Executive Summary of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting
November 20-21, 2009

I. Attendees

Meeting Co-chairs:

Matthew Kulke, M.D.
James Yao, M.D.

Speakers, session moderators, breakout session leaders:

Jacqueline Benedetti, Ph.D.
Al B. Benson, III, M.D.
Emily Bergsland, M.D.
Jordan Berlin, M.D.
David Bushnell, M.D.
David Cella, Ph.D.
Herbert Chen, M.D.
Steven Cohen, M.D.
Douglas Evans, M.D.
George Fisher, M.D., Ph.D.
Richard Goldberg, M.D.
Daniel Haller, M.D.
Timothy Hobday, M.D.
Kyle Holen, M.D.
Robert Jensen, M.D.
Matthew Kulke, M.D.
Dik Kwekkeboom, M.D.
Irvin Modlin, M.D.
Kjell Öberg, M.D., Ph.D.
James Pingpank, Jr., M.D.
Mitchell Posner, M.D.
Larry Schwartz, M.D.
Manisha Shah, M.D.
Lillian Siu, M.D.
Laura Tang, M.D., Ph.D.
Eric Van Cutsem, M.D., Ph.D.
Alan Venook, M.D.
James Yao, M.D.

General attendees

Eddie Abdalla, M.D.
Michael Anderson, M.A.
Lowell Anthony, M.D.
Rudolf Arnold, M.D.
John Babich, Ph.D.
Michaela Banck, M.D.
Adam Berger, M.D.
Marla Jo Brickman, Ph.D.
Jennifer Chan, M.D., M.P.H.
Richard Chao, M.D.
Carla Chieffo, V.M.D., Ph.D.
Dimitrios Chondros, M.D.
Michael Choti, M.D., M.B.A.
Dan Chung, M.D.
Elaine Clark, M.D.
Vikram Deshpande, M.D.
Chaitanya Divgi, M.D.
Lee M. Ellis, M.D.
Amy Evenson, M.D.
Joel Freiman, M.D.
Charles Fuchs, M.D.
Germo Gericke, M.D.
Joseph Germino, M.D.
Edda Gomez-Panzani, M.D.
John Hohneker, M.D.
Deborah Jaffe, Ph.D.
Hagen Kennecke, M.D.
Eric Krenning, M.D.
Pamela Kunz, M.D.
Larry Kvols, M.D.
Norman LaFrance, M.D.
Jerome Landry, M.D.
David Lebwohl, M.D.
Heinz-Josef Lenz, M.D.
Stephen Marx, M.D.
Robert Mayer, M.D.
David Metz, M.D.
Margaret Mooney, M.D.
Ravi Murthy, M.D.
Eric Nakakura, M.D.
Sue O'Dorisio, M.D.
Thomas O'Dorisio, M.D.
Alexandria Phan, M.D.
Diane Reidy, M.D.
Larry Rubinstein, Ph.D.
Ramesh Shivdasani, M.D., Ph.D.
Virginia Steele
Jonathan Strosberg, M.D.
Keith Stuart, M.D.
Richard Swanson, M.D.
Joel Tepper, M.D.
Jack Welch, M.D., Ph.D.

II. Meeting Description

NETs have recently been shown to be more common than previously suspected, and their diagnosed incidence is increasing. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the estimated annual incidence of carcinoid tumors in 2004 was 5.25 per 100,000 population, and the 29-year limited duration prevalence in the United States was estimated to exceed 100,000 individuals.[1] The NET Task Force of the National Cancer Institute (NCI) GI Steering Committee was created to encourage clinical and translational research in NETs and to facilitate the development and coordination of relevant clinical trials in this disease. As part of this effort, the task force convened a clinical trials planning meeting (CTPM) to identify key unmet needs, and to formulate priorities for future NET studies for the US cooperative group program. Other key meeting objectives included the development of recommendations for appropriate study endpoints and imaging techniques and standardization of clinical trial inclusion criteria. Participants in this day and a half meeting included clinical, translational and laboratory-based investigators in neuroendocrine cancer as well as representatives from the patient advocacy community, pharmaceutical industry, and the National Cancer Institute. The meeting was structured to include brief didactic presentations during an initial half-day session, summarizing recent developments and current questions in the field. Subsequently, participants participated in breakout sessions where they discussed clinical trial priorities in specific areas. Recommendations from the breakout sessions were then brought back to the larger group for consensus on the second day of the meeting. Ideas and concepts from the meeting were further developed and refined during subsequent meetings of the NET Task Force, leading to the key recommendations outlined below. Final detailed recommendations from this meeting were recently published.[2]

References

1. Yao JC, Hassan M, Phan A, et al: One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. Journal of Clinical Oncology 26:3063-72, 2008

2. Kulke MH, Siu LL, Tepper JE, Fisher G, Jaffe D, Hailer DG, Ellis LM, Benedetti JK, Bergsland EK, Hobday TJ, Van Custem E, Pingpank J, Oberg K, Cohen SJ, Posner MC, Yao JC. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011; 29(7):934-43.

III. Key Meeting Recommendations

CLASSIFICATION OF NEUROENDOCRINE TUMORS

- Carcinoid tumors and pancreatic NETs should be examined separately in clinical trials. Stratification of carcinoid tumors by primary site should be considered in larger, randomized studies.
- The American Joint Committee on Cancer (AJCC) staging system for NETs should be used as the staging standard in clinical trials.
- A formal assessment of grade or differentiation should be required for clinical trial enrollment; well differentiated and poorly differentiated NETs should be studied separately.
- While large-scale, prospective studies specifically enrolling patients with specific molecular subtypes are not currently indicated, useful information regarding the activity of specific drugs in molecular subtypes can be gained from retrospective analyses of tumors and annotated clinical data.

ADJUVANT TRIALS IN PATIENTS WITH RESECTED NEUROENDOCRINE TUMORS

- Adjuvant therapy is not currently indicated in patients with completely resected NETs. Additional data regarding time to recurrence and OS of patients with resected NETs will be necessary to design adequately powered studies in this setting.

EVALUATION OF THERAPEUTIC AGENTS FOR CARCINOID SYNDROME

- Refractory carcinoid syndrome is an unmet medical need. The successful clinical development of new agents for this indication has proven challenging due to difficulty in selecting appropriate entry criteria and clinical trial endpoints.
- Use of a somatostatin “washout” in trials of novel agents for carcinoid syndrome should be avoided when possible.
- A symptom severity index based on a composite score of flushing and diarrhea would provide an appropriate measure of patient-reported outcomes, and could be used as an endpoint in trials of novel agents for carcinoid syndrome. Randomized, placebo-controlled studies incorporating such an index, in conjunction with more general quality of life measures, are recommended for the investigation of novel agents in this indication.

HEPATIC DIRECTED THERAPY

- Because of the highly selected nature of patients undergoing either hepatic resection or orthotopic liver transplantation, randomized controlled trials evaluating patient outcomes with these treatment modalities would likely be difficult to perform.
- Hepatic artery embolization is commonly performed in patients with unresectable, hepatic-predominant disease. A variety of techniques, including bland, chemo-, or radio-embolization are currently employed but have never been compared in a controlled setting. Randomized phase II trials exploring the relative efficacy and toxicity of these techniques are recommended.

PEPTIDE RECEPTOR RADIOTHERAPY (PRRT)

- Randomized phase III studies comparing peptide receptor radiotherapy to standard systemic therapy are warranted.

CLINICAL TRIALS OF NOVEL SYSTEMIC AGENTS FOR ADVANCED NEUROENDOCRINE TUMORS

Study design and endpoints

- Overall survival is not a practical endpoint for most advanced NET studies. Progression-free survival (PFS) is recommended as the primary endpoint for phase III studies, as well as for phase II studies where a delay in progression is expected in the absence of significant radiologically-defined tumor responses.
- Randomized phase II studies, requiring disease progression prior to study entry and using PFS as a primary endpoint, should be used to screen novel agents in NETs.

- Randomized trials in NETs investigating novel therapies need to account for the potential anti-tumor activity of somatostatin analogs.

Imaging considerations

- Cross-sectional anatomic imaging of the abdomen should be performed with either multi-phasic CT or MRI.
- Study baseline cross-sectional anatomic imaging should include chest, abdomen, pelvis, and any additional know sites of disease.
- Somatostatin scintigraphy should not be used to assess tumor response in clinical trials.

Incorporation of Biomarkers

- Serial measurements of plasma chromogranin A should be incorporated into prospective clinical trials.
- Assessment of tumoral MGMT expression is warranted in future studies of alkylating agents.
- Imaging with perfusion CT should be considered in future studies of anti-angiogenic agents.

Specific recommendations for ongoing and future studies

Advanced Carcinoid:

- Successful completion of the ongoing phase III study of bevacizumab versus interferon in patients with advanced carcinoid tumors (SWOG0518) may define the role of bevacizumab in patients with advanced carcinoid tumors.
- The results of a phase III study of everolimus plus octreotide versus octreotide alone may define the role of everolimus in patients with advanced carcinoid tumors
- Randomized studies of tyrosine kinase inhibitors targeting VEGFR should be considered in patients with advanced carcinoid tumors.

Advanced Pancreatic Neuroendocrine Tumors:

- Sunitinib and other tyrosine kinase inhibitors targeting VEGFR are active in patients with advanced pancreatic NETs
- Everolimus is active in patients with advanced pancreatic NETs. A randomized phase II study comparing everolimus alone to the combination of everolimus plus bevacizumab in patients with pancreatic NET will build on the recent observation of activity with everolimus alone, and may help define the potential additive activity of bevacizumab in this setting.
- In contrast to carcinoid tumors, there is now substantial evidence that pancreatic NETs are sensitive to alkylating agents. Randomized studies assessing the relative efficacy of streptozocin or temozolomide, and assessing the efficacy of temozolomide alone or *a* temozolomide-based doublet are warranted.