Mutations in three key genes associated with poor outcomes in lung cancer patients treated with KRAS G12C inhibitors

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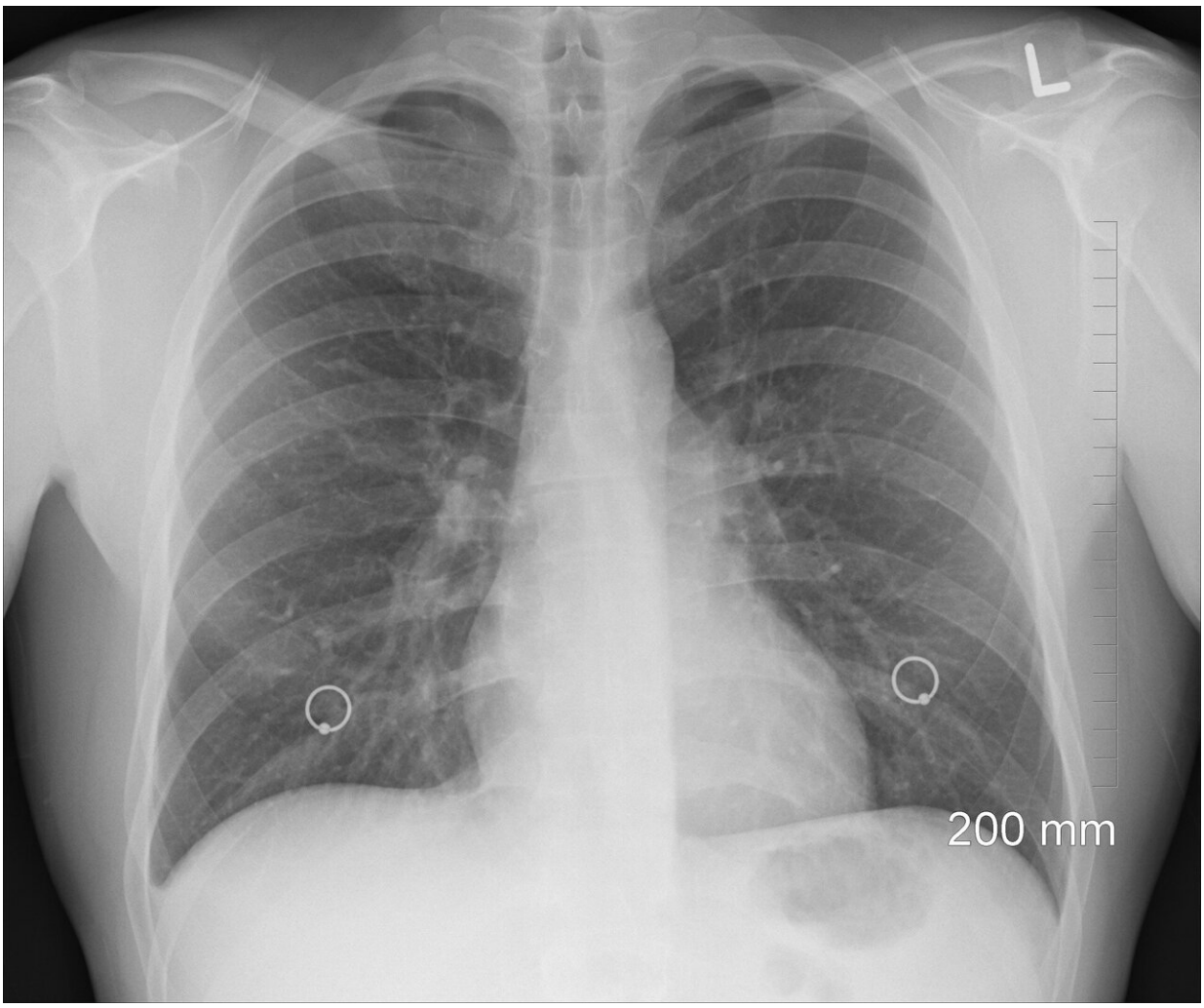

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A new study led by researchers at The University of Texas MD Anderson Cancer Center has discovered that co-occurring mutations in three tumor suppressor genes—KEAP1, SMARCA4 and CDKN2A—are linked with poor clinical outcomes in patients with KRAS G12C-mutant non-small cell lung cancer (NSCLC) treated with the KRAS G12C inhibitors adagrasib or sotorasib.

The findings were presented today at the American Association for Cancer Research (AACR) Annual Meeting 2023 and published in *Cancer Discovery*. This study, which encompasses the largest cohort to date of patients with KRAS G12C-mutant NSCLC treated with either agent, provides a framework for clinicians and scientists to stratify patients by predicted clinical outcomes and to develop more effective treatment strategies for those unlikely to benefit from KRAS G12C inhibitors alone.

"KRAS G12C inhibitors have revolutionized the care of patients with lung cancer, but we see non-uniform clinical outcomes when these drugs are used as single agents," said lead author Marcelo V. Negrao, M.D., assistant professor of Thoracic/Head and Neck Medical Oncology. "Therefore, it is important to understand biomarkers and to define subgroups of patients that will have better outcomes from single-agent therapy as well as patients that will require a different treatment strategy."

The KRAS protein is responsible for regulating normal cell growth and proliferation, but activating mutations drive abnormal growth and cancer development. KRAS is the most common oncogenic driver of non-squamous NSCLC, with mutations found in 25-30% of patients. The KRAS G12C mutation is found in approximately 13% of cases. Both adagrasib and sotorasib are approved by the Food and Drug Administration to treat patients with advanced KRAS G12C-mutant NSCLC following failure of at least one prior line of standard systemic

therapy.

Unfortunately, while many patients benefit from these targeted therapies, most do not achieve durable disease control from either agent as a monotherapy. Thus, the median progression-free survival (PFS) for patients treated with either drug is approximately 6-7 months, Negrao explained.

To better understand molecular factors associated with response or resistance to KRAS G12C inhibitors, the researchers assembled a cohort of 424 patients from 21 centers in the U.S. and Europe, who were treated with single agent adagrasib or sotorasib. Across all patients, the overall response rate (ORR) was 34% and the median PFS was 5.2 months. There were no significant associations between outcomes and the specific KRAS G12C inhibitor used.

The researchers compared patients with distinct clinical outcomes to adagrasib and sotorasib, including those with durable benefit (PFS of at least 6 months) and those with early progression (PFS of 3 months or less). An unbiased analysis of co-occurring mutations in each group revealed that mutations in KEAP1, SMARCA4 and CDKN2A were significantly enriched in patients with early progression. Mutations in each gene were independently associated with significantly shorter PFS and overall survival. In contrast, mutations in STK11 and TP53—two frequently mutated genes—did not appear to be associated with outcomes to either drug.

When assessed together, mutations in KEAP1, SMARCA4 and CDKN2A were present in about one-third of patients in the cohort and accounted for approximately half of those who exhibited early disease progression with single agent KRAS G12C inhibitors. These three genes routinely are sequenced with current tumor profiling panels, so this knowledge can be used to readily stratify patients into groups with

distinct clinical outcomes, Negrao explained.

In an exploratory analysis, co-mutations in genes involved with DNA damage repair and the ATRX/DAXX pathway were associated with improved outcomes, whereas additional alterations in RAS genes and mutations in PI3K/AKT/MTOR pathway genes were linked with inferior outcomes. However, these mutations were less prevalent in this cohort and require additional investigation.

"This study establishes the co-mutational landscape of early disease progression with KRAS G12C inhibitor monotherapy, and it provides a blueprint for personalizing treatment approaches with distinct combination strategies," said presenter and senior study author Ferdinandos Skoulidis, M.D., Ph.D., associate professor of Thoracic/Head and Neck Medical Oncology. "Going forward, we plan to dig deeper into these molecularly defined subgroups and try to identify the best individualized therapeutic strategy for each group of patients."

Skoulidis notes this study has helped to form rational hypotheses about which treatment strategies might work best in each subgroup. MD Anderson researchers are actively engaged in developing new KRAS G12C inhibitor-based combination therapies as well as novel immunotherapy approaches as a next step to address unmet needs for these patients.

More information: ABSTRACT 3431: Marcelo V. Negrao et al, Molecular determinants of KRAS p.G12C inhibitor efficacy in advanced NSCLC

Marcelo V. Negrao et al, Co-mutations and KRAS G12C inhibitor efficacy in advanced NSCLC, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-22-1420