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Machine learning classification of small cell lung cancer using plasma multiomics in IMPower133

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Background

Tissue RNA-Seq analysis of extensive-stage small cell lung cancer (ES-SCLC) tumors in the IMpower133 trial (NCT02763579) identified four ES-SCLC subsets (SCLC-N, SCLC-A, SCLC-I-NE, SCLC-I-non-NE), with the SCLC-I-NE subset showing longer overall survival with atezolizumab plus chemotherapy compared to chemotherapy alone, in contrast to the SCLC-I-non-NE subset (Nabet et al, Cancer Cell). To assess the feasibility of determining ES-SCLC subsets based on liquid biopsy, we developed machine learning models using plasma multiomics data.

Methods

We analyzed cell-free DNA (cfDNA) and circulating proteins from 140 patients from IMpower133. We measured CpG methylation at over 250,000 loci by targeted sequencing and inferred gene expression and transcription factor activities from cfDNA fragment patterns. Logistic regression models were trained on individual analyte classes as well as their combinations to classify tumors into one of four subsets.

Results

Plasma multiomics assays effectively differentiate SCLC subsets, with the methylation-based model showing average area under curve (AUC) of 0.84 across the four subsets, while models based on inferred gene expression and proteomics showed AUCs of 0.80 and 0.75. All models were also effective in distinguishing NE from non-NE tumors as a two-class problem (AUCs 0.78-0.89). Features related to subset-associated markers identified in tumors were detected in plasma and contributed to classifier performance. This included lower promoter methylation of NEUROD1 and REST in SCLC-N and SCLC-I-non-NE tumors, respectively. Inferred expression of immune biomarkers such as IFNG (IFN-γ) and CSF3 (G-CSF), was significantly different ($p<0.01$) between I-NE tumors and I-non-NE tumors. Among proteins quantified in serum, there was an enrichment for protein abundance patterns that matched tumor RNA expression, e.g. TFF3 in ASCL1-driven tumors.

Conclusions

We demonstrate that plasma multiomics assays accurately differentiate ES-SCLC subsets, particularly in distinguishing NE from non-NE tumors. These data underscore the potential of plasma multiomics as a noninvasive tool for clinically relevant SCLC subtyping.

Clinical trial identification

NCT02763579.

Legal entity responsible for the study

F. Hoffmann-La Roche.

Funding

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Disclosure

M. Reck: Financial Interests, Personal, Invited Speaker: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Merck, Novartis, Regeneron, Roche, Sanofi, GSK, Pfizer, Pierre Fabre; Financial Interests, Personal, Advisory Board: Amgen, AstraZeneca, BMS, BioNTech, Boehringer Ingelheim, Daiichi Sankyo, Gilead, MSD, Mirati, Pfizer, Regeneron, Roche, Sanofi, GSK, Lilly, Pierre Fabre; Financial Interests, Personal, Other, Member of DMSB: Daiichi Sankyo; Financial Interests, Personal, Other, Member of Data Monitoring Committee: Servier, CureVac; Financial Interests, Personal, Coordinating PI: AstraZeneca; Financial Interests, Institutional, Steering Committee Member: Amgen, Boehringer Ingelheim, BeiGene, Daiichi Sankyo, GSK, BMS, Lilly, MSD, Regeneron, Roche; Financial Interests, Institutional, Local PI: Pfizer Seagen, Nuvalent. R. Gupte: Financial Interests, Personal, Full or part-time Employment: Freenome; Financial Interests, Personal, Stocks/Shares, Employee: Freenome. T. Qing: Financial Interests, Institutional, Full or part-time Employment, I am a current employee of Freenome Holdings: Freenome Holdings; Financial Interests, Institutional, Stocks/Shares: Freenome Holdings. V. Cheung, A. Tang, A. Cauwels, A. Tseng, K. Walter, E. Tabari, V. Chubukov, A. Lovejoy, J. Lin: Financial Interests, Personal, Full or part-time Employment: Freenome Holdings. V. Gayevskiy, J. Sullivan, M. Ballinger, M. Srivastava, B. Nabet: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc. D. Shames: Financial Interests, Personal, Full or part-time Employment: BeiGene. S.V. Liu: Financial Interests, Personal, Advisory Board, Consultant: AstraZeneca, Daiichi Sankyo, Genentech / Roche, Jazz Pharmaceuticals, Merck, Novartis, Regeneron; Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, RAPT Therapeutics, Gilead, Guardant Health, Merus, Takeda, Revolution Medicines, Amgen, AbbVie, Boehringer Ingelheim, Mirati, Pfizer, Lilly, Natera, Johnson & Johnson; Financial Interests, Personal, Invited Speaker: OSE Immunotherapeutics, Yuhan; Financial Interests, Personal, Other, Consultant: GSK; Financial Interests, Institutional, Local PI: Alkermes, Elevation Oncology, Gilead, Merck, Merus, Nuvalent, RAPT, AbbVie, AstraZeneca, Puma, Ellipses, Bristol Myers Squibb, Cogent Biosciences, Duality, Synthekine, SystImmune, Medilink; Financial Interests, Institutional, Steering Committee Member: Genentech; Financial Interests, Institutional, Coordinating PI: OSE Immunotherapeutics; Non-Financial Interests, Member: ASCO, IASLC.