Neuroendocrine Tumor Task Force Statement on the investigation of Vascular Endothelial Growth Factor (VEGF) pathway inhibitors in neuroendocrine tumors

The Neuroendocrine Tumor Task Force consists of North American experts in neuroendocrine tumors from multiple disciplines including medical oncology, radiation oncology, surgery, biostatistics, radiology and pathology. In addition, patient advocacy is represented in the Task Force. The mission of the Neuroendocrine Tumor Task Force is to facilitate the development of large clinical trials by oncology cooperative groups to improve the treatment of patients with neuroendocrine tumors.

The Neuroendocrine Tumor Task Force has become aware of concerns among patients regarding the use of vascular endothelial growth factor (VEGF) pathway inhibitors in neuroendocrine tumors. These concerns have arisen in part due to reports in laboratory animal models suggesting that treatment with VEGF inhibitors may enhance metastatic potential under some circumstances.(1) These studies, however, do not suggest that the clinical investigation of VEGF inhibitors in patients with metastatic neuroendocrine tumors should be discouraged. In fact, in mouse models of neuroendocrine tumors, therapies targeting VEGF and angiogenesis have been found to inhibit tumor growth and improve survival.(2-4) As with other cancer therapies, however, resistance to VEGF-pathway inhibitors eventually occurs, and understanding how to minimize, avoid, or delay resistance remains an area of intense investigation.(5) In human studies, VEGF inhibitors are effective in slowing tumor growth or improving survival in patients with advanced and metastatic cancers (see below), although their role as adjuvant therapy (for prevention of recurrence after complete resection of the tumor) has not been established. The National Cancer Institute and its cooperative oncology groups sponsor a number of current and planned studies with VEGF inhibitors such as bevacizumab (Avastin™), and motesanib in patients with neuroendocrine tumors. The Neuroendocrine Tumor Task Force and its members strongly endorse the ongoing accrual of patients to these studies.

Experience with VEGF pathway inhibitors in human malignancies: The vascular endothelial growth factor pathway comprises VEGF together with its receptors. A number of anti-tumor agents have been developed targeting this pathway including bevacizumab, sunitinib (Sutent™) and sorafenib (Nexavar™). VEGF pathway inhibitors have been used in thousands of cancer patients (either alone or in combination with other therapies), and have led to documented increases in overall survival in patients with advanced kidney, liver, colorectal and lung cancer.(6-8)

VEGF pathway inhibitors in neuroendocrine tumors: The information regarding VEGF inhibitors in patients with neuroendocrine tumors is not as mature as that for other cancers, since fewer trials of VEGF inhibitors have been completed in patients with these diseases. Nevertheless, there is an emerging body of evidence suggesting that VEGF pathway inhibitors are active in human neuroendocrine tumors:

- In a small phase II study of patients with carcinoid tumors, treatment with bevacizumab was associated with an overall tumor response rate (tumor shrinkage) of 18%.(9)
- In another small phase II study, patients with pancreatic neuroendocrine tumors, treatment with sunitinib was associated with an overall tumor response rate (tumor shrinkage) of 16%.(10)
- A recent larger randomized phase III study of sunitinib also showed that such therapy may delay tumor growth in pancreatic neuroendocrine tumors. Preliminary results showed prolongation in progression-free survival from 5.5 months to 11.1 months.(11)

Given the demonstrated efficacy of VEGF pathway inhibitors in other malignancies, as well as the promising initial data regarding the use of VEGF pathway inhibitors in neuroendocrine tumors, the NCI and other groups have designed additional clinical trials to further evaluate the efficacy of VEGF pathway inhibitors in patients with neuroendocrine tumors. Based on the available data, the Neuroendocrine Tumor Task Force believes that VEGF inhibitors may represent an effective therapeutic strategy for neuroendocrine tumor patients. In order to define the potential role of VEGF inhibitors in the treatment of neuroendocrine tumors, the Task Force strongly supports clinical trials involving these agents.

The following members of the Neuroendocrine Tumor Task Force support the above statements:

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