alterations with DFS through Cox regression models. Concordance probability estimate (CPE) was used to discriminate performance between the existing TNM model and the developed prediction models.

**Results:** The median age was 70 years (range, 55-84), one-third were female (n=35), 55% (N=52) were pathologic stage I, and 98% (N=93) were ever-smokers. Median follow-up was 2 years. Recurrence occurred in 20% (19/95) and DFS was 74% (95% CI, 84-96%) at two years. Clinicopathologic features associated with DFS were lymphovascular invasion, visceral-pleural invasion, and pathologic stage. Tumor genomic analysis revealed alterations in the transcription factor BCL6 were independently associated with worse DFS (HR 5.23, 95% CI 1.73, 15.9, p=0.009), while mutations in the tumor suppressor ARID1A were associated with a worse OS (HR 2.98, 95% CI 0.91, 9.77, p=0.07). Pathway-centric analyses revealed no associations with our primary or secondary endpoints. Our prognostic clinicopathologic model outperformed the internally validated TNM model (CPE, 0.74 vs. 0.70) for prediction of DFS and our clinicopathologic model, adjusted for BCL6 genomic alterations, further improved discrimination (CPE=0.77).

**Conclusions:** We show that integration of high-risk clinicopathologic and tumor genomic profiling better predicts DFS than TNM classification alone in early-stage, surgically resected LUSC and a genomic pro

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**A24**

**The Genome-Wide Mutational Landscape of Lung Cancer in Never-Smokers: The Women’s Health Initiative (WHI) Cohort**


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Lung cancer is the leading cause of cancer deaths worldwide, and a positive history of smoking remains one of the most significant risk factors for lung cancer development. However, about 20% of lung cancer diagnoses are reported in individuals with no smoking history. Lung cancer in never-smokers (LCNS) is clinically distinct from tobacco-induced lung cancer, with a greater proportion of LCNS occurring in women and having adenocarcinoma histology. One of the key challenges in identifying the cancer-promoting genetic events that drive LCNS is the relatively small number of tumors that have been sequenced using genome- or exome-wide approaches. We address this gap through the collection and exome sequencing of lung tumor tissue and matched blood-derived normal DNA from 77 women who participated in the Women’s Health Initiative (WHI), the majority of whom have light or no smoking history. Samples were sequenced with a custom exome approach at the Center for Cancer Genome Discovery (CCGD), Dana-Farber Cancer Institute, with baits for all protein coding regions of the genome and noncoding regions that are frequently rearranged/translocated in lung cancer, such as introns within the ALK gene. Somatic mutations were identified using MuTect2 and mutational significance was determined using MutSig2CV. Preliminary analysis involving 18 tumor/normal pairs identified an enrichment of somatic alterations in genes such as **EGFR** and **TP53**. Additionally, tumor purity and copy number alterations were estimated using ichorCNA. Translocation analysis was performed using BreaKmer identifying a CD74-ROS1 fusion. 72% of the cases harbored previously known oncogenic drivers of lung adenocarcinoma such as mutations in **EGFR**, **KRAS**, **RIT1**, and **MET** with mutations that are clinically targetable using FDA-approved or investigational agents. Overall this project will double the number of exome profiles from never-smokers and, importantly, leverage the extensive metadata curated under the WHI to evaluate secondary/environmental factors such as second-hand smoke and radon exposure and their potential role in LCNS.

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**A25**

**PTPRH Mutations in NSCLC Regulate EGFR Phosphorylation**

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The dysregulation of receptor tyrosine kinases (RTK) has garnered plenty of interest within the cancer field, and attention has begun to turn to phosphatases regulating RTK behavior. Under normal cellular conditions, protein tyrosine phosphatases remove phosphate groups from tyrosine residues, thus maintaining signaling homeostasis. In whole-genome sequencing of primary mouse mammary tumors from the polyoma virus middle T antigen (PyMT) mouse model, we found a mutation in the protein tyrosine phosphatase receptor type H (Ptprh) gene. Targeted resequencing of 45 mouse tumors showed a conserved heterozygous or homozygous mutation present in 80% of tumors. This C->T mutation results in a valine-to-methionine shift within one of the fibronectin domains of PTPRH. Previous literature has shown interactions between PTPRH and epidermal growth factor receptor (EGFR). To determine the relevancy of PTPRH mutations in human cancer, data from The Cancer Genome Atlas (TCGA) were analyzed and revealed PTPRH mutations in 5% of non-small cell lung cancer (NSCLC) patients. Moreover, patients with a mutation in PTPRH were mutually exclusive from those with mutation or amplification of EGFR. We hypothesize a mutation in PTPRH results in a failure of PTPRH to dephosphorylate EGFR, resulting in inappropriate maintenance of downstream signaling pathways important for proliferation and evading apoptosis. Since NSCLC patients with EGFR mutations are successfully treated with tyrosine kinase inhibitors (TKI), we also hypothesize tumors with a mutation in PTPRH will be sensitive to TKIs. In support of this, we demonstrated mouse tumors with a mutation in Ptprh had increased phosphorylated EGFR (pEGFR). Furthermore, CRISPR-mediated knockout of PTPRH in H23 NSCLC cells leads to increased pEGFR. Pathway signature analysis applied to microarray gene expression data from the Breast TCGA dataset (due to low sample size in the NSCLC dataset), and single sample gene set enrichment analysis applied to RNA sequencing data from the NSCLC TCGA dataset both predicted an increase in PI3K and AKT activity. This suggested the EGFR residue targeted by PTPRH was tyrosine 1197. Western blots on Ptp rh mutant mouse tumors confirmed increased levels of pAKT. Additionally, immunohistochemistry for pEGFR 1197 revealed increased staining in mouse tumors with a mutation in Ptprh, with subcellular location in the nucleus rather than the membrane. To determine whether TKIs may be an effective treatment for NSCLC patients who harbor a PTPRH mutation, H1155 and H2228 NSCLC cell lines with PTPRH mutations in the fibronectin and phosphatase domains, respectively, were subjected to a dose response curve with the TKI osimertinib. These lines show significant growth differences as compared to the negative control cell line A427. While more work is needed to elucidate the role of mutant PTPRH in NSCLC, preliminary data suggest mutant PTPRH fails to dephosphorylate EGFR, and patients with a mutation in PTPRH may benefit from TKI therapy.

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**A26**

**Deciphering the Functional Redundancy of USP4 and USP15**

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Ubiquitin-specific proteases (USPs) are a class of deubiquitinating enzymes that catalyze the removal of ubiquitin from various proteins and are involved in many cancers. Previous work established the USP paralogs USP4 and USP15 emerged from an ancestral USP about 500 million years ago from a whole genome duplication, and the majority of