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NCCN Guidelines Panel: Neuroendocrine Tumors

Dear Ms. McClure,

On behalf of the Oncology Business Unit at Pfizer Inc, I am submitting the following to the NCCN Guidelines Panel requesting the Panel's consideration for inclusion in the NCCN Compendia listings.

- Request for NCCN Guidelines Panel to consider review of data for a specific indication
  - SUTENT® (sunitinib malate) is indicated for the treatment of pancreatic neuroendocrine tumors (pancreatic NET). The proposed dose of Sutent for the treatment of pancreatic NET is 37.5 mg once daily on a continuous dosing schedule.

- Specific changes recommended within the NCCN Guidelines
  - For patients with Islet Cell Tumors (Pancreatic Endocrine Tumors) with distant metastases and Stage IV disease that targeted therapy with SUTENT (sunitinib malate) is listed as a treatment option (in addition to systemic chemotherapy and clinical trial).

- Statement of whether the submitted use is or is not FDA approved for that indication
  - The submitted use has not been approved by the FDA for this indication. A submission package is being prepared with a request for a priority review by the Agency.

- Rationale for recommended change
  - While currently, patients with pancreatic NET have limited treatment options with low response rates and/or high toxicity profiles, the results from a recent randomized, double-blind Phase 3 study show that the progression-free survival for sunitinib was 11.1 months compared with placebo at 5.5 months, with an acceptable toxicity profile.

- Citation of literature support and complete articles supporting recommended change
  - Raymond E, Raoul J, Niccoli P, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours. *Ann Oncol* 2009;20(suppl 7):vii11.
  - Raymond E, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours. Presented at 11th World Congress on Gastrointestinal Cancer, Barcelona, Spain. Session V – Rare Tumors: Neuroendocrine Tumors and Gastrointestinal Stromal Tumors (GIST), 25 June 2009.
  - Raoul J, Niccoli P, Bang, Y, et al. Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: results of a Phase III, randomized, double-blind trial. Abstract. Accepted as an oral presentation at ECCO/ESMO 23 September 2009, Berlin, Germany.

- M.H. Kulke et.al.;Activity of Sunitinib in Patients with Advanced Neuroendocrine Tumors, *JCO* 26 (20)3403-3410, 2008.
- Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, Bello C, Deprimo S, Brega N, Massimini G, Armand JP, Scigalla P, Raymond E. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol*. 2006 Jan 1;24(1):4-5.
- US Prescribing Information

On 25 February 2009, an independent Data Monitoring Committee (DMC) was convened specifically to review Protocol A6181111 ("A Phase III Randomized, Double-Blind Study of Sunitinib (SU011248, SUTENT®) versus Placebo in Patients with Progressive Advanced/Metastatic Well-Differentiated Pancreatic Islet Cell Tumors") safety data by treatment arm. In addition the DMC reviewed Progression-Free Survival (PFS) data. The DMC determined that the trial demonstrated a clinically significant advantage for the sunitinib arm in terms of PFS. The median PFS was 5.5 months for placebo and 11.1 months for sunitinib. The Z value with 73 events was 3.684, which exceeds the predetermined boundary ($Z \geq 2.958$) for the planned interim analysis of 130 events. The HR was 0.397 with 95% CI (0.243, 0.649) and 2-sided p-value <0.001 in favor of treatment with sunitinib. The DMC noted that conditional power predicted a 91% chance for stopping the study at the specified interim analysis of 130 events, using the upper limit of the 95% confidence interval of the observed HR (0.649) as the true HR (conservative approach). The DMC also noted that there was acceptable toxicity with sunitinib administration. Based upon these data, the DMC unanimously recommended that the study be closed for efficacy because the study had met its primary endpoint of PFS and that subjects on both treatment arms be offered the opportunity to receive open-label sunitinib.

In addition to the Phase III data, the nonclinical data, and data from Phase I and Phase II trials (articles and current label attached) support the mechanism of action, clinical safety, and clinical efficacy of sunitinib in patients with pancreatic islet cell tumors.

We appreciate the Panel's thorough consideration of Pfizer's submission for SUTENT (sunitinib malate) for the treatment of pancreatic NET.

Sincere regards,

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