Meeting Summary: New Therapeutic Options in Thyroid Cancer
Held Wednesday, March 14, 2007
Natcher Conference Cancer Center Rooms F1/F2
NIH

Dr. James Doroshow, DCTD Director welcomed the participants and was followed by Dr. John Wright of NCI CTEP who organized the meeting and who provided an overview of the planned presentations, putative discussion topics and overall objectives of the meeting.

The meeting objectives included:

1. Updating and informing the investigators in the thyroid community about the current status of NCI support for thyroid cancer studies and thyroid cancer-related translational studies, specifically through the SPORE program and the CTEP clinical trials program
2. Introducing the investigators to novel clinical trial design and statistical approaches that have been developed with the intent to facilitate evaluation of rare tumor types, such as thyroid cancer
3. Identifying novel therapies for thyroid cancer with a focus on small molecule kinase inhibitors and assessing potential new agents that warrant evaluation in thyroid cancer based on new information about the molecular biology of thyroid cancer
4. Focusing on the potential for combinations of targeted therapies in the treatment of thyroid cancer
5. Preliminary discussion about further efforts to organize thyroid cancer investigators including endocrinologists, surgeons, head and neck oncologists and translational scientists and organizing priorities for future NCI-sponsored trials of promising agents.

The meeting began with a presentation by Dr. Wright describing the novel investigational agents in the CTEP Investigational Drug Branch portfolio and the Targeted Agents Combination Trials initiative that has been spearheaded by CTEP. This latter program has resulted in the initiation of dozens of combination trials combining investigational agents from several different companies and was made possible by the development of Intellectual Property language that was accepted by the majority of pharmaceutical companies.

Dr. Larry Rubinstein from the NCI Biostatistical Research Branch gave a presentation that focused on several new innovations in design of randomized phase II trials and hybrid trial endpoints (objective response and progression free survival). Dr. Rubinstein provided a comprehensive review of selection and screening designs for randomized phase II trials as well as statistical analysis and power calculations for hybrid endpoint designs. These randomized phase II trial designs are particularly suited for the assessment of new therapeutic agents for relatively rare cancers like thyroid cancer.

Dr. Lalitha Shankar from the NCI Imaging Program gave a presentation that focused on the extensive experience she has had personally as a nuclear medicine radiologist working with thyroid cancer patients. She also compared and contrasted various imaging modalities for the assessment of response in thyroid cancer and discussed the NCI-supported imaging network organized around ACRIN and the potential resources in this group for imaging assessment in thyroid cancer trials.

Dr. Ivan Ding discussed the SPORE program and the limited support of the Head & Neck SPORE for thyroid cancer therapy trials. It was agreed by most participants that the support for thyroid trials through the SPORE mechanism should be increased.

Dr. Margaret Mooney gave a provocative presentation about the newly established Steering Committees that have been formed as a result of the recommendations of the Clinical Trials Working Group. The Head and Neck Steering committee will have oversight of thyroid trials and phase III proposals would need to be reviewed by a thyroid task force and approved before being sent on to the H&N Steering committee for prioritization review. Dr. Mooney was asked numerous questions about the selection of committee members and the process for generating phase III proposals.

The afternoon session commenced with presentations by company representatives and investigators of clinical trials with targeted agents and preclinical work supporting future clinical trials. Peter Langmuir from Astra-Zeneca presented a comprehensive review of preclinical studies and updated clinical trials status of the multikinase inhibitor AZD-6474. Significant activity is being observed with this agent in medullary thyroid carcinoma patients, attributed to the ret inhibitory activity of the compound. Dr. Ezra Cohen discussed the Pfizer compound, Axitinib, which is another multikinase inhibitor of all VEGFR isoforms. Dr. Cohen is conducting a phase II trial of Axitinib at University of Chicago in patients with advanced thyroid cancer refractory to conventional therapy. He emphasized that axitinib appears to be comparable or more effective that doxorubicin, considered a standard therapy for thyroid cancer. Results from approximately 60 patients entered on the trial are listed below:

Best Response Evaluation Criteria in Solid Tumors

Response	**Number**	**Percentage**
Partial response	18	30
Stable disease (≥ 16 weeks)	25	42
Number with any tumor shrinkage	23	38
No response	17	28
Progression	7	12
Indeterminate or unknown	10	17

Manish Shah of Ohio State University discussed the multiple sorafenib studies she is conducting in follicular thyroid cancer as well as medullary thyroid cancer. Sorafenib is

an agent from Bayer/Onyx Pharmaceuticals that is a multikinase inhibitor of VEGFR, PDGFR as well as Raf, including B-Raf which is sometimes mutated and activated in various types of thyroid cancer. Dr. Shah has seen significant activity with sorafenib, particularly as measured by decreased thyroglobulin levels and tumor size reduction. Dr. Steven Sherman discussed the studies he has initiated at M.D. Anderson with the proteasome inhibitor Bortezomib and with the hypomethylating agent decitabine. These trials are being conducted in two groups of thyroid patients with distinct clinical presentations. Finally, Dr. Al Copland presented some preclinical studies he has been conducting that evaluate the combination of paclitaxel and a PPAR inhibitor in a thyroid tumor model and that will provide the rationale for a clinical trial of this combination.

A closed session was held at the end of the meeting to discuss the potential for combination therapy with targeted agents. It was agreed that combinations of sorafenib, axitinib or AZD-6474 in combination with VEGF-ligand directed anti-angiogenic agents (e.g. bevacizumab) were regimens with significant potential. Combining bortezomib with histone-deacetylase inhibitors was another attractive combination for evaluation in thyroid cancer. There was considerable discussion about formalizing entry criteria for thyroid cancer patients to achieve more homogenous populations for clinical trials but there was continued skepticism that this could be achieved because of the considerable heterogeneity of the patients presenting with this disease. It was agreed that a Thyroid Cancer consortium to facilitate the evaluation of agents selected by the NCI would be a significant contribution to the field.