As Director of the Lung Cancer Program at the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, I am pleased to send this inaugural newsletter to introduce our Multidisciplinary Lung Cancer team.

As you know, lung cancer is the leading cause of cancer-related mortality in the US and worldwide. In 2007, it is estimated that more than 160,000 Americans will die from this disease, including more than 19,000 persons in Wisconsin, Illinois, Minnesota, Iowa, and Michigan. Members of the UW Multidisciplinary Lung Cancer team are dedicated to reducing these devastating statistics by incorporating the latest discoveries in thoracic oncology to patient care, in a seamless ‘bench-to-bedside’ transition. We believe that it is only through applying the most recent scientific advances in lung cancer biology that improvements in lung cancer treatment will be gained.

The cornerstone of our Multidisciplinary Lung Cancer team is our weekly Multidisciplinary Lung Cancer Clinic. This Clinic brings together lung cancer specialists from medical, surgical, and radiation oncology on-site in order to offer patients a comprehensive diagnostic and treatment plan through an interdisciplinary approach.

In addition to standard treatment options, our team offers patients a broad range of phase I, II, and III clinical trial options for all stages of disease. My medical oncology colleagues, Drs. Tien Hoang and Toby Campbell, and I specialize in the development of novel, targeted anti-cancer agents and their incorporation with cytotoxic chemotherapeutics and radiotherapy. Dr. Tracey Weigel from Thoracic Surgical Oncology and Dr. Minesh Mehta from Thoracic Radiation Oncology are the Co-Directors in the Multidisciplinary Lung Cancer team. Both Drs. Weigel and Mehta are national leaders in their respective fields. Dr. Weigel’s clinical expertise includes performing minimally invasive thoracic surgeries (such as VATS lobectomies), endobronchial ultrasound for diagnosis and staging, and extrapleural pneumonectomies as part of a tri-modality treatment plan for selected patients with mesothelioma. Her research interests include minimally invasive and robotic thoracic surgical techniques. Dr. Mehta provides expertise in the newest radiation therapy technologies, such as tomotherapy, stereotactic body radiosurgery, and endobronchial brachytherapy.

Physicians from other specialties, including Dr. Lucille Marchand from Integrative Medicine, and our clinical and research nurses, oncology pharmacists, social workers, health psychologists, and nutritionists contribute greatly to the Multidisciplinary Lung Cancer team.

I invite you to review the material in this newsletter. We plan to bring you regular updates on the latest advances in the field, as well as on our featured lung cancer protocols. I look forward to collaborating with you and our regional partners in these efforts to bring patients innovative and improved cancer treatment. It is these types of research endeavors that can lead to a better tomorrow for our patients.

Sincerely,
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Angiogenesis is essential for tumor growth and progression. One of the most potent promoters of angiogenesis is the vascular endothelial growth factor (VEGF). The binding of VEGF to its tyrosine kinase receptor on the endothelial cell surface results in receptor dimerization and phosphorylation, leading to activation of various signal transduction pathways. This process is essential for vascular proliferation, permeability, and survival of the cancer.

Bevacizumab is an anti-VEGF recombinant humanized monoclonal antibody. It acts by blocking the binding of VEGF to its receptors, preventing angiogenesis. Bevacizumab is approved for use with chemotherapy (paclitaxel and carboplatin) as first-line therapy in metastatic non-squamous NSCLC.

**Study Design**

This is a randomized phase II study with three arms. Patients will receive standard chemotherapy regimen of paclitaxel and carboplatin in combination with either AMG 706 daily (arm A) or twice daily (arm B), or with bevacizumab (arm C). The goal of this trial is to compare treatment of carboplatin, paclitaxel, and the investigational agent AMG 706 to the control regimen of carboplatin, paclitaxel, and bevacizumab.

AMG 706 is a novel oral multi-kinase inhibitor that restricts the tyrosine kinase activity at the VEGF receptors, thus preventing formation of tumor blood vessels and impeding tumor growth.

MKC-1 belongs to a novel class of antimitotics and apoptosis-inducers with in vitro efficacy against a wide range of human tumor cell lines, including NSCLC and multi-drug resistant lines. MKC-1 acts by inhibiting importin-beta, a protein essential in the energy-driven transport of other proteins from the cytosol into the nucleus. Proteins transported by importin-beta include transcription factors, ribosomes, oncogenes, and cell cycle mediators. This inhibition disrupts spindle formation, which induces M-phase arrest and leads to apoptosis. Preclinical studies demonstrated that MKC-1 inhibited proliferation and induced apoptosis in NSCLC cell lines. Additive anti-tumor effects were observed in animal models when MKC-1 was combined with chemotherapy.

**Study Design**

In this single arm open-label phase I/II study, MKC-1 is taken orally for 14 days of a 21-day cycle in combination with IV pemetrexed, an anti-folate agent which is already approved for use in NSCLC patients who progressed after first-line chemotherapy. The phase I portion of this study which determined the maximally tolerated dose (MTD) was recently completed. At present, the phase II portion is open to accrual. The primary objective is to evaluate the antitumor activity of MKC-1 in combination with pemetrexed in NSCLC patients who have progressive disease following initial chemotherapy. Patients will receive a maximum of 6 cycles of combination therapy and may continue with MKC-1 monotherapy.

MKC-1 has been shown to destabilize microtubules in vitro.
Our Current Protocols

Chemotherapy Protocols

Non-Small Cell Lung Cancer (NSCLC)
- A Phase II, Multicenter, Open Label, Randomized Trial of AMG 706 or Bevacizumab in Combination with Paclitaxel and Carboplatin for Advanced Non-Squamous NSCLC.
- Phase I Study of Erlotinib and Sunitinib in NSCLC.
- A Phase II Study of Oral AINC-1 Administered Twice Daily for 14 Consecutive Days every Three Weeks in Combination with Pemetrexed.
- A Combined Phase I and II Study Investigating the Combination of RAD001 and Erlotinib in Patients with Advanced NSCLC Previously Treated Only with Chemotherapy.
- A Phase II Study of Adjuvant Cisplatin, Docetaxel, and Bevacizumab in Early Stage (I-IIIA) NSCLC.

Small Cell Lung Cancer (SCLC)
- A Randomized Phase III Trial of Pemetrexed and Carboplatin versus Etoposide and Carboplatin in Extensive-Stage SCLC.
- Phase II study of AZD 2171 in patients with recurrent SCLC.

Radiation Protocols

- The Use of Helical Tomotherapy to Achieve Dose-per-fraction Escalation in Lung Cancer.
- Phase I Study of Image Guided Stereotactic Body Radiosurgery for Small Lung Malignancies.
- Phase III Trial Comparing Whole Brain Radiation and Stereotactic Radiosurgery Alone versus Tamoxifen or Gefitinib in Patients with NSCLC and One to Three Brain Metastases.
- Phase II Efficacy and Safety Study of SU011248 in Patients with NSCLC and Brain Metastases.
- An Open-label, Multi-center, Phase II Study to Evaluate the Activity of Patupilone (EP0906), in the Treatment of Recurrent or Progressive Brain Metastases in Patients with NSCLC.
- Phase I Trial of Helical Tomotherapy Simultaneous Boost (SIB) Treatment for Patients with Brain Metastases.
- Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases.

Other Protocols

- A Phase III Chemoprevention Trial of Selenium Supplementation in Persons with Resected Stage I NSCLC.

Prophylactic cranial irradiation (PCI) reduces symptomatic brain metastases and prolongs progression free and overall survival in extensive disease small cell lung cancer after a response to chemotherapy
B. Slotman et al, Abstr. 4

In a randomized phase III study conducted by EORTC, 286 extensive SCLC patients who responded to 4-6 cycles of chemotherapy were randomized to receive PCI (20-30 Gy in 5-12 fractions) versus observation. At randomization, approximately 75% of patients in either arm still had disease at primary sites and 70% had disease at metastatic sites (lymph nodes, bone, lung, etc). The investigators found that PCI not only significantly reduced the risk of symptomatic brain metastases (17% vs. 41%, HR 0.27, p<0.001), but also prolonged six-month progression-free survival (23% vs. 13%, HR 0.68, p=0.003). There was no difference in extracranial progression. Indeed, the majority of patients in both arms (85-93%) developed extracranial disease progression, and most died within 2 years. PCI was well-tolerated with adverse effects being mostly grade 2 headache, nausea/vomiting, fatigue, and skin reactions. It was concluded that PCI should be offered to all patients with extensive disease who respond to first-line chemotherapy.

Consolidation docetaxel is associated with toxicity and does not improve survival in inoperable stage III non-small cell lung cancer treated with radiation given concurrently with cisplatin and etoposide
N. Hanna et al, Abstr. 7512

This randomized phase III trial was designed to evaluate the value of docetaxel consolidation in the regimen reported in the phase II study SWOG 9504. Patients with unresectable stage III, PS 0-1, and FEV >1L were treated with cisplatin (50mg/m^2 days 1, 8, 29, 36) and etoposide (50mg/m^2 days 1-5 and 29-33) given concurrently with radiation (59.4 Gy). Patients with non-progressive disease were randomized to receive either 3 cycles of docetaxel (75mg/m^2) or observation. After 203 patients were accrued, with 147 randomized and 62 deaths, the study was closed early based on recommendation of the Data and Safety Monitoring Board. There was no difference in progression-free (13.3 mo vs. 12.9 mo), median (21.5 mo vs. 24.1 mo) or 3-year survival (27.2% vs. 27.6%) between the docetaxel and observation arms. In the docetaxel arm there were more grade 3/4 infections (11% vs. 0%), pneumonitis (9.6% vs. 1.4%), hospitalizations (29% vs. 8%) and deaths (9.6% vs. 1.4%). Thus, docetaxel consolidation does not add benefit to this concurrent chemoradiation regimen.

For more information about referring patients to the UW Paul P. Carbone Comprehensive Cancer Center, contact Cancer Connect, (800) 622-8922 or (608) 262-5223

A complete listing of all clinical trials at the UW Carbone Cancer Center is also available on our website, www.cancer.wisc.edu.

Breaking News From ASCO 2007...

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UW currently offers approximately 20 different phase I, II and III clinical trials involving novel drugs for lung cancer at all stages.

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Save the Date:

Oct 19, 2007:
6th Annual Fall Symposium: Focusing on Cancer Survivorship
Monona Terrace, Madison, WI

Oct 20, 2007:
Wisconsin Oncology Fall Network Meeting
Monona Terrace, Madison, WI

Nov 13-15, 2007:
Lung Cancer Awareness Week
UW Hospital and Clinic
Madison, WI

Nov 15, 2007:
Lung Cancer Public Awareness Event
Madison Marriott West
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Together We Can Save Lives

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