

GENOMIC DETERMINANTS OF RESPONSE TO CHEMORADIATION AND DURVALUMAB CONSOLIDATION FOR STAGE III NON-SMALL CELL LUNG CANCER

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Background Durvalumab consolidation after chemoradiation for unresectable stage III non-small cell lung cancer (NSCLC) improves overall survival. However, up to 25% of patients progress within 18 months following durvalumab consolidation. Little is known regarding the genomic determinants of response to therapy.^{1 2}

Methods We retrospectively reviewed medical records of 76 patients with stage III NSCLC who received definitive chemoradiation and durvalumab consolidation between 2015–2020 at a large tertiary academic center. Tumor characteristics, molecular profiling, and clinical outcomes including response, progression-free survival (PFS), and overall survival (OS) were documented in an IRB-approved database. Outcomes were assessed by molecular alterations identified from diagnostic biopsy samples using Kaplan-Meier analysis.

Results Of 76 patients with stage III NSCLC treated with definitive chemoradiation and durvalumab consolidation, 74 were evaluable for PFS and OS. Median age at diagnosis was 66.5 years and 43% were women (n=32). Histology included adenocarcinoma (55%, n=41) and squamous cell carcinoma (32%, n=24). Median follow-up time was 23.0 months from start of durvalumab. The cohort's median PFS was 15.9 months with 36 patients having documented radiographic progression. Overall survival for the cohort was 32.0 months with 28 deaths. Molecular profiling was performed at time of diagnosis in 35 patients (47%), of which 30 had adenocarcinoma histology. 18 patients had *KRAS* mutations including *KRAS* p.G12C (n=8), which were mutually exclusive with 8 patients who had other clinically targetable alterations (*EGFR* mutations n=1, *ALK* fusion n=1, *RET* fusion n=1, *MET* exon 14 skipping mutation n=1, or *ERBB2* mutation n=4). Three patients had non-targetable mutations (*BRAF* non-p.V600E, *STK11*, *KEAP1*) and the remaining six patients lacked an identifiable alteration. There was no significant difference in PFS (p=0.92 by log-rank) or OS (p=0.36 by log-rank) between patients with *KRAS* mutations, other targetable alterations, non-targetable mutations, or those without molecular profiling. Within patients with *KRAS* mutations, there was no significant difference in PFS (p=0.33 by log-rank) or OS (p=0.69 by log-rank) when comparing *KRAS* p.G12C to non-p.G12C mutations.

Conclusions Our study of real-world cohort of patients with stage III NSCLC examined genomic determinants of response to treatment with definitive chemoradiation and durvalumab. Results from this retrospective study suggest that patients with *KRAS*-mutated tumors derive similar benefit from therapy than patients with other targetable, non-targetable or no identifiable genomic alterations. Future directions for this cohort include analysis of post-progression therapy, subgroup analysis comparing genomic alterations to patterns of progression, and examination of molecular signatures of patients with progression.

REFERENCES

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Ethics Approval This retrospective chart review study has obtained ethics approval from the Institutional Review Board at the Johns Hopkins School of Medicine (number: IRB00232313).

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