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# Genetic and Prognostic Significance of KRAS G12C Mutations in NSCLC Patients Treated with Stereotactic Radiosurgery for Brain Metastases

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## Abstract

Objectives:

Non-small cell lung cancer (NSCLC) is the most common cause of brain metastases (BM), affecting nearly 50% of patients. KRAS-mutant (KRASm) NSCLC is particularly aggressive, and it has been suggested that these patients may have a greater propensity for BM and that there may be differences in outcome between KRAS G12C and non-G12C tumors. The clinical features of patients with KRASm NSCLC BM are poorly described, and there is an absence of data examining outcomes following definitive local therapy with stereotactic radiosurgery (SRS). There are no known genomic correlates of intracranial outcome in patients with KRASm NSCLC BM. To address this knowledge gap, we performed a large retrospective analysis of clinical outcomes and genomic correlates of treatment-naïve patients with either G12C or non-G12C KRASm NSCLC BM managed with definitive intracranial SRS.

Methods:

Demographics, clinical features, and genomic profiles of 210 patients with KRASm NSCLC BM who underwent first-line SRS at MSKCC from 2010-2022, and their CNS-specific outcomes, including intracranial progression free survival (iPFS), local failure, regional failure, and leptomeningeal disease progression were evaluated in an IRB-approved retrospective research protocol. Each patient had at least one tumor sample genomically profiled with one of four versions of MSK-IMPACT (341, 410, 468, 505), an FDA-approved next-generation tumor sequencing assay with 700X coverage, and paired and serial sampling from the primary tumor, extracranial metastasis, resected BM, blood or CSF was obtained in many cases. Tumor sequencing data were analyzed for most common genomic co-alterations and molecular pathway enrichment changes. Genetic alterations were stratified as either drivers or variants of unknown significance using OncoKb, and visualized using the cBioPortal for Cancer Genomics. Baseline clinical characteristics and genomic alteration frequencies were compared using a two-sided Fisher's exact test. Continuous variables were compared using a Wilcoxon test. Kaplan-Meier curves were generated using overall survival and intracranial progression-free survival data (iPFS). All analyses were performed using R v3.6.1.

Results:

Median follow-up from the time of BM diagnosis was 17 months (IQR 8-31). The number of patients with either 1 lesion (G12C 42%, non-G12C 51%), 2 to 5 lesions (G12C 50%, on-G12C 38%), 6 to 15 lesions (G12C 6.2%, non-G12C 9.7%), and greater than 15 lesions (G12C 1.2%, non-G12C 0.8%) were similar across G12C and non-G12C. The rates of either 0, 1, 2, 3 or 4 lesions greater than 1cm at time of BM diagnosis were similar between G12C (29%, 51%, 14%, 3.8%, 2.5%) and non-G12C (24%, 54%, 13%, 5.3%, 1.8%) patients. Median overall survival in G12C and non-G12C patients was 19.4 and 27.3 months, respectively (HR 1.06, 95%CI 0.77 – 1.46). Median iPFS from BM diagnosis in G12C and non-G12C patients were 12.1 and 12.9 months (HR 1.04, 95%CI 0.75 – 1.43). The frequency of co-alterations was calculated across all sequenced samples for STK11 (G12C 43%, non-G12C 34%), CDKN2A (G12C 32%, non-G12C 23%), KEAP1 (G12C 28%, non-G12C 23%), SMARCA4 (G12C 19%, non-G12C 16%), ATM (G12C 20%, non-G12C 14%), RBM10 (G12C 19%, non-G12C 13%), MYC (G12C 9%, non-G12C 8%), and TP53 (G12C 48%, non-G12C 48%). Two of these genes had different proportions of co-alterations upon comparison between 121 primary samples and 61 BM: CDKN2A (primary 18%, BM 34%, p< 0.008) and TP53 (primary 43%, BM 61%). Upon comparing sequencing data of samples from primary, BM, or other metastatic locations, there is a trending and

significant difference between the frequency of oncogenic pathway alterations involving the TP53 pathway (primary 53%, BM 71%, p=0.067) and genes involved in the cell cycle (primary 28%, BM 50%, p< 0.002). A trend towards enrichment was seen in SWI/SNF pathways when comparing BM and primary samples.

Conclusion(s):

Herein, we report the largest-ever assembled cohort of KRASm NSCLC BM patients with detailed clinical outcomes following definitive SRS and the only study to include detailed and matched genomic profiles. We report expected patterns of failure and excellent iPFS, and identify genomic features of G12C and non-G12C KRASm NSCLC that may impact CNS tropism and disease progression. Further interrogation of genomic biomarkers in the context of NSCLC BM is warranted and may assist in risk profiling and treatment selection in such patients.