Identification of subjects with locally advanced lung cancer who are likely to respond to standard-of-care chemoradiotherapy by a longitudinal monitoring of circulating tumor DNA (ctDNA) using a comprehensive ultra-sensitive NGS assay

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Background: Only ~20% of patients with locally advanced non-small cell lung cancer (NSCLC) have long term benefit from chemoradiation treatment. Analysis of ctDNA may be superior to other conventional approaches (e.g. CT imaging) in early detection of recurrent disease and can facilitate personalization of treatment strategies. Here we evaluate association between ctDNA levels and survival in subjects with locally advanced NSCLC using an ultra-sensitive next-generation sequencing (NGS) assay.

Methods: Treatment naive tumor and longitudinally collected plasma specimens were analyzed using a 197-gene NGS assay (AVENIO ctDNA Surveillance Kit and AVENIO Tumor Tissue Surveillance Kit prototype, Research Use Only). Mutations detected in pre-chemotherapy tumor specimens and in pre-chemotherapy or pre-radiation therapy plasma specimens were monitored in post-treatment plasma samples by measuring the number of Mutant Molecules Per Milliliter-of-plasma (MMPM). MMPM values were correlated with disease control (as evaluated by RECIST1.1). Kaplan-Meier curves and Cox proportional hazards models were used to assess association of tumor burden with subject survival.

Results: We sequenced 36 tumor and 160 plasma specimens from 40 subjects. At least one mutation reporter was identified in 92% (n=33/36) of pre-chemo or 100% (n=37/37) of pre-radiation plasma specimens. The best predictive performance of the assay was observed using tumor pre-treatment reporters and MMPM cutoff of 8 in plasma samples collected at completion of the scheduled chemoradiation regimen. Subjects with MMPM below the cutoff had a mean overall survival (OS) benefit of 18.5 months (n=27, Tarone p-value=0.013, HR = 3.73, 95%CI = 1.37-10.12). A similar trend was observed using plasma pre-chemo reporters (n=31, Tarone p-value=0.024, HR = 2.08, 95%CI = 0.91-4.74).

Conclusions: Circulating tumor DNA monitoring with an ultra-sensitive NGS-based assay identifies subjects with a locally advanced NSCLC who will have a more favorable outcome when treated with a stand-of-care chemoradiation therapy.

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