



Joseph Germino, MD, PhD
Vice President
US Medical Affairs Specialized Therapeutics
Bayer Healthcare Pharmaceuticals
6 West Belt Parkway
Wayne, NJ 07470
(973) 305-5184
joseph_f.germino@bayer.com

Homa Yeganegi
Vice President
Global Medical and Scientific Affairs
Onyx Pharmaceuticals, Inc
249 E. Grand Ave.
South San Francisco, CA 94080
(650) 266-2556
hyeganegi@onyx.com

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NCCN Thyroid Carcinoma Guidelines Panel:

On behalf of Dr. Joseph Germino at Bayer HealthCare Pharmaceuticals and Homa Yeganegi at Onyx Pharmaceuticals, I am pleased to provide you with updated literature available regarding Nexavar[®] (sorafenib) as therapy for patients with metastatic thyroid cancer. We acknowledge that sorafenib is listed in the NCCN Guidelines[®] and the NCCN Compendium[®] as a category 2a recommendation for metastatic thyroid cancer. We respectfully request the NCCN Thyroid Guidelines and Compendium be updated to include sorafenib as a category 1 recommendation for thyroid cancer, based on recent results of the Phase III DECISION trial.

Specific Changes: Recommend the update of the NCCN Thyroid Guidelines and Compendium to change sorafenib to a category 1 recommendation for metastatic thyroid cancer.

FDA Clearance: Nexavar[®] (sorafenib) is a kinase inhibitor indicated for the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma.¹

Rationale: In patients with metastatic thyroid cancer, single-agent sorafenib has demonstrated activity in five phase II trials.²⁻⁶ The results of DECISION trial, the first phase III study of a targeted agent in chemotherapy-naïve, RAI-refractory DTC, were presented at the 2013 ASCO Annual Meeting.⁷ The DECISION trial is summarized below.

- The primary endpoint in this study was progression free survival (PFS). Sorafenib significantly prolonged the median PFS by 5 months compared with placebo [10.8 vs 5.8 months (HR: 0.587; 95% CI: 0.454–0.758; $P < .0001$)]. The PFS benefit was maintained in all predefined subgroups.
- The main secondary efficacy endpoints included overall survival (OS), response rate (RR) and disease control rate (DCR).
 - The median OS has not been reached, but is unlikely to be different as the study design allowed for patients randomized to placebo to cross-over to sorafenib at the time of disease progression. At the time of



- progression, 71% of the placebo patients received open-label sorafenib, as well as 27% of the patients on the sorafenib arm.
- The RR for sorafenib was 12.2% compared to 0.5% for placebo ($p < 0.0001$). DCR, which includes CR+PR+SD \geq 6months, was 54.1% for sorafenib compared to 33.8% for placebo ($p < 0.0001$).
 - Safety results were consistent with the known safety profile of sorafenib. No new safety signals were identified.

Should you have any questions regarding the content of this letter, please do not hesitate to contact me.

Sincerely,

Mary Ann Watson, PharmD
Director, Medical Communications
Onyx Medical and Scientific Affairs
(503) 831-1162

Enclosures (2): Indicated in blue in Reference List below

Reference List

1. Nexavar [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc. and South San Francisco, CA: Onyx Pharmaceuticals, Inc. June 2013. http://labeling.bayerhealthcare.com/html/products/pi/Nexavar_PI.pdf
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4. Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *J Clin Oncol*. 2010;28:2323-2330.
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6. Schneider TC, Abdulrahman RM, Corssmit EP, et al. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial. *Eur J Endocrinol*. 2012;167(5):643-650.
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