Identification of Non-Small Cell Lung Cancer (NSCLC) Patient Subgroups with Poor Response to Immunotherapy Using Subgroup-Level Meta-Analyses

Kinisha Gala*, Darko Medin, Ankit Kalucha, Judith Pérez Granado, Bruno Larvol, Mark Gramling.

Silver Spring, MD, USA; LARVOL, San Francisco, CA, USA

Background: Given the heterogeneity of clinical outcomes for patients with NSCLC treated with immunotherapy, there remain subpopulations for which immunotherapy has poor efficacy. Identification of these subgroups allows for better stratification within the NSCLC treatment paradigm and may also allow for the development of novel subject-specific therapeutics. We aimed to identify subgroups with poor responses to immunotherapies by performing subgroup-level meta-analyses.

Methods: A systematic search of LARVOL CLIN was performed to identify randomized phase 3 trials comparing at least one immunotherapeutic agent (pembrolizumab, cemiplimab, nivolumab, atezolizumab, durvalumab, tislelizumab, toripalimab or avelumab) to non-immunotherapy regimens for NSCLC. Trials that did not report overall survival (OS) hazard ratios (HR) for patient subgroups were excluded. The data was organized into 24 binarized subgroup pairs based on subject demographics, clinical factors and mutation status and evaluated for each of the eight drugs. The DerSimonian and Laird method was used to perform meta-analyses for each subgroup pair across all eight immunotherapeutic agents. The relative performance of each subgroup was assessed based on the difference in HR across all trials.

Results: 175 trials of NSCLC involving immunotherapeutic agents were identified of which 34 met criteria. The subgroup pair of male versus female had the largest number of trials at 26 trials across the eight agents. EGFR mutation (HR difference: 0.26, p-value<0.05), PD-L1<50% (HR difference: 0.14, p-value<0.001), and TMB<16 (HR difference: 0.24, p-value<0.001) were all identified as subgroups with poor responses to immunotherapies across all eight agents. The presence of NOTCH 1–4 mutations was identified as a subgroup with favorable response to immunotherapy across all eight agents (HR difference: -0.53, p-value<0.01) (figure 1).

Conclusions: Consistent with previous data, our subgroup-level meta-analyses identified low PD-L1 expression, low tumor mutation burden and the presence of EGFR mutations as subgroups that do not have favorable responses to immunotherapy. Additionally, we found that NOTCH 1–4 mutations predict a favorable response to immunotherapy. These data present the most comprehensive study of NSCLC subgroups response to immunotherapy and the methodology presented here can be expanded upon to identify previously unknown subgroups that may benefit from alternative treatment paradigms.

Abstract 903 Figure 1 Subgroup-level meta-analysis by drug for binarized NSCLC subgroups. Effect size for subgroups was considered as the different between the OS HRs and was presented as a color on the heatmap. Red represents non-favorable outcomes, green represents favorable outcomes, and yellow represents neutral favorablility. *p<0.5, **p<0.01, ***p<0.001.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0903