therapy with sorafenib was evaluated in two Phase II studies in patients with metastatic RAIR DTC who had progressed on sorafenib or non-anaplastic progressive TC with no prior treatment with sorafenib or mTOR inhibitors.^{3,4} In the first Phase II single arm study, patients with metastatic RAIR DTC who had progressed on prior sorafenib were started on a dose of sorafenib 200 mg/day combined with everolimus 5 mg/day.³ If tolerated, the doses of everolimus and sorafenib were increased to a maximum daily dose of 10 mg/day and 800 mg/day

respectively. Primary endpoint of the study was PFS by Kaplan Meier analysis. Secondary endpoints were objective response rate, best response, time to disease progression, duration of response and safety. Thirty five patients were enrolled on the study and thirty were evaluable for response. The primary endpoint median PFS was 13.9 months (95% CI: 7.15-24.75). One patient (3%) had a PR and 21 patients (70%) had SD >6 months. Clinical benefit rate (PR+SD>6 months) was 73%.³ In the second Phase II, 2-stage design combination study, patients with non-anaplastic progressive TC with no prior sorafenib or mTOR inhibitors therapy were treated with everolimus 5 mg daily and sorafenib 400 mg twice daily. Seventeen of 28 patients (61%) with DTC (papillary, follicular, hurthle cell and poorly differentiated) experienced PR, ten of 28 (36%) had SD and one patient (4%) had progression. Median duration on study in DTC cohort was 14.1 months (0.9-46.6+).⁴

The most common ($\geq 5\%$) Grade 3/4 treatment related adverse events (AEs) in the first monotherapy study (n=38) were mucositis (15%), diarrhea (10%), neutropenia (5%) and hypertriglyceridemia (5%). One patient (2%) discontinued everolimus due to Grade 4 treatment related interstitial pneumonitis.¹ In the second monotherapy study (n=48) the most common (> 2) Grade 3/4 AEs were infection (n=5), weight loss (n=3), leukopenia (n=3), thrombocytopenia (n=3) and fatigue (n=3).² In the first combination study (n=33) of everolimus plus sorafenib the most common ($\geq 5\%$) Grade 3/4 AEs considered possibly or higher related to the treatment were anemia (24.2%), hypokalemia (21.2%), leukopenia (15.2%), hypophosphatemia (12.1%) and hypocalcemia (6.1%).³ In the second combination study (n=41) the most common (≥ 5) Grade 3/4 AEs were leukopenia (n=5), hypocalcemia/hypophosphatemia (n=5), hypertension (n=9), rash (n=10) and hyperglycemia (n=5).⁴

Specific changes recommended for the Guidelines & Compendium

Please add everolimus in combination with sorafenib as an option in the treatment of patients with metastatic differentiated thyroid cancer.

FDA Status

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

Rationale for recommended change

PI3K/Akt pathway is a potentially important target in thyroid cancer as many genetic alterations in this pathway were observed.¹ Patients on sorafenib monotherapy eventually become resistant to therapy and progress. In the tissues analyzed from patients treated with sorafenib, activation of PI3K/Akt/mTOR pathway was implicated in the progression of DTC.³

Literature support

1. Lim S.M, Chang H, Yoon M et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. *Annals of Oncology* 2013; 24:3089-3094.
2. Lorch J, Busaidy N, Ruan D et al. A phase II study of everolimus in patients with aggressive RAI refractory (RAIR) thyroid cancer. Poster presented at American Society of Clinical Oncology; June 2013: Chicago, IL. Poster 6023
3. Brose M, Troxel A, Yarchoan M et al. A phase II study of everolimus and sorafenib in patients with metastatic differentiated thyroid cancer who have progressed on sorafenib alone. Poster presented at American Society of Clinical Oncology; May 29-June 2, 2015: Chicago, IL. Poster 6072.
4. Sherman E, Ho A, Fury M et al. Combination of everolimus and sorafenib in the treatment of thyroid cancer: update on phase II study. Poster presented at American Society of Clinical Oncology; May 29-June 2, 2015: Chicago, IL. Poster 6069.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Thyroid Carcinoma 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