Dr. Robert Weinberg speaks on Cancer Stem Cell Targeting Therapies

Dr. Weinberg focused on the importance of cancer stem cells in mesothelioma. The concept of a stem cell origin of cancer was first described over fifty years ago as a small subset of cells capable of re-initiating a clonal tumor, and there is evidence for both a stem cell origin of mesothelioma, and a stem cell population in the mesothelioma tumor microenvironment. These cells play an essential role in the invasion-metastasis cascade, they are risk to conventional chemotherapy, and are believed to underlie resistance and relapse in mesothelioma.

Neoadjuvant Therapy and Surgery- Dr. Raphael Bueno

Standard therapy for malignant pleural mesothelioma (MPM) has not advanced significantly in the past 10 years and new approaches to treatment are needed. Results from genomic studies indicate that mesothelioma is not a “disease of mutations” and those associated with disease are well known. These studies have shown that MPM is associated with changes in copy number, most often recurrent loss. Biological agents are being developed that can have significant activity in specific cancers based on mutation or other aberrant patterns and several have demonstrated significant activity in animal models and early phase clinical studies. There is an urgent need to rapidly evaluate these agents and identify biomarkers predictive of clinical responses. An attractive cohort for studies of this type is pre-operative with lower disease burden, availability of tumor for biomarker analysis, and the potential for standardization of prognostic markers. This approach is currently being taken with defactinib, a potent inhibitor of focal adhesion kinase in a biomarker-driven study with safety and pharmacokinetics with as secondary end points. Patients enrolled in this study have histologically confirmed MPM that is not metastatic or unresectable and are eligible to undergo excisional surgery such as extrapleural pneumonectomy or pleurectomy/decortication or any other mesothelioma surgery. Additional agents that might be evaluated in this should have: Rational targets predictive of efficacy in MPM based on preclinical studies Demonstrated activity in phase 1 trials

New Molecules and New Therapies – Advancing Mesothelioma Care

Keynote, Dean Fennell presents on treatment developments for mesothelioma

Paul Baas summarizes evidence from studies showing specific targeting of cancer stem cells by defactinib, a novel inhibitor of FAK

Role of Focal Adhesion Kinase (FAK) Inhibition in Mesothelioma

- Ravi Salgia

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that plays an important role in signal transduction pathways that are initiated at sites of integrin-mediated cell adhesions and by growth factor receptors. It is a key regulator of survival, proliferation, migration and invasion, all of which are all involved in the development and progression of cancer. FAK has also been implicated in the phosphorylation of several focal adhesion associated proteins, including paxillin. Overexpression and/or increased activity of FAK is common in a wide variety of human cancers and a large and growing body of literature has provided strong evidence that FAK has important roles in tumor formation and metastasis.
Inhibition or modulation of FAK would appear to be a potential way to treat multiple cancers, including mesothelioma. However, since FAK is a strong mediator of survival signaling, tumor cells with high levels of FAK could be more resistant against classic anti-cancer therapy. There are now multiple agents that specifically target FAK and inhibit this kinase. Studies of FAK inhibitors in vitro and in animal models of different cancers have shown that these agents effectively decrease tumor growth, decrease invasion and metastasis, and inhibit pancreatic tumor microenvironment components, such as tumor associated fibroblasts and macrophages. FAK inhibition also promotes apoptosis and modulates the activity of nuclear factor E2-related factor 2 (Nrf2). The effects of FAK inhibition on Nrf2 activity may be particularly important since the Nrf2 signal pathway may function to protect cancer cells from against drug-induced cell death. Clinical trials with FAK inhibitors in patients with mesothelioma are now in progress.

Raphael Bueno presents the design of the phase II study of the new FAK inhibitor, defactinib for the treatment of patients with mesothelioma

Cancer Stem Cell-directed Therapy: Synergy of a Novel Combination

The Cancer Stem Cell Inhibitors VS-6063 (Defactinib) and VS-5584 Exhibit Synergistic Anticancer Activity in Preclinical Models of Mesothelioma

Dr. Mitch Keegan discusses new finding indicating synergistic effects of defactinib (VS 6063), a FAK inhibitor, and VS-5584, a potent and selective small molecule inhibitor of PI3K and mTORC1 and mTORC2, in an animal model of mesothelioma.