Clinical profile of SMARCA4/SMARCB1-altered Non-Small Cell Lung Carcinomas: a retrospective study in a Spanish institution

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BACKGROUND

SMARCA4 (also known as BRG1) and SMARCB1 are components of the Switch/Sucrose Non Fermenting (SWI/SNF) protein complex, which has a fundamental function on chromatin-remodeling activity. Inactivation by either truncating mutations, rearrangements or homozygous deletions has a role in the development, early dedifferentiation and metastasis of up to 20% of solid tumors, through the loss of transcription factor activity in specific genes (1).

OBJECTIVES

1. Define the prevalence and clinical characteristics of NSCLC patients with SMARCA4-altered tumors in a real world setting
2. Characterize the immunological features of SMARCA4/B1 altered NSCLC patients and responses to immune checkpoint blockade therapy.
3. Describe different SMARCA4 alteration mechanisms and co-occurring mutations detected by NGS in NSCLC patients.
4. Explore the feasibility of NGS-derived data as an aid in clinical decision making in immunotherapy

RESULTS

Figure 1: Prevalence and clinical characteristics of SMARCA4/B1-altered tumors. We identified 17 patients with SMARCA4/B1 alterations (10.5%), with a median age of 62 years (range 40-82), a dominance of men (12 patients), 70% and tobacco exposure (15 patients, 88%). The most common histology was adenocarcinoma (65%).

Figure 2: Immunological profile of patients. Median TMB was 13.87 mut/Mb (range 1.26-60.52). Six patients (35%) had a tumoral PD-L1 expression ≥ 50%, 3 pts presented 1-49% and another 6 patients had a negative PD-L1 expression.

Figure 3: Genetic SMARCA4 alteration mechanisms and co-occurring mutations. SMARCA4 alterations consisted of point mutations in 13 patients (76.5%). Only 2 patients presented point mutations in SMARCB1. The most frequently altered gene was TP53, (14 patients, 82.4%) followed by CDKN2A/B loss and RICTOR mutations. Pathological alterations in KRAS and EGFR were detected in 4 and 3 patients respectively.

Figure 4: Clinical responses to antiPD-1 based immune checkpoint blockade (ICB). ICB was administered in 12 patients (1st line pembrolizumab in monotherapy or in combination in 83% for metastatic disease). Median PFS for all immunotherapy-treated patients was 360 days (95%CI 158-662). Median OS was not reached.

METHODS

We performed an observational retrospective study at Hospital Clínico Universitario San Carlos (Madrid) in 162 Stage IV NSCLC patients undergoing NGS testing of their disease between July 2019 and December 2021. We analyzed clinical data, response to immunotherapy, tumor mutational burden (TMB) and accompanying genetic alterations.

CONCLUSIONS

1. NSCLC patients harboring SMARCA4/B1 alterations can be identified through NGS testing and have a distinct clinical profile, with a predominance of adenocarcinoma histology without ruling out potential therapeutic targets.
2. In our retrospective, single-center cohort, patients with genetic alterations in SMARCA4/SMARC41 genes presented high TMB and prolonged responses to immunotherapy.
3. Further preclinical and clinical research on the immunological features of lung carcinomas with alterations in SMARCA4/B1 genes is needed.
4. The incorporation of NGS in the management of lung cancer refines clinical profiling of patients and can be helpful in treatment selection.

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DISCLOSURES

None related to this topic.

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REFERENCES