2024 Libby's Lungs Research Update

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A new year is underway with renewed aspirations as we all honor Elizabeth's memory. Elizabeth's courage, resilience, and passion inspired countless lives, leaving a permanent mark on every one of us. Her memory lives on through the lives she touched and serves as an inspiration every single day to continue our fight against lung cancer. With a new year of blank pages in front of us, let us all honor Elizabeth's memory by carrying forward the Libby's Lungs mission that she so passionately pursued.

We continue our research to address the gap in knowledge regarding lung cancer risk, biology, and prognosis among females and never smokers. We published our findings interrogating differential treatment response to immunotherapy in women versus men in the journal Scientific Reports ([Male sex and pretreatment weight loss are associated with poor outcome in patients with advanced non-small cell lung cancer treated with immunotherapy: a retrospective study | Scientific Reports (nature.com)](#)). This work stemmed from our interest in the contribution of sex hormones to the pulmonary immune response which could influence lung cancer risk as well as response to treatment. We found that women had a significantly better outcome compared to men treated with first-line immunotherapy. We are now expanding this study by sequencing tumor tissue from responders and non-responders to evaluate estrogen and immune pathways as predictors for treatment response. As we found that we were only able to obtain ~1/3 of the tumors from this study through pathology, our goal this year is to establish a biobank of biospecimens from never smokers with lung cancer which will be crucial to our research.

We are also making progress on a project aimed at understanding the contribution of western PA environmental exposures to never smoking lung cancer which was named a Hillman Innovative Cancer Research Project. We completed whole genome sequencing of tumor tissue from never smoking lung cancer patients. The residential address for each person was geocoded to obtain geographic coordinates and used to estimate air pollution and radon exposure levels. We are currently linking the resulting mutational signatures to residential exposure levels and a blood-based "exposome" signature. Using our preliminary data from these and other ongoing studies, we submitted a proposal to the NIH to evaluate

the unique pulmonary immunopathology in women versus men to understand how these changes may increase susceptibility to lung cancer in female never smokers.

We also continue our research on oncogene-driven lung cancer, specifically the MET pathway and its role in lung cancer brain metastasis and resistance to targeted therapies, such as EGFR and ALK inhibitors. Using our preclinical models in the lab, we have data supporting the role of the MET pathway in promoting metastasis to the brain, evidence of a unique tumor biology, and are testing novel treatment and prevention approaches. We are also pleased to report that a clinical trial stemming from our laboratory work is now open to accruing patients. This trial is evaluating a MET inhibitor in lung cancer patients with MET amplified brain metastasis as detected in circulating tumor cells in the blood. Additionally, we have developed a radiomic-based brain metastasis prediction model in collaboration with our radiology colleagues and are in the validation stage with a large independent cohort. We expect to publish our findings this year. This model uses standard-of-care chest CT images to predict future occurrence of brain metastasis and was presented at the 2023 American Association for Clinical Oncology Annual Meeting and several lung cancer-focused meetings. We plan to evaluate this model prospectively and ultimately translate this into a practice-changing tool to improve patient outcomes by identifying those in need of MRI surveillance. There are currently no modalities used in clinical practice to identify those at high risk of brain disease who would benefit from a more frequent brain screening and surveillance strategy. At the 2023 American Association for Cancer Research Annual Meeting, we presented an early detection study using high-resolution imaging of sputum as a non-invasive way to detect early lung cancer and are currently preparing a manuscript on these findings.

Your unwavering support is truly invaluable to continue this important lung cancer research and is deeply appreciated. It is because of compassionate individuals like you that we can pursue groundbreaking research in underfunded areas, push the boundaries of knowledge, and strive toward a future where lung cancer is no longer a devastating diagnosis but a conquerable challenge.