TO: Breathe California of the Bay Area

FROM: Dr. Heather Wakelee, Stanford University School of Medicine

RE: Lung cancer research projects

DATE: December 3, 2013

The Stanford University lung cancer research group has had another busy year. Most recently we returned from the biannual World Conference on Lung Cancer (WCLC) that was held in October 2013 and included several talks and posters from our group.

First to highlight our work in anti-angiogenesis (drugs that change the blood vessel formation of tumors) I'll include updates from several projects. We presented a poster at the WCLC 2013 from our trial of the anti-angiogenesis agent dovitinib in combination with erlotinib. Erlotinib is a pill drug used commonly in lung cancer patients and dovitinib is a new oral medication that is being investigated in many types of cancer. We were hoping the combination would be effective without any increase in toxicity. Unfortunately, we found that there were additional side effects from the combination and will likely have to halt this study earlier than expected. We are currently completing some of the analysis on blood work collected during the study but do not have any patients currently being treated. Dr. Millie Das, a former research fellow who is now on faculty at the Veterans Affairs Hospital in Palo Alto and also sees patients at Stanford one day a week, and Dr. Sukhmani (Suki) Padda, a current 3rd year research fellow, have worked very hard on this project. We are disappointed with the outcome of course, but this reinforces why we need to do clinical trials. There was an unexpected interaction between the 2 drugs, which we presented and will be publishing.

Dr. Padda presented another poster at the WCLC 2013 that focused on the anti-angiogenic properties of a new drug, cabozantinib. Cabozantinib, formerly XL184, is a drug I have been researching for many years and it has clear activity in lung cancer both by itself and in combination with erlotinib. Dr. Padda was able to use blood taken during a large clinical trial with the drug and perform detailed analysis looking at many different molecules that are involved in the angiogenesis pathways. We have samples from both before and after treatment that allows for careful comparisons of changes over time. Her poster was well received and she is working on the manuscript from this work, which was supported by Breathe California and the Colombo Trust.

To build on this work, Dr. Joel Neal and Dr. Heather Wakelee are leading a trial with the Eastern Cooperative Oncology Group (ECOG) looking at the combination of cabozantinib and erlotinib for advanced stage lung cancer patients who have already had chemotherapy. The study opened to patients in 2013 and has been enrolling well.

Our final publication from work with aflibercept (VEGF-TRAP), an intravenous drug that also works on angiogenesis and is approved to treat colon cancer, has been accepted for publication. That manuscript includes work by Dr. Jonathan Riess, a former Stanford fellow who completed fellowship in 2013 and recently took a faculty job at UC Davis, looking at how aflibercept may

also alter red blood cell formation and glucose (sugar) metabolism.

In other news, the ECOG adjuvant trial with the anti-angiogenesis drug bevacizumab for patients with early stage lung cancer that has been removed with surgery, has now completed enrollment of all 1500 patients. Results are not expected for another 2-3 years, but this is a major milestone. We are now thinking about correlates to do to help better understand the patient populations benefitting most from bevacizumab in this setting.

We currently have 3 Stanford medical oncology fellows working on lung cancer related projects, Dr. Manali Patel, Dr. Suki Padda and Dr. Kim-Son Nguyen. Our Stanford lung cancer research database has been moving forward. One particularly interesting project to come from this is work by Dr. Nguyen looking at gene mutations in lung cancer from Vietnamese American patients. We have found that the frequency of some of the known lung cancer mutations is higher in Vietnamese Americans. Dr. Nguyen is now working on a project to compare these results from Stanford to results from a patient population in Hue, Vietnam, where he has established collaborations.

This project highlights how we have been moving more towards molecularly targeted therapy approaches. Lung cancer is no longer thought of as one disease, but many diseases that are similar, but are driven by different gene mutations in the cancers. These different gene mutations mean that the tumors respond differently to specific medications. This has been a major change in our treatment decisions and options for patients. Another major change has been in the development of drugs that can alter the immune system in ways that allow improved treatment of cancers, including lung cancers. In the past year we have opened 2 trials with immune targeted drugs and are looking at 3 others to open in 2014. We are also still focused in better diagnostic options. Our group has been collaborating with other Stanford investigators on improved techniques to identify gene changes in tumors, including detecting these changes from tumor cells that are “shed” into the blood stream. We expect this technique to be widely adopted in the next year or two.