A SYSTEMATIC REVIEW OF PREDICTIVE BIOMARKERS FOR IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background Immunotherapy, particularly immune checkpoint inhibitors, has improved the effectiveness of NSCLC treatment. However, as not all patients benefit from them, identifying predictive biomarkers could be highly valuable in guiding immunotherapy decision-making and highlighting unmet medical needs. Here, we systematically review predictive biomarkers to determine the associated immunotherapy response in NSCLC.

Methods We systematically searched predictive biomarkers in NSCLC using LARVOL VERI, a knowledgebase of 5500 biomarkers and 3500 treatments in oncology. We programmatically compiled a list of conflicting biomarkers associated with immunotherapy sensitivity and resistance. We reviewed their associated evidence documented in LARVOL VERI and evaluated potential biomarker-associated response patterns. The levels of evidence follow the consensus standards established by the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.

Results We identified 183 biomarkers predictive of response to immunotherapy in NSCLC, 154 of which were associated with sensitivity and 46 of which were associated with resistance. We highlight 16 biomarkers, which are highly relevant to the clinical context, as responses to these biomarkers may differ depending on the immunotherapeutic approach used (figure 1). As expected, PD-L1 overexpression emerged as sensitive to immunotherapy in NSCLC, with supporting regulatory approvals and guidelines. There are notable early trials and case-study-level evidence that suggest KEAP1 and STK11 mutations are resistant to single-agent immunotherapy and may respond more favorably to combination therapies. Similarly, when addressing rare molecular alterations, FGFR3 amplification and PD-L1 overexpression are resistant to nivolumab alone. EGFR mutations were present in clinical trial inclusion criteria and EGFR mutation status was associated with varied responses to immunotherapy, suggesting that the EGFR mutations are an area of active research within NSCLC.

Conclusions This comprehensive review of predictive biomarkers of immunotherapeutic response in NSCLC may benefit both NSCLC treatment decisions and strategic development decision-making. Our results highlight KEAP1 and STK11 alterations as mutations that may respond more favorably to combination therapies and EGFR mutations as an area of active research in NSCLC. There are promising findings related to EGFR mutation response to immunotherapy combined with chemotherapy or tyrosine kinase inhibitors. Our analysis uncovers the unmet medical needs in areas of demonstrated resistance to immunotherapy.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0893

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