BRIEF REPORT

Brief Report: Clinical Characteristics and Outcomes of Patients With Thoracic SMARCA4-Deficient Undifferentiated Tumors

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ABSTRACT

Introduction: Thoracic SMARCA4-deficient undifferentiated tumors (SMARCA4-UTs) are a recently defined group of aggressive cancers in which the effectiveness of standard treatments for lung cancer is unknown.

Methods: We collected clinical, pathologic, and demographic variables from five institutions for patients whose tumors met criteria for SMARCA4-UTs (undifferentiated phenotype and loss of SMARCA4 (BRG1) by immunohistochemistry).

Results: We identified 92 patients with SMARCA4-UTs; 58 (63%) had stage IV disease at diagnosis and 16 (17%) developed recurrent or metastatic disease after initial diagnosis. Median overall survival from metastatic diagnosis was 7.3 (95% confidence interval [CI]: 4.6–12.8) months. Of patients with metastatic disease, 58 (78%) received first-line systemic treatment. Most often, patients received chemo and immunotherapy combination (41%), chemotherapy alone (33%), or immunotherapy alone (16%). Median progression-free survival from start of systemic therapy was 1.9 (95% CI: 1.4–14.5) months for chemo and immunotherapy, 1.6 (95% CI: 1.1–5.8) months for chemotherapy, and 3.3 (95% CI: 1.2–undefined) months for immunotherapy alone. Five patients had durable responses (≥2 y); all received immunotherapy as part of first-line regimens. Nine (16%) of 55 tumor samples tested had programmed death-ligand 1 expression more than or equal to 50%, with 24 (44%) negative samples. Tumor mutational

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burden was available in 48 cases (52%), and median was 10.5 (range: 2–48) mutations per megabase.

Conclusions: This multi-institution retrospective cohort analysis revealed a population of patients with short progression-free survival to standard therapies and poor overall survival. A few patients had remarkable response to regimens including immunotherapy. Prospective clinical studies are urgently needed to identify better therapeutic approaches to treat this aggressive malignancy, and this analysis may serve as a benchmark for future clinical trial design.

Keywords: SMARCA4-deficient undifferentiated thoracic tumors; Immunotherapy; Outcomes; Rare tumors

Introduction

SMARCA4, a member of the switch sucrose nonfermentable chromatin remodeling complex, encodes the BRG1 protein[1] and has been implicated in transcription, differentiation, and DNA repair. SMARCA4-deficient undifferentiated thoracic tumors (SMARCA4-UTs) are a recently identified tumor type, defined primarily by loss of the SMARCA4 protein and undifferentiated phenotype.[2,3] Importantly, SMARCA4-UT is distinct from the more common *SMARCA4*-mutant NSCLC. SMARCA4-UTs have different clinical, molecular, and histologic features and may require distinct management strategies.[3]

In recognition of unique pathologic features and near-uniform poor prognosis for patients, SMARCA4-UT is classified as an "other epithelial tumor of the lung" in the fifth edition of *WHO Classification of Thoracic Tumors*. Since its inclusion in the *WHO Classification* in 2021, diagnosis of this entity has increased, but there are still few published data regarding the characteristics and outcomes of affected patients[4–8] and no treatment guidelines exist.

As this distinct disease subtype has been defined from a pathologic perspective, it has become clear that patient outcomes need to be elucidated as well. In this multicenter, retrospective cohort study, we report the largest cohort study of clinical characteristics and treatment outcomes for patients with SMARCA4-UT.

Materials and Methods

We conducted a longitudinal analysis of data retrospectively collected from five academic institutions. Patients diagnosed before January 1, 2024, were included if their tumors met the criteria for SMARCA4-UT (undifferentiated phenotype and SMARCA4 (BRG1) loss by immunohistochemistry) and clinical information was available. A thoracic pathologist at each institution was involved in case identification. After institutional review board approval, clinical information was gathered through chart review of notes, medication administration history, and radiologic studies and pathologic reports. Next-generation sequencing (NGS) data were derived from approved assays (see Supplementary Material).

For all patients in longitudinal analyses, we determined the date of metastatic diagnosis, systemic therapy initiation, progressive disease (by treating physician's assessment), or death. Primary end points were overall survival (OS), ending at the date of death of any cause, and progression-free survival (PFS), ending at the earliest date between those of death or tumor progression. Their lengths were computed starting either from the date of metastatic diagnosis or the date of systemic therapy initiation in separate analyses and censored at the date of last contact before data cutoff.

Data were summarized, and differences across groups assessed, using appropriate descriptive statistics. We also summarized the distribution of OS and PFS durations using Kaplan-Meier curves. GraphPad (Prism) (Dotmatics) and R (R Core Team) were used for statistical analyses.

Results

Demographic Information

We identified 92 patients with SMARCA4-UT and clinical information available for analysis (Table 1). At diagnosis, median age was 65 (range, interquartile range [IQR]: 32–89, 16.5) years; 15 (16%) were younger than 50 years old at diagnosis. In addition, 58 (63%) were men and 64 (70%) white. Only 3% had never smoked cigarettes; those with a tobacco history had a median of 40 (range, IQR: 1.5–126, 35) pack-years of exposure. Stage at diagnosis was I for six (7%), II for six (7%), III for 22 (24%), and IV for 58 (63%) patients.

Tumor Pathologic Characteristics

Of the 92 patients, programmed death-ligand 1 (PD-L1) tumor expression was available for 55 (60%) cases. Of these 55, nine patients (16%) had PD-L1 tumor proportion score more than or equal to 50% and 24 patients (44%) had negative result (tumor proportion score less than 1%). Tumor mutational burden (TMB) was available in 48 of 92 cases (52%). Among these 48 patients, median TMB was 10.6 mutations per megabase (range 2–48). NGS was performed in 66 of 92 cases (71%) using standard clinical panels at each institution. In these 66 patients, mutations of interest included *SMARCA4* (77%), *TP53* (71%), *KEAP1* (26%), *STK11* (18%), and *KRAS*

Table 1. Characteristics of Patients With SMARCA4-UT

Characteristics	n (%), n = 92
Age, median (range), y	65 (32-89)
Male	58 (63)
Current or former tobacco history	89 (97)
Pack-years, median (range)	40 (1.5-126)
Presented with metastatic disease	58 (63)
Ever developed metastatic disease	74 (80)
Patients treated for metastatic disease	n = 58
Received 1 line	32 (55)
Received 2+ lines	26 (45)
First-line therapy	n = 58
Chemotherapy and immunotherapy	24 (41)
Chemotherapy	19 (33)
Immunotherapy	9 (16)
Clinical trial	4 (7)
Other	2 (3)
First-line treatment duration, median (d)	38
PD-L1 expression	n = 55
<1%	24 (44)
1%-49%	22 (40)
≥50%	9 (16)
Genomic alterations	n = 66
SMARCA4	51 (77)
TP53	48 (71)
KEAP1	17 (26)
STK11	12 (18)
KRAS	10 (15)
Tumor mutational burden	n = 48
Median (range)	10.6 (1.6-48)

PD-L1, programmed death-ligand 1; SMARCA4-UT, SMARCA4-deficient undifferentiated tumor.

(15%) (Fig. 1). Furthermore, 16 tumors (24%) had three of the aforementioned mutations concurrently; six (9%) had four or more. Of 51 tumors that harbored *SMARCA4* mutations, all were classified as pathogenic by a molecular pathologist (SRY). Of 10 tumors with *KRAS* mutations, only one was G12C.

Clinical Outcomes

Early stage cancers were treated according to accepted standards for treating lung cancer (i.e., patients with stage I cancer were treated with local therapy such as resection or radiation, and patients with more advanced disease were treated with concurrent chemoradiation or surgical resection in combination with perioperative systemic therapy). After a median of 8 (range, IQR: 2–78, 13.9) months from initial diagnosis, 16 (47%) patients had metastatic recurrence of the 34 initially diagnosed with stages I to III disease. Recurrence rates seemed to be tied to stage of presentation as is for NSCLC: one of six patients with stage I cancer recurred (17%), two of six patients with stage II cancer recurred (33%), and 13 of 22 patients with stage III cancer recurred (59%). Of all 74 patients with metastatic disease, 54 (73%) died after metastatic diagnosis, 17 were censored, and three had unknown OS censoring status. Median OS from metastatic diagnosis was 7.3 (95% confidence interval [CI]: 4.6–12.8) months.

Of the 74 patients with metastatic disease, seven (9%) were deemed too ill to receive treatment at presentation, whereas 58 (78%) received first-line systemic treatment. These 58 patients received a median of one (range, IQR: 1–5, 1) line of therapy for metastatic disease. The most common first-line treatments were combination chemotherapy and immunotherapy (n = 24, 41%), chemotherapy alone (n = 19, 33%), immunotherapy alone (n = 9, 16%), or a clinical trial (n = 4, 7%). Chemotherapy agents were mostly platinum doublet regimens with or without immunotherapy: platinum and pemetrexed (20), platinum and squamous-directed agent (paclitaxel, nab-paclitaxel) (13), or other partner (etoposide, gemcitabine, vinorelbine) (7). Of patients who had PFS more than 6 months to first-line treatment who were not exceptional responders (median PFS range 7.4 mo–22.6 mo), five of six patients received platinum and pemetrexed regimen.

Among the 58 patients with metastatic disease who started first-line therapy, 42 (72%) had PFS after a median of 1.9 (95% CI: 1.4–5.4) months from therapy start, 12 were censored, and four had unknown PFS censoring status. Median PFS from therapy start was 1.9 (95% CI: 1.4–14.5) months for those who received chemotherapy-immunotherapy, 1.6 (95% CI: 1.1–5.8) months for those who received chemotherapy, and 3.3 (95% CI: 1.2–undefined) months for those who received immunotherapy alone (Fig. 2*A*).

Five patients experienced durable responses (≥2 y): two received combination chemotherapy and programmed cell death protein 1 (PD-1) inhibitor, two received PD-1 inhibitor monotherapy, and one received PD-1 and CTLA-4 inhibitor doublet immunotherapy (Fig. 2*B*). There were no apparent characteristics that distinguished these patients from others who received first-line therapy. Median age of these patients was 65 (range: 45–76) years, and they were mostly male (n = 4, 80%) and current or former smokers (n = 5, 100%). All but one patient presented with metastatic disease. PD-L1 expression was high in only one of these patients. Median TMB was 10.7 (range: 9.1–31.6) mutations per megabase in these tumor samples. NGS did not identify unique patterns for these patients, whose tumors harbored mutations in *SMARCA4*, *TP53*, *STK11*, and *KEAP1* similar to other patients (Table 2).

Discussion

In a nascent but developing literature, characteristics of patients with SMARCA4-UT are starting to be defined.

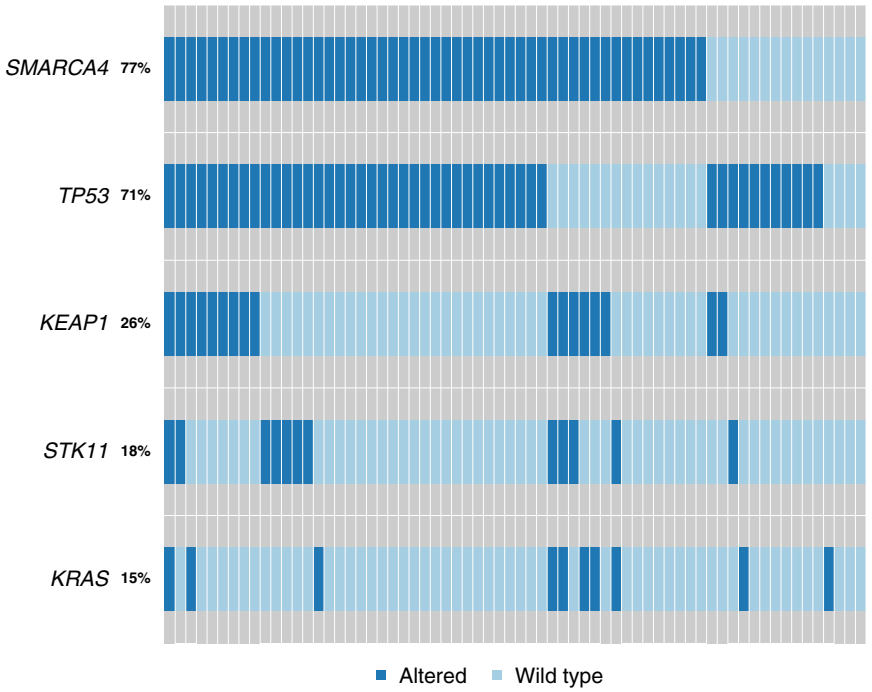

Figure 1. OncoPrint depicting alterations of interest in the tumors with next-generation sequencing performed. Each column represents one patient with changes in genes as noted (altered = dark blue, wild type = light blue).

Previous small studies have revealed that patients with SMARCA4-UT tended to be male, have heavy smoking history, and have slightly younger age at presentation than other patients with lung cancer. Presentation with metastases is common, and median OS ranges from 4 to 7 months. Tumor characteristics include high TMB and

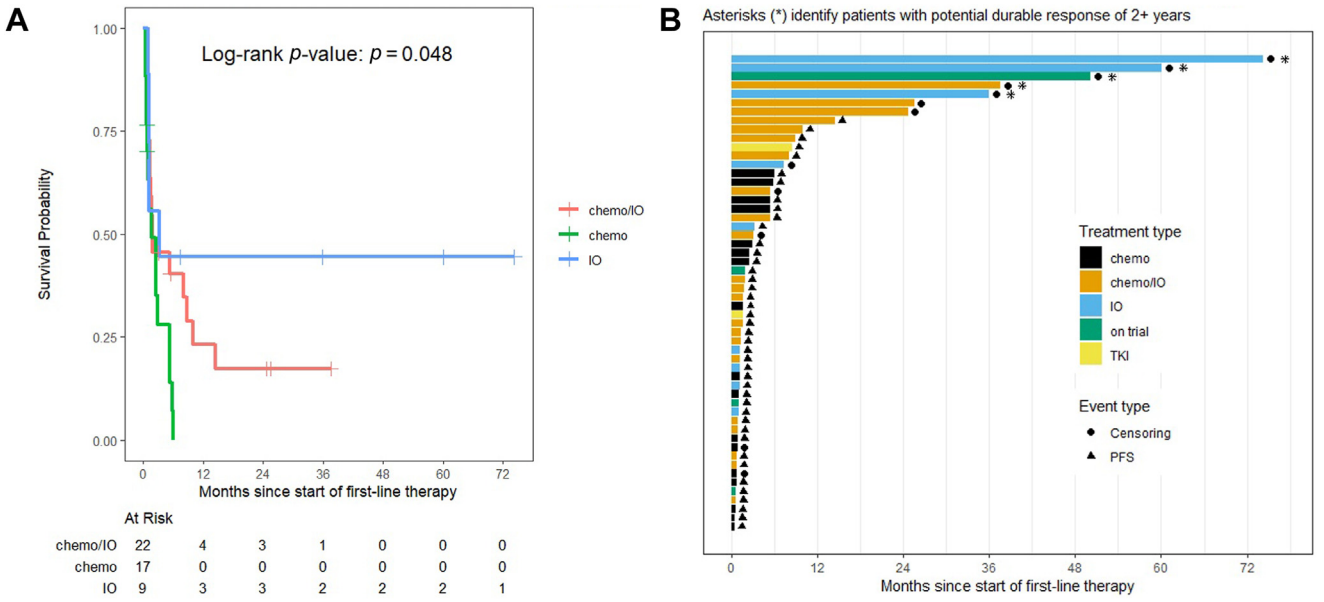

Figure 2. (*A*) Kaplan-Meier curves for PFS from start of systemic therapy. Median PFS is 1.9 (95% CI: 1.4–14.5) months for those who received chemo-IO as first-line treatment, 1.6 (1.1–5.8) months for those who received chemo, and 3.3 (1.2–undefined) months for those who received IO. (*B*) Swimmers' plot of PFS duration since start of first-line therapy. Outlined in bold are the five patients with durable responses more than 2 years since the start of first-line therapy, with their respective regimens color-coded according to the legend. The patient on trial received PD-1 inhibitor as part of the regimen. Chemo, chemotherapy; CI, confidence interval; IO, immunotherapy; PD-1, programmed cell death protein 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Table 2. Characteristics of Exceptional Responders

Characteristics	n (%), n = 5
Age, median (range), y	65 (45-76)
Male	4 (80)
Current or former tobacco history	5 (100)
Pack-years, median (range)	35 (20-60)
Presented with metastatic disease	4 (80)
Ever developed metastatic disease	5 (100)
First-line therapy	
Chemotherapy and immunotherapy	1 (20)
Immunotherapy monotherapy or doublet	3 (60)
Clinical trial with immunotherapy	1 (20)
First-line treatment duration, median (d)	326
PD-L1 expression	n = 4
<1%	1 (25)
1%-49%	2 (50)
≥50%	1 (25)
Genomic alterations	n = 5
SMARCA4	4 (80)
TP53	4 (80)
KEAP1	3 (60)
STK11	1 (20)
KRAS	0 (0)
Tumor mutational burden	
Median (range)	10.7 (9.1-31.6)

PD-L1, programmed death-ligand 1.

mutations in *SMARCA4*, *TP53*, *KRAS*, *STK11*, and *KEAP1*.[2,4,9,10]

In this largest cohort study yet reported of patients with a newly described rare malignancy, SMARCA4-UT, most patients presented with or developed metastatic disease and nearly 10% were too ill at presentation to tolerate systemic treatment. Standard therapies generally afforded short PFS and OS for patients with metastatic disease, consistent with previous reports. These data emphasize that alternative and perhaps escalated regimens are potentially necessary for the clinical management of patients with this diagnosis and may serve as a benchmark for future clinical trial design. It is reasonable to consider regimens involving antineoplastic agents with varied mechanisms of action, such as chemotherapy and doublet immunotherapy, or chemotherapy, immunotherapy, and antivascular epithelial growth factor therapy.[11] Novel agents such as EZH2 inhibitors have been considered promising in capitalizing on a therapeutic vulnerability for SMARCA4-UT, but preliminary data have been mixed.[12,13] SMARCA2 (BRM) degraders, thought to be an efficacious treatment strategy for SMARCA4-mutant NSCLC,[14] will generally not be a fruitful endeavor for SMARCA4-UT, as these tumors are highly likely to lack SMARCA2 expression.[3]

As with other reports of exceptionally durable responses to immune checkpoint inhibition,[6,7] we also identify individuals with robust responses to PD-1 with or without CTLA4 inhibition, in a period of more than 2 years. Demographic characteristics and potential biomarkers including PD-L1 expression, TMB, and NGS were unrevealing as predictors of exceptional response. This highlights that novel biomarkers predicting response are sorely needed.

Our study is limited by the relatively small number of patients in the three first-line treatment subgroups. During the length of time this study spanned, standard of care for first-line treatment of NSCLC evolved to include immunotherapy with or without chemotherapy. This analysis established disease progression by chart review of radiology reports and treating physicians' assessment, rather than Response Evaluation Criteria in Solid Tumors. In addition, analyses across institutions used differing approved assays to assess TMB and NGS.

As recognition of this recalcitrant and aggressive malignancy grows,[15] it is imperative that further studies to potentially identify biomarkers of treatment response are prioritized, both to understand the underlying biological mechanisms associated with exceptional response and to identify mechanisms of resistance in patients with poor outcomes to standard chemoimmunotherapy.

CRediT Authorship Contribution Statement

Alissa J. Cooper: Conceptualization, Data curation, Investigation, Formal analysis, Writing – original draft, Writing – review and editing.

Andrea Arfe: Formal analysis, Methodology, Writing – review and editing.

Biagio Ricciuti: Data curation, Writing – review and editing.

Andréanne Gagné: Data curation, Writing – review and editing.

Lynette M. Sholl: Data curation, Writing – review and editing.

Alessandro Di Federico: Data curation, Writing – review and editing.

Mark M. Awad: Data curation, Writing – review and editing.

Mihaela Aldea: Data curation, Investigation, Writing - review and editing.

Maria Rosa Ghigna: Data curation, Writing – review and editing.

Miruna Grecea: Data curation, Writing – review and editing.

Phoebe Clark: Data curation, Writing – review and editing.

Jamie E. Chaft: Methodology, Supervision, Writing – review and editing.

Mark G. Kris: Methodology, Supervision, Writing – review and editing.

Gregory J. Riely: Methodology, Supervision, Writing – review and editing.

Charles M. Rudin: Methodology, Supervision, Writing – review and editing.

Ibiayi Dagogo-Jack: Data curation, Writing – review and editing.

Mari Mino-Kenudson: Data curation, Writing – review and editing.

Lingzhi Hong: Data curation, Writing – review and editing.

Neda Kalhor: Data curation, Writing – review and editing.

Natalie Vokes: Data curation, Writing – review and editing.

Anita Bowman: Investigation, Methodology.

Soo-Ryum Yang: Investigation, Methodology.

Natasha Rekhtman: Methodology, Supervision, Writing – review and editing.

Adam J. Schoenfeld: Conceptualization, Methodology, Supervision, Writing – review and editing.

Disclosure

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Therapeutics (inst), Merck (inst), Bristol-Myers Squibb (inst), Harpoon Therapeutics (inst), AffiniT Therapeutics (inst), Legend Therapeutics (inst), and Amgen (inst). The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100759.

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