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UH No.: 00
Re: Smith, Jane
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Dear Ms. Smith:

Thank you for seeking a remote second opinion from UCHealth Cancer Care – Anschutz Medical Campus – University of Colorado Cancer Center for evaluation of your recently diagnosed stage IV non-small cell lung cancer. You will be familiar with your own history, but I will summarize it for our records below.

You are a 28-year-old Caucasian female, who in 03/2009 following an episode of syncope and increasing shortness of breath was diagnosed with primary pulmonary hypertension. You were initially treated with 24-hour continuous intravenous infusions of prostacyclin for approximately six months, which you report normalized your pulmonary pressures. During this period of time, a spot on your right lung was noted, which over time seemed to be enlarging. In 10/2009, an open lung biopsy was performed, which revealed an adenocarcinoma from the right upper lobe. This was reported as being TTF-1 positive, negative for thyroglobulin. Positive for cytokeratin 7. Negative for cytokeratin 20, CTX-2, estrogen receptor, progesterone receptor, WT-1 and CEA. Subsequent molecular testing performed at <OTHER CENTER> revealed no KRAS mutation and no EGFR mutation.

Prior to the full molecular information being known, you were initially treated with erlotinib (Tarceva) at 150mg daily for a short number of weeks in late 2009. Specifically you reported having a grade 3 rash, particularly on the scalp, and the erlotinib was discontinued because of this lack of tolerance before any restaging scans were conducted and therefore it was not stopped for known lack of efficacy. However, the absence of any EGFR mutation meant the chances of a significant response were probably slim.

You were then commenced on first-line treatment in approximately 01/2010 with a combination of carboplatin and pemetrexed, Receiving seven treatments in total with a good radiological response. You then proceeded on to maintenance therapy with pemetrexed, adding in bevacizumab. The pemetrexed was discontinued in 11/2010, apparently not because it was not tolerated nor because it was not working, just because a fixed number of cycles had been given. However, it was felt that maintenance with single agent bevacizumab might be sufficient. You continued on the bevacizumab alone until the end of 12/2010, when a PET-CT scan performed on 01/14/2011 showed evidence of progression. Specifically, the PET-CT scan from that date reports that in comparison to on the PET-CT scan from 03/2010, showed the following: Extensive patchy opacities right lower lobe compatible with carcinoma.

The largest measures 2.7 cm having increased from 2 cm, SUV 6.3 which is also increased. Additional multifocal opacities within the right lung more superiorly increased in size and number since 03/2010. Interval development 2.1 cm mass left upper lung, SUV 5.2. Subcentimeter nodules in the left lung which are not FDG avid but suspicious for small metastases. Minimal right pleural effusion. Hypermetabolic foci in the mediastinum and left hilum. 2.4 cm mass cephalad to the left main pulmonary artery, SUV 8.8. New left hilar lymphadenopathy, SUV 5.5. Right supraclavicular region lymphadenopathy and right axillary lymphadenopathy measuring 2 cm, maximal SUV 6.5. Within the skeletal system several foci are noted within the left iliac bone, upper dorsal vertebral body sternal lesion. Overall the sites of disease reported were lung, mediastinal lymph nodes, supraclavicular fossa lymph nodes, axillary lymph nodes, and bone lesions. Of note, the report of the CT scan of the chest, abdomen and pelvis performed in 10/2010, which would have been a more relevant comparator given its interval timing was reviewed by me. This reports the largest right lower lobe lesion to be 2.3 cm. We do not have the images on disk and therefore direct comparison is hard to call but the possibility of some minor progression seems apparent on the bevacizumab monotherapy earlier on.

I am pleased to hear that you currently feel well. The objective measure of your ECOG Performance status is 1. You have some grade 1 shortness of breath on exertion, and some grade 1 intermittent cough. You deny having any pain but you do have some vague grade 1 discomfort at the site of the thoracotomy, which is intermittent. When on the prostacyclin for your pulmonary hypertension you report some grade 1 intermittent headaches and flushing depending on the dose. Apparently your blood pressure was fine when on the bevacizumab and certainly you report feeling more short of breath off the bevacizumab, although whether this is your primary pulmonary hypertension or the underlying lung cancer is uncertain. I also noted on review of the following systems nothing else of importance: constitutional, respiratory, cardiovascular, gastrointestinal, neurologic, musculoskeletal, dermatological, psychiatric; ears, nose, throat and eyes.

PAST MEDICAL HISTORY:
Your past medical history includes the following: Primary pulmonary hypertension. Non-small cell lung cancer. You have no known history of heart attack, stroke, epilepsy, asthma, diabetes, tuberculosis, or rheumatic fever. You had a cholecystectomy in 2004.

CURRENT MEDICATIONS:
Revatio 20 mg b.i.d. occasionally increasing to 3 times a day depending on how you feel, multivitamin and folic acid. Mucinex as needed.

ALLERGIES:
You get a rash with PENICILLIN, LEVAQUIN and ZYVOX.

FAMILY HISTORY:
You were born in Fremont, Michigan and then at a fairly young age moved to Jacksonville, Florida. Your mother and father now live in Denver. No other first degree relatives have been diagnosed with cancer to your knowledge.

SOCIAL HISTORY:
You have smoked probably about 20 cigarettes in your entire life. You drink a minimal amount of alcohol and take no other recreational drugs. You are married to a post-office worker and have one daughter aged 3 years. You are currently on disability having

previously been an insurance telephone sales operator. You have one younger sister who is fit and well.

EXAMINATION:
Physical examination was not performed because of the nature of the remote second opinion program.

However, a note from your local doctor dated 23rd February 2011 reports no abnormal physical findings.

SUMMARY:
You are 28-year-old Caucasian female with known non-small cell lung cancer with bone, lung, and lymph node deposits. In addition to the lung cancer your major issues relate to your primary pulmonary hypertension and its effect on your breathing and her shortness of breath, plus any contribution from your underlying malignant lung disease. You have received treatment briefly with erlotinib which was poorly tolerated and then had an excellent response to pemetrexed and carboplatin, followed by pemetrexed and bevacizumab maintenance therapy, then bevacizumab maintenance therapy followed by recent progression. You are now seeking a second opinion as to both the nature of your lung cancer and the best treatment options at this point.

DATA REVIEWED:
All notes were reviewed and summarized as above. In addition, blood results were reviewed from 02/1011 which revealed an unremarkable complete blood count. A comprehensive metabolic panel from 02/12/2011, shows a normal creatinine, glucose slightly high at 100, calcium normal, AST, ALT and alkaline phosphatase normal. Bilirubin normal. Albumin normal. Urinalysis normal.

IMAGING:
Specifically, the PET-CT scans including the most recent from the 01/14/2011, and the CT scan showed the abdomen and pelvis from 10/2010, were reviewed and summarized above. Unfortunately, for the last of these we did not have the images on disk.

PLAN:
We reviewed your original biopsy specimen and our expert pathologist confirms that this in indeed an adenocarcinoma of the lung (the most common histological subtype of NSCLC). Although it is clear that you have stage IV cancer from the scans – none of the scans have imaged the brain directly. Many PET/CT scans pass through the brain but the signal from the normal brain tissue is often so bright that abnormal signals can be missed. Therefore to fully stage your cancer I would recommend getting an MRI of the brain. Approximately 20% of lung cancers have deposits in the brain when they are first diagnosed and it is good to find this out before you have any symptoms. Deposits in the brain if present may be treated with radiation therapy, or occasionally surgery.

Some of the biggest breakthroughs in lung cancer have come from being able to molecularly profile tumors more and more. I note that you have had both EGFR and KRAS testing done, both of which were reported as negative. Firstly, in the case of a negative result – looking at the details of the test is important. Reassuringly, the amount of material present in the tested specimen appeared adequate and for the EGFR – the gene associated with erlortinib sensitivity - exons 18 through 21 were all sequenced. Therefore I am confident in the result shown. What is more intriguing is that in a young woman, with adenocarcinoma of the lung

who has little or no smoking history, a relatively recently described molecular subtype of cancer – called ALK gene rearranged cancer may be particularly common. In addition, we now know from information we have submitted for publication but that is not yet in the public domain, is that ALK positive patients often have very dramatic and prolonged Reponses to pemetrexed alone or pemetrexed containing regimens, just as you did. Putting all of these things together we performed additional molecular testing on your tumor, including ALK testing by fluorescence in-situ hybridization. I am very pleased to tell you that your tumor does indeed have an ALK gene rearrangement.

As mentioned above, this is a new molecularly defined subtype of non-small cell lung cancer. It is not particularly associated with smoking exposure. It is in the tumor and not something that as far as we know is inherited or something that you can pass on. To put it another way – the cancer is abnormal – not you.

In terms of treatment options, as you have not technically progressed while on the pemetrexed (being only on the bevacizumab at the time) the possibility of returning to the pemetrexed is there. However, you could keep this in reserve in addition to other cytotoxic chemotherapies. There is one drug currently in clinical trials which has very specific activity against the rearranged ALK gene which is PF 02341066 or crizotinib. This is currently available in three different studies; a phase 1 and a paired phase 2 and phase 3 study. The phase 3 study is a randomized study in the second-line setting comparing PF 02341066 to either docetaxel or pemetrexed. In your case it would be compared to docetaxel given your prior pemetrexed exposure. There is a companion phase 2 study which allows patients who are randomized to the chemotherapy arm to have access to PF 02341066 following completion of the chemotherapy arm. Reviewing clinicaltrials.gov it appears that no centers with these studies are open near your home in Florida at present. Within the centers involved in the initial phase 1 study until the phase 2 and 3 studies are open, patients may still enter into the expanded cohort, which is currently the situation at the University of Colorado. It is important for me to point out that in the current setup if one starts on the phase 1 study one cannot transition to centers which have the phase 2 and phase 3 study, and therefore you would be committed to care at the University of Colorado while on the study, but as we chatted about on email, since your family has moved here you may be happy with this. I did also print off the information on the phase 3 and phase 2 studies including the contact number for Pfizer to track if any centers open up in Florida. Your last treatment was nearly two months ago. I think we would track your disease either by a PET-CT scan or by CT scan of the chest and abdomen with intravenous but no oral contrast. We would also have to get up to date laboratory tests too once you had signed a consent form for the study. I gave you information on the phase 1 program here as well as contact details of Sharon Johnson, the coordinator of the study, and my own contact details as well.

Please do not hesitate to contact me should you require any additional information in the next few weeks.