Original Article

A retrospective study of the efficacy and safety of immune checkpoint inhibitors combined with chemotherapy for the treatment of SMARCA4-deficient thoracic tumors

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Background: Thoracic tumors characterized by a deficiency in SMARCA4 are highly aggressive and linked to a poor prognosis. This retrospective study explores the efficacy and safety of immune checkpoint inhibitors (ICIs) in combination with chemotherapy for SMARCA4-deficient undifferentiated tumors (SMARCA4-dUT) and SMARCA4-deficient non-small cell lung cancer (SMARCA4-dNSCLC).

Methods: A cohort of 59 individuals was analyzed, including 35 patients with SMARCA4-dUT and 24 with SMARCA4-dNSCLC.

Results: Clinical characteristics as gender, age, smoking status, and metastatic sites did not significantly vary between SMARCA4-dUT and SMARCA4-dNSCLC. Nonsense and frameshift mutations in the SMARCA4 gene can result in the loss of its protein expression. Following a median follow-up of 7.6 months, the median progression-free survival (mPFS) notably increased with ICIs-based combination therapy compared to chemotherapy, the mPFS was 12.60 *vs.* 4.03 months in the SMARCA4-dUT subgroup (P=0.007) and not reached *vs.* 3.42 months in the SMARCA4-dNSCLC subgroup (P=0.03). In stage IV patients, the risk of disease progression and death decreased with ICIs-based combination therapy *vs.* chemotherapy [ICIs-based therapy *vs.* chemotherapy: hazard ratio (HR) =0.076; 95% confidence interval (CI): 0.009–0.624]. The most prevalent grade 3 or higher adverse events (AEs) in both groups were hematologic decreases, consistent with typical chemotherapy AEs. No treatment-related AEs led to patient fatalities.

Conclusions: The combination of ICIs and chemotherapy is more effective than chemotherapy for patients with advanced SMARCA4-deficient thoracic tumors (SMARCA4-dTT), and the safety is manageable.

Keywords: SMARCA4-deficient thoracic tumors (SMARCA4-dTT); SMARCA4-deficient undifferentiated tumors (SMARCA4-dUT); SMARCA4-deficient non-small cell lung cancer (SMARCA4-dNSCLC); immune checkpoint inhibitors (ICIs); chemotherapy

Submitted Aug 08, 2024. Accepted for publication Nov 26, 2024. Published online Dec 27, 2024.
doi: 10.21037/tlcr-24-691
View this article at: https://dx.doi.org/10.21037/tlcr-24-691

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Introduction

Lung cancer ranks as the leading cause of both incidence and mortality for malignant tumors on a global scale as well as in China (1). Non-small cell lung cancer (NSCLC) represents about 80 to 85 percent of all lung cancer diagnoses, with the majority of patients being diagnosed at advanced stages. Even with intensive treatment approaches, including surgery, chemotherapy, radiation, and targeted therapies, the survival rates for NSCLC continue to be disappointingly low (2). Approximately 15–50% of human primary NSCLC samples lack BRG1 subunit expression, and mutations in the BRG1 gene are identified in around 35% of NSCLC cell lines (3-6). Additionally, 4% to 6% of NSCLC cases are found to have SMARCA4 expression deficiency (7). SMARCA4-deficient non-small cell lung cancer (SMARCA4-dNSCLC) was identified by Wong *et al.* (8) in 2000 for the first time who reported that BRG1 might act as a tumor suppressor and represent a target for tumor cell destruction. In 2015, Le Loarer and colleagues proposed the term "SMARCA4-deficient thoracic sarcoma (DTS)", and indicated these type of tumors have distinct histologic, immunohistochemical and clinical characteristics compared to SMARCA4-dNSCLC (9).

In the 5th edition of the World Health Organization (WHO) classification of thoracic tumors, this category is delineated into two distinct groups: SMARCA4-deficient undifferentiated tumors (SMARCA4-dUT) and SMARCA4-dNSCLC (10). SMARCA4-dUT is a type of tumor predominantly found in adults, with significant involvement in the thoracic region. Immunohistochemical analysis typically reveals a deficiency in SMARCA4 (BRG1). In contrast, SMARCA4-dNSCLC is a subtype of NSCLC that displays a wide range of histological features. The classification covers a spectrum of malignant thoracic tumors, ranging from well-differentiated to poorly-differentiated, encompassing various subtypes such as solid and mucinous adenocarcinomas, acinar and papillary adenocarcinomas, squamous cell carcinomas, large cell carcinomas, rhabdoid tumors, as well as malignancies with spindle or signet ring cell features (11-14). Both SMARCA4-dUT and SMARCA4-dNSCLC are associated with a history of smoking and are more prevalent in males (15). Genetically, tumors deficient in SMARCA4 are often characterized by the presence of mutations in the *KRAS*, *TP53*, and *KEAP1* genes, mutations involving *EGFR*, *ALK* fusions, or *ROS1* rearrangements are infrequently identified within these tumors (6,16). The efficacy of targeted therapies for such genetic alterations remains largely unknown and requires further investigation. The unique clinical and pathological characteristics of these tumors highlight the necessity for precise diagnosis and suggest the possibility of personalized therapeutic approaches. Understanding the molecular underpinnings of these tumors is crucial for developing effective therapeutic approaches and improving patient outcomes. Indeed, several case studies have suggested that patients with SMARCA4 deficiency may derive benefits from immune checkpoint inhibitors (ICIs) (17-20). Certain individuals with SMARCA4-dNSCLC exhibit sustained responses to treatment with nivolumab or pembrolizumab (21-23). Kawachi and colleagues documented three instances of SMARCA4-deficient thoracic tumors (SMARCA4-dTT) treated initially with the combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP), resulting in partial responses (PRs), a median progression-free survival (PFS) (mPFS) of over 6 months, and a sustained response exceeding one year in one patient (24). Yang *et al.* reported a 51-year-old Chinese man who was diagnosed with a SMARCA4-dUT. The patient who was treated with a second-line regimen containing tislelizumab, etoposide, and carboplatin (TEC) seemed to have a reduction in tumor burden observed for more than 10 months (25). ICIs could be a new treatment option for patients with SMARCA4-dUT and SMARCA4-dNSCLC. In this observational study, we enrolled a cohort of 59 patients presenting with SMARCA4 (BRG1) deletions in Second Affiliated Hospital of Army Medical

Highlight box

Key findings

- The study showed promising efficacy and safety of immune checkpoint inhibitors (ICIs) in the treatment of SMARCA4-deficient thoracic tumors (SMARCA4-dTT).

What is known and what is new?

- It is well known that there are currently no effective treatments for SMARCA4-dTT, and there is an urgent need to explore and identify effective therapeutic options to improve patient outcomes.
- ICIs have demonstrated significantly better progression-free survival in patients with SMARCA4-dTT compared to chemotherapy alone, and they have a manageable safety profile.

What is the implication, and what should change now?

- ICIs have shown the potential to serve as a first-line treatment for patients with SMARCA4-dTT. This study was conducted using a retrospective approach; therefore, to apply these findings to clinical practice, it is necessary to further design and carry out large-scale prospective clinical trials.

University from January 2020 to March 2024. This group included 35 patients with SMARCA4-dUT and 24 patients with SMARCA4-dNSCLC, we compared the molecular, clinicopathological characteristics and survival, as well as safety. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-691/rc).

Methods

Patients cohort

This study conducted a retrospective analysis of patients diagnosed with SMARCA4-dUT and SMARCA4-dNSCLC at Second Affiliated Hospital of Army Medical University from January 2020 to March 2024. To be eligible for inclusion, patients must meet the following specific criteria: (I) they must have a pathological or cytological diagnosis indicating a deficiency in SMARCA4 (BRG1); (II) they must be 30 years of age or older. These criteria were essential for study participation; (III) they had not previously enrolled in other clinical trials. Patients were excluded if there were significant gaps in their medical records, such as incomplete treatment details or a lack of necessary follow-up data, including the absence of imaging study dates and results needed to evaluate disease progression or treatment efficacy. Furthermore, patients who did not have measurable lesions as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were also excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the protocol was approved by the Second Affiliated Hospital Medical Ethics Committee of Army Medical University (No. 2024-210). Given the retrospective nature of this study, the requirement for obtaining informed consent was dispensed with.

Data collection and clinicopathological evaluation

Our database was carefully reviewed to assess various parameters including age, gender, smoking status, clinical T and N stages, histological subtypes, molecular profiles, treatment plans, and survival outcomes. Survival status data were extracted from patients' clinical records. Tumor node metastasis (TNM) staging followed the 8th edition guidelines of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Histopathological diagnosis criteria were based on the 2021 WHO classification for lung tumors. Molecular test findings, whether performed in-house or in collaboration with other institutions, were systematically collected and analyzed.

Statistical analyses

The interval defined as PFS spanned from the initial diagnosis to either the detection of disease progression or the date of death due to any cause. Overall survival (OS) was characterized as the duration from the point of diagnosis to the date of death. The combined objective response rate (ORR) and disease control rate (DCR) were assessed according to the RECIST version 1.1, with ORR representing the percentage of patients achieving a complete response (CR) or PR and DCR indicating the proportion of patients with CR, PR, or stable disease (SD). For the analysis of categorical variables, we utilized either the Chi-squared test or Fisher's exact test. In contrast, the comparison of continuous data between the two groups was performed using the Student's *t*-test for parametric data or the Wilcoxon rank-sum test for non-parametric data. The estimation of PFS and OS was accomplished through the Kaplan-Meier method. The log-rank test was utilized to appraise the disparities in PFS and OS among different histological groups in a univariate analysis framework. Both univariate and multivariate analyses were conducted using the Cox proportional hazards model to determine the statistical significance. A P value of less than 0.05 was considered the threshold for statistical significance in pooled analyses. Statistical computations were carried out using SPSS software (version 26; IBM Corp, Armonk, NY, USA) in conjunction with GraphPad Prism (version 9.5) for comprehensive data analysis and interpretation.

Results

Clinicopathologic characteristics in SMARCA4-dUT and SMARCA4-dNSCLC

A total of 59 patients were enrolled in the study, with 35 cases diagnosed with SMARCA4-dUT and 24 with SMARCA4-dNSCLC. The patient selection process is illustrated in *Figure 1*. Some patients did not receive systematic treatment due to economic reasons. The detailed clinicopathological characteristics of these individuals are available in *Table 1*. The average age at disease onset was similar between the SMARCA4-dUT group (64.46±9.42 years) and the SMARCA4-dNSCLC group (61.92±8.41 years). Both groups predominantly consisted of male patients, with 34

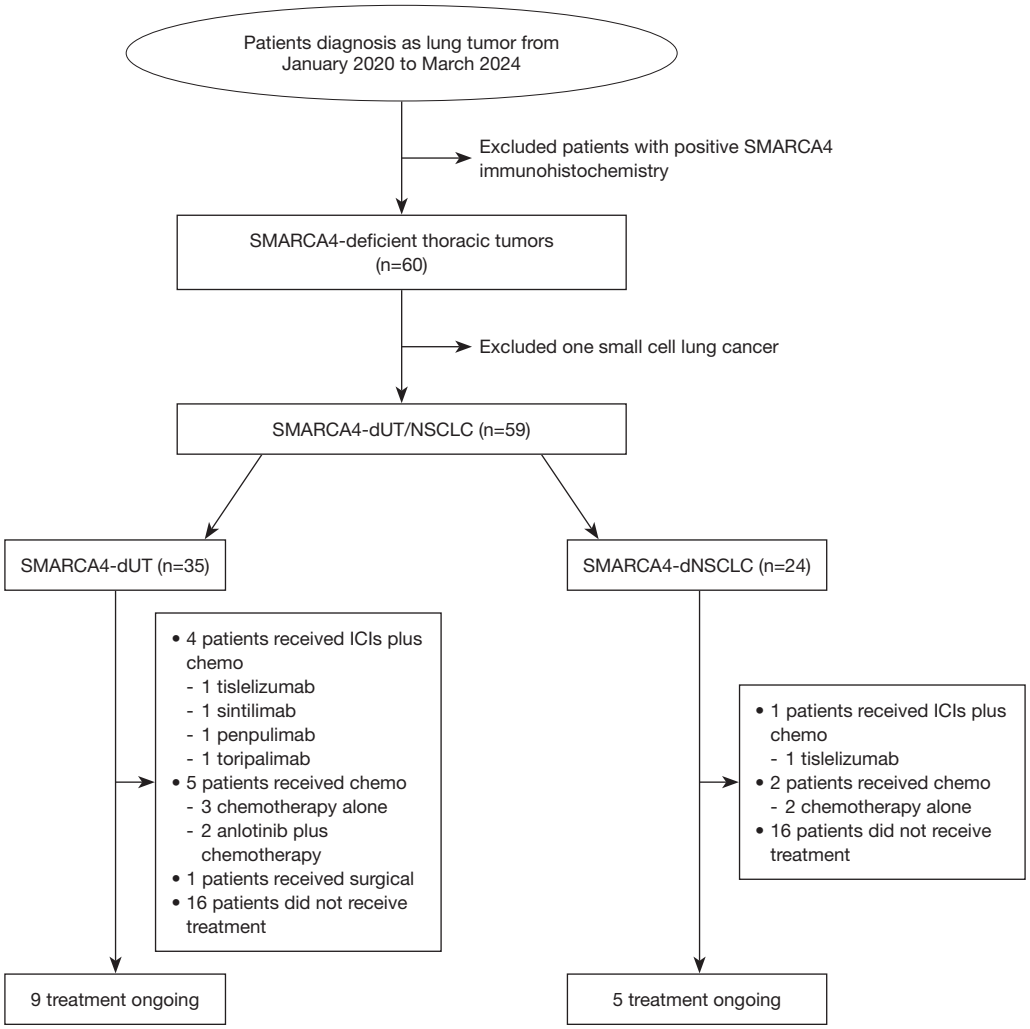

Figure 1 The selection process of eligible patients. SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer; ICIs, immune checkpoint inhibitors; Chemo, chemotherapy.

(97.14%) in the SMARCA4-dUT group and 22 (91.67%) in the SMARCA4-dNSCLC group. The average pack-year smoking history was 39.29 pack-years for SMARCA4-dUT and 35.27 pack-years for SMARCA4-dNSCLC.

Upon initial diagnosis, most patients were found to have stage III or advanced disease, with 29 (82.86%) in the SMARCA4-dUT group and all 24 (100.00%) in the SMARCA4-dNSCLC group, indicating that many were not eligible for surgery. The patterns of metastasis observed in both groups were similar, with bone being the primary site of metastasis. Despite the significantly higher tumor mutational burden (TMB) in SMARCA4-dUT patients compared to SMARCA4-dNSCLC patients (19.81 *vs.* 8.38 mean/Mb, P=0.03), no significant difference was observed in the expression of programmed cell death ligand 1 (PD-L1) between the two groups.

Genomic alterations in patients

Of the 59 patients, 24 underwent next-generation sequencing using the Illumina NovaSeq 6000 platform, or target gene capture sequencing through circulating single-molecule amplification and resequencing technology (cSMART), as well as the ANDiS 500 fully automated closed-tube gene sequencing library preparation instrument. Among these, 10 were diagnosed with SMARCA4-dUT, and 14 were diagnosed with SMARCA4-dNSCLC. The SMARCA4 gene mutations observed in these patients

Table 1 Clinicopathologic characteristics in SMARCA4-dUT and SMARCA4-dNSCLC

Clinical features	SMARCA4-dUT (n=35)	SMARCA4-dNSCLC (n=24)	P value
Age (years)	64.46±9.42	61.92±8.41	0.29
Gender			0.56
Male	34 (97.14)	22 (91.67)	
Female	1 (2.86)	2 (8.33)	
Smoking status (pack-years)	30 (30, 75)	40 (11.5, 50)	0.96
Never smokers	4 (11.43)	4 (16.67)	
≥20	1 (2.86)	4 (16.67)	
<20	23 (65.71)	16 (66.67)	
Unknown	7 (20.00)	0	
ECOG			0.30
0	17 (48.57)	15 (62.50)	
1	18 (51.43)	9 (37.50)	
≥2	0	0	
Stage at diagnosis			0.08
I–IIIA	4 (11.43)	0	
IIIB–IV	29 (82.86)	24 (100.00)	
Unknown	2 (5.71)	0	
Pathological diagnosis			–
Undifferentiated carcinoma	35 (100.00)	0	
Adenocarcinoma	0	23 (95.83)	
Squamous cell carcinoma	0	1 (4.17)	
Common metastatic sites throughout patients' clinical course			0.91
Brain	4 (11.43)	5 (20.83)	
Bone	8 (22.86)	9 (37.50)	
Liver	3 (8.57)	2 (8.33)	
Adrenal gland	4 (11.43)	6 (25.00)	
TMB (mean/Mb)	19.81 (13.31, 28.66)	8.38 (5.84, 12.29)	0.03*
<10	0	7 (29.17)	
≥10	6 (17.14)	4 (16.67)	
Unknown	29 (82.86)	13 (54.17)	
PD-L1			0.47
<1%	5 (14.29)	6 (25.00)	
1–49%	1 (2.86)	7 (29.17)	
≥50%	1 (2.86)	0	
Untest	28 (80.00)	11 (45.83)	

Data are presented as mean ± standard deviation, n (%) or median (25%, 75%). *, statistically significance (P<0.05). SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; TMB, tumor mutational burden; PD-L1, programmed cell death ligand 1.

A

Gene	Mutation site	Mutation type
SMARCA4	c.771del (p.N259Tfs*44)	Frameshift
	c.478C>T (p.Q160*)	Nonsense
	c.2483_2484delinsTCT (p.S828Ffs*117)	Frameshift
	c.3480dup (p.L1161Afs*15)	Frameshift
	c.C3121T (p.Q1041*)	Nonsense
	c.3706C>T (p.Q1236*)	Nonsense
	c.1141C>T (p.R381*)	Nonsense
	c.3496C>T (p.Q1166*)	Nonsense
	c.299C>G (p.S100*)	Nonsense
	c.291del (p.M98Cfs*205)	Frameshift
	c.2481del (p.S828Pfs*3)	Frameshift
	c.4471C>T (p.R1491*)	Nonsense
	c.152C>A (p.S51*)	Nonsense
	c.152C>G (p.S51*)	Nonsense
	c.3147del (p.Y1050Tfs*56)	Frameshift
	c.991C>T (p.Q331*)	Nonsense
	c.726del (p.G243Afs*60)	Frameshift
	c.1077_1078delinsT (p.G360Afs*51)	Frameshift
ALK	c.2147G>T (p.S716I)	Missense
	c.823G>C (p.E275Q)&	Missense&
	c.4391G>A (p.R1464Q)	Missense
	c.C4587G (p.D1529E)&	Missense&
	c.A4573G (p.K1525E)&	Missense&
	c.A4472G (p.K1491R)&	Missense&
	c.A4381G (p.I1461V)	Missense
EGFR	c.866C>A (p.A289D)	Missense
	c.2573T>G (p.L858R)	Missense
	c.2096C>T (p.P699L)	Missense
ROS1	c.3648_3648+1delinsTT (p.S673N)	Missense
	c.4196A>G (p.D1399G)	Missense
	c.4625A>G (p.H1542R)	Missense
MET	MET copy number gain	Amplification
	c.3028G>T (p.D1010Y)	Missense
KARS	2exon	Unclear
	c.183A>C (p.Q61H)	Missense
	c.34G>T (p.G12C)	Missense
	c.35G>T (p.G12V)	Missense
	c.34G>A (p.G12S)	Missense

B

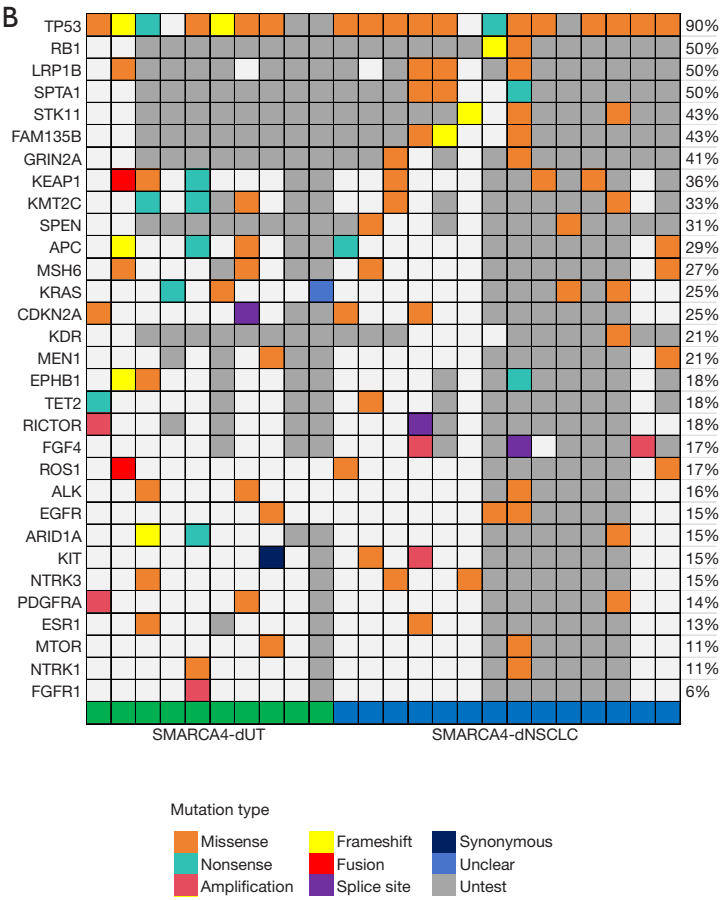

Figure 2 Genetic alterations of SMARCA4-dUT and SMARCA4-dNSCLC. (A) Mutation type of selected genes of SMARCA4-deficient tumors. (B) Genetic alterations of thoracic SMARCA4-dUT and SMARCA4-dNSCLC. A column represents a case and each row represents a gene. SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer.

included nonsense and frameshift mutations, along with some missense and synonymous mutations. *KRAS* mutations were identified in five patients, with specific mutations such as *Q61H*, *G12C*, *G12V*, *G12S*, and an indeterminate mutation in *exon two*. Among potential targetable driver genes, three patients had *ALK* missense mutations, three had *EGFR* mutations (two missense mutations and one *EGFR p.L858R* mutation), a *MET* copy number gain, a *MET* missense mutation, and three cases with *ROS1* missense mutations were detected (*Figure 2A*). Notably, only the *EGFR p.L858R* mutation is considered to have clinical significance.

The most commonly mutated genes were *TP53* (19 of 21 patients, 90%), *RB1* (2 of 4 patients, 50%), *LRP1B* (4 of 8 patients, 50%), *SPTA1* (3 of 6 patients, 50%), and *STK11* (3 of 7 patients, 43%) (*Figure 2B*). This in-depth molecular analysis offers a comprehensive view of the genetic abnormalities in SMARCA4-deficient tumors and can guide tailored therapeutic strategies for these individuals. The presence of targetable mutations like *ALK*, *EGFR*, and *ROS1* highlights the crucial role of genetic testing in directing personalized treatment plans for patients with these tumor types (*Figure 2B*).

ICIs-based therapy shows good results in SMARCA4-dUT and SMARCA4-dNSCLC

Twenty-six patients with locally advanced (stage IIIB) or metastatic (stage IV) disease were treated. Among them, 18 had SMARCA4-dUT, and eight had SMARCA4-dNSCLC.

Table 2 Best overall response in in patients with advanced squamous disease treated with ICIs plus chemotherapy or chemotherapy

Response	ICIs-based therapy (n=17)		Chemo (n=9)	
	SMARCA4-dUT	SMARCA4-dNSCLC	SMARCA4-dUT	SMARCA4-dNSCLC
CR, n (%)	1 (5.88)	0	0	0
PR, n (%)	4 (23.53)	4 (23.53)	1 (11.11)	1 (11.11)
SD, n (%)	3 (17.65)	1 (5.88)	3 (33.33)	1 (11.11)
PD, n (%)	0	1 (5.88)	2 (22.22)	0
NE/missing, n (%)	3 (17.65)	0	1 (11.11)	0
DCR (%)	47.06	29.41	44.44	22.22
ORR (%)	29.41	23.53	11.11	11.11

ICIs, immune checkpoint inhibitors; SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer; ICIs-based therapy, immune checkpoint inhibitors plus chemotherapy; Chemo, chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DCR, disease control rate; ORR, objective response rate.

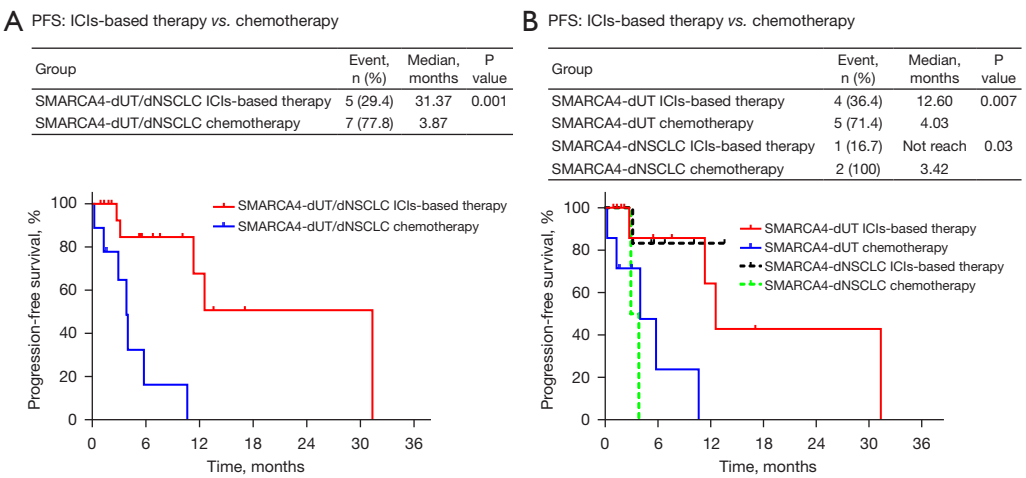

Figure 3 PFS between ICIs-based therapy and chemotherapy. (A) Kaplan-Meier plots of PFS in patients with SMARCA4-dUT/SMARCA4-dNSCLC treated with ICIs-based therapy and those treated with chemotherapy. (B) Kaplan-Meier plots of PFS in patients with SMARCA4-dUT and SMARCA4-dNSCLC treated with ICIs-based therapy and those treated with chemotherapy. PFS, progression-free survival; ICIs, immune checkpoint inhibitors; SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer.

Of these, 17 patients were treated with ICIs-based therapy, while nine patients received chemotherapy. There were no significant differences in clinical baseline characteristics between patients receiving ICI-based therapy and those undergoing chemotherapy, as detailed in Table S1. Among patients receiving ICI-based therapy, the most commonly used immune agent was tislelizumab (35.3%), while the chemotherapeutic agents were paclitaxel and nedaplatin. After observing a median follow-up time of 7.6 months [95% confidence interval (CI): 4.8–10.4 months]. While there was no significant difference in DCR between ICIs-based therapy and chemotherapy (76.5% *vs.* 66.7%), a marked difference was observed in the ORR, favoring ICI-based therapy (52.9% *vs.* 22.2%) (*Table 2*).

ICIs-based therapy compared to chemotherapy markedly extended mPFS (31.37 *vs.* 3.87 months, P=0.001; *Figure 3A*). A similar noteworthy improvement in mPFS was observed in the SMARCA4-dUT subgroup (12.60 *vs.* 4.03 months,

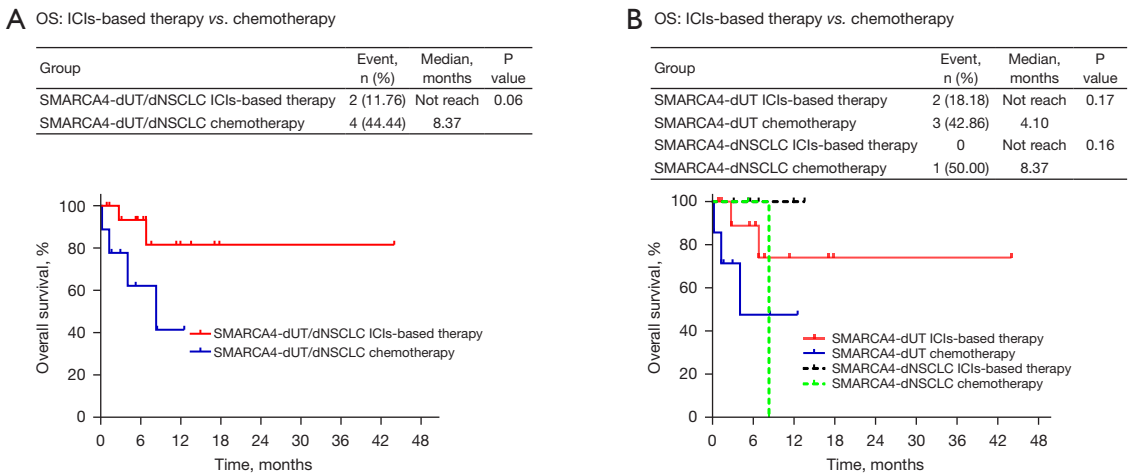

Figure 4 OS between ICIs-based therapy and chemotherapy. (A) Kaplan-Meier plots of OS in patients with SMARCA4-dUT/SMARCA4-dNSCLC treated with ICIs-based therapy and those treated with chemotherapy. (B) Kaplan-Meier plots of OS in patients with SMARCA4-dUT and SMARCA4-dNSCLC treated with ICIs-based therapy and those treated with chemotherapy. OS, overall survival; ICIs, immune checkpoint inhibitors; SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer.

P=0.007; *Figure 3B*) and SMARCA4-dNSCLC subgroup (not reached *vs.* 3.42 months; P=0.03; *Figure 3B*) with ICIs-based therapy and chemotherapy.

Regarding OS, with a median follow-up of 6 months, the OS data were not yet mature, showing no significant differences between ICIs-based therapy and chemotherapy (P=0.06; *Figure 4A*). Similarly, no distinctions were noted in the SMARCA4-dUT (P=0.17; *Figure 4B*) and SMARCA4-dNSCLC (P=0.16; *Figure 4B*) subgroups. Nevertheless, patients undergoing long-term treatment with platinum-based therapy demonstrated a notably prolonged survival, with the longest survivor reaching 44 months. These results highlight the potential advantages of ICIs-based therapy for managing SMARCA4-dUT and SMARCA4-dNSCLC, emphasizing the need for further exploration to optimize treatment strategies for these individuals.

Under the same treatment protocols, the prognostic analysis revealed no significant differences in PFS and OS between the SMARCA4-dUT and SMARCA4-dNSCLC groups, as shown in *Figure 5*.

Due to the limited follow-up duration and small sample size, in most subgroups, the addition of ICIs to chemotherapy did not lead to a PFS extension compared to chemotherapy (*Figure 6*). However, in patients with stage IV disease, the risk of disease progression and mortality was lower in those receiving ICIs than in those undergoing chemotherapy [ICIs-based therapy *vs.* chemotherapy: hazard ratio (HR) =0.076; 95% CI: 0.009–0.624].

Almost all patients experienced treatment-related adverse events (AEs) (*Table 3*). The most prevalent treatment-related AEs in all groups were hypoalbuminemia and anemia. Grade 3 or higher AEs mainly occurred in the group receiving ICIs combined with chemotherapy, presenting as declines in the blood system, such as neutrophil, leukopenia, and neutropenia, consistent with known chemotherapy-related AEs. Following dose adjustment or symptomatic management, AEs were effectively controlled, with no patient fatalities attributed to the treatment. Furthermore, one patient developed immune-related pneumonitis, graded as mild to moderate (grade 1–2), and did not necessitate discontinuation of subsequent treatment.

Discussion

In this retrospective study, frameshift and nonsense mutations in the SMARCA4 gene led to the loss of its protein expression. After a median study follow-up of 7.6 months, the combination of ICIs with chemotherapy improved the PFS of patients with locally advanced or metastatic disease.

SMARCA4-dUT is characterized by highly clinical aggressiveness, rapid progression, poor prognosis and no clear treatment. Diagnosis of SMARCA4-dTT relies on loss of SMARCA4 in immunohistochemistry, and expression of

A PFS: ICIs-based therapy *vs.* chemotherapy

Group	Event, n (%)	Median, months	P value
SMARCA4-dUT ICIs-based therapy	4 (36.36)	12.60	0.66
SMARCA4-dUT chemotherapy	1 (16.67)	Not reach	
SMARCA4-dNSCLC ICIs-based therapy	5 (71.43)	4.03	0.28
SMARCA4-dNSCLC chemotherapy	2 (100.00)	3.42	

B OS: ICIs-based therapy *vs.* chemotherapy

Group	Event, n (%)	Median, months	P value
SMARCA4-dUT ICIs-based therapy	2 (18.18)	Not reach	0.32
SMARCA4-dUT chemotherapy	0	Not reach	
SMARCA4-dNSCLC ICIs-based therapy	3 (42.86)	4.10	0.82
SMARCA4-dNSCLC chemotherapy	1 (50.00)	8.37	

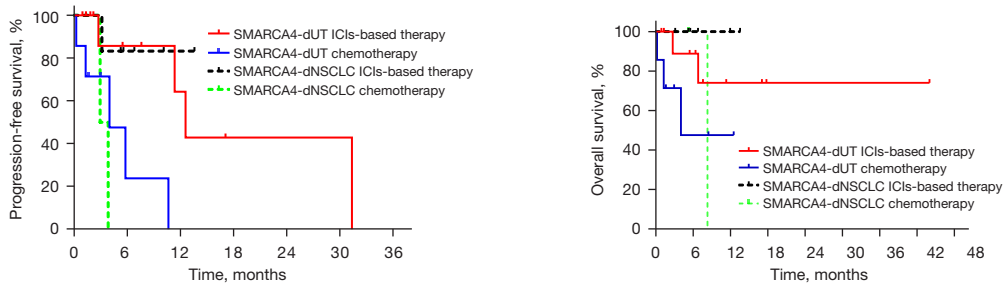

Figure 5 ICIs-based therapy *vs.* chemotherapy in SMARCA4-dUT and SMARCA4-dNSCLC. (A) Kaplan-Meier plots of PFS in SMARCA4-dUT and SMARCA4-dNSCLC patients receiving ICIs-based therapy, and patients receiving chemotherapy. (B) Kaplan-Meier plots of OS in SMARCA-dUT and SMARCA-dNSCLC patients receiving ICIs-based therapy, and patients receiving chemotherapy. PFS, progression-free survival; ICIs, immune checkpoint inhibitors; SMARCA4-dUT, SMARCA4-deficient undifferentiated tumors; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer; OS, overall survival.

Study	Events/ patients, No	HR for PD or death (95% CI)
Overall	11/26	0.10 (0.02–0.488)
Man	10/24	0.05 (0.01–0.41)
Age <60 years	5/14	0.12 (0.04–1.17)
Age ≥60 years	6/12	0.11 (0.01–1.01)
Current or former had smoking	7/16	0.01 (0–11.26)
Tumor size ≤7 cm	6/13	0.07 (0.01–0.62)
Tumor size >7 cm	4/10	0.01 (0–168.26)
Tumor stage IV	9/19	0.08 (0.01–0.62)
PD-L1 ≥1%	4/11	0.08 (0.01–0.91)
TMB <10 Muts/Mb	2/4	0.41 (0.03–6.62)
TMB ≥10 Muts/Mb	3/7	0.00 (0–17064.83)
Radiotherapy	6/13	0.29 (0.05–1.79)
Without radiotherapy	5/13	0.01 (0–102.18)

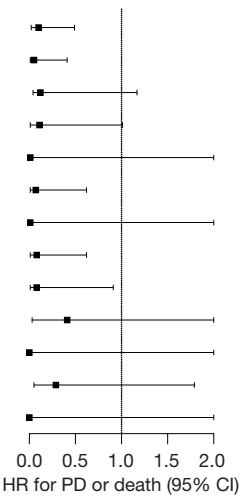

Figure 6 Subgroup analysis of ICIs-based therapy *vs.* chemotherapy in SMARCA4-deficient thoracic tumors. Forest plots showing hazard ratios of ICIs-based therapy for progression-free survival in different subgroups. HR, hazard ratio; PD, progressive disease; CI, confidence interval; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; ICIs, immune checkpoint inhibitors.

CD34, SOX2 or SALL4 expression or localized Claudin-4 expression are important markers that distinguish SMARCA4-dUT from SMARCA4-dNSCLC (26).

The mechanisms by which SMARCA4 gene mutations alter protein expression are not fully understood, with effects ranging from transcriptional issues to protein recombination (27,28). Our study found that frameshift and nonsense mutations are the main causes of SMARCA4 deficiency, which is consistent with previous research findings (29). Curiously, we encountered cases where patients exhibited a lack of protein expression despite no identifiable mutations, suggesting the involvement of alternative factors such as regulatory mechanisms or epigenetic influences. Previous studies have indicated that patients with point mutations in

Table 3 Incidence of treatment-emergent adverse events occurring in patients

Adverse events	ICIs-based therapy (n=17)		Chemo (n=9)	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Hypoalbuminemia	16 (94.12)	0	7 (77.78)	0
Anemia	14 (82.35)	1 (5.88)	6 (66.67)	0
Decreased appetite	11 (64.71)	0	6 (66.67)	0
Decreased white blood cell count	11 (64.71)	3 (17.65)	4 (44.44)	0
Increased ALT levels	11 (64.71)	1 (5.88)	3 (33.33)	0
Nausea	10 (58.82)	0	5 (55.56)	0
Decreased platelet cell count	10 (58.82)	4 (23.53)	1 (11.11)	0
Increased AST levels	4 (23.53)	1 (5.88)	2 (22.22)	0
Increased blood bilirubin levels	4 (23.53)	0	1 (11.11)	0
Decreased neutrophil levels	3 (17.65)	3 (17.65)	3 (33.33)	0
Pyrexia	3 (17.65)	0	1 (11.11)	0
Immune-related pneumonitis	1 (5.88)	0	0	0
Rash	0	0	1 (11.11)	0

ICIs, immune checkpoint inhibitors; ICIs-based therapy, immune checkpoint inhibitors plus chemotherapy; Chemo, chemotherapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TP53, but without nonsense mutations, tend to have better clinical benefits when treated with PD-1/PD-L1 therapies compared to those with wild-type *TP53*. This aligns with our findings of a higher frequency of *TP53* mutations, which provides direction for exploring the mechanisms underlying the effectiveness of ICIs in SMARCA4-deficient tumors on a molecular level (30).

These genetic insights may elucidate the suboptimal efficacy of certain NSCLC treatments. The research further indicates the potential for employing immunosuppressive therapies irrespective of modest PD-L1 expression levels. This idea makes us think again about how we treat NSCLC and look into using immunomodulatory therapies for more patients, regardless of their PD-L1 status.

Grasp of the intricate interplay between genetic alterations and protein levels is essential for crafting tailored and potent therapeutic strategies against NSCLC. This deeper knowledge could lead to better strategies for patients in the future. Our research identified a case where an individual was initially diagnosed with SMARCA4-dNSCLC and subsequently received a revised diagnosis of SMARCA4-dUT at our institution. It shows that there are some close connections between SMARCA4-dUT and SMARCA4-dNSCLC that we do not know yet. In the study by Lin *et al.* a case was described where a patient presented with SMARCA4-dNSCLC at the primary tumor site and SMARCA4-dUT at the metastatic site. This finding hints at a potential link between the emergence of SMARCA4-dUT and SMARCA4-dNSCLC, shedding additional light on the intricate interplay between these two unique malignancies (19). As reported by Rekhtman *et al.* the initial co-deletion of SMARCA4 and SMARCA2, or the subsequent loss of SMARCA2 on the basis of SMARCA4 deficiency, represents a potential pattern of evolution for SMARCA4-dUT (15).

Regarding potential targetable driver genes, in contrast to previous reports (31) we have identified the presence of driver gene mutations in SMARCA4-dTT. Patients diagnosed with SMARCA4-deficient tumors still need to undergo potential targetable driver genes testing. Although the patient with *EGFR* (p.L858R) mutation in our study did not receive treatment, it could provide a new therapeutic option. Additionally, we have observed the loss of SMARCA in small cell lung cancer, which is a distinct finding.

In the context of limited-stage patients who receive radical treatment, a rapid relapse pattern was observed in those with SMARCA4-dUT. Nevertheless, these patients exhibited a 13-month long-term survival rate, which was higher than those untreated or treated solely with

chemotherapy. This discrepancy, while promising, should be interpreted with caution due to the small sample size and the possibility that patients who underwent surgery may still be in the early phases of follow-up. Despite these limitations, surgery continues to be regarded as the optimal primary treatment for thoracic tumors characterized by SMARCA4 deficiency. The aggressive nature of SMARCA4-dUT necessitates a multidisciplinary approach, and surgery (17,32), when feasible, offers the best chance for disease control and potential cure. Additional studies are vital for enhancing and tailoring treatment approaches to better outcomes, particularly in pinpointing biomarkers that forecast the efficacy of treatments and facilitate customized medical care. There was a notable enhancement in mPFS among patients on ICIs-based therapies compared with chemotherapy, evident in both the SMARCA4-dUT and SMARCA4-dNSCLC subgroups. The majority achieved PR or SD swiftly after two cycles of ICIs-based therapies, leading to sustained disease management.

Although good therapeutic effects were observed in patients receiving immunosuppressive agents, patients having low levels of PD-L1 expression, and no efficacy of ICIs were observed in all TMB subgroups. Extended monitoring and an expanded data pool are necessary to validate the enduring efficacy of this therapeutic strategy.

In terms of AEs, ICIs-based therapy is consistent with the established safety profile of previously reported PD-1/PD-L1 inhibitors (18) and chemotherapy (33,34). Most AEs were hematological in nature, aligning with the known toxicities of the chemotherapy backbone; however, treatment discontinuations due to treatment-emergent AEs were not observed in our study.

Due to reliance on historical data, there may be issues with incomplete or inaccurate records. Some patients discontinued follow-up treatment for economic reasons, leading to missing data. Since SMARCA4-dTT are a rare disease, our study had a small number of cases, the PFS and subgroup analyses may be biased due to individual cases.

Conclusions

Our study provides compelling evidence for the potential of ICI-based therapy compared to conventional chemotherapy in the treatment of SMARCA4-dTT. Additionally, our research is dedicated to exploring the heterogeneity of genetic mutations in patients with SMARCA4-dTT. We have conducted an in-depth analysis of clinical characteristics, tumor classification, and gene expression. Although the ICI-based treatment protocol has shown positive effects in treating SMARCA4-dTT, these findings are preliminary and require further validation through larger-scale, prospective studies.

Acknowledgments

The authors would like to thank the patients and their families for giving their time and commitment to participate in this study.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-691/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-691/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-691/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-691/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Second Affiliated Hospital Medical Ethics Committee of Army Medical University (No. 2024-210). The need for obtaining informed consent was waived because of the retrospective nature of the study.

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Cite this article as: Wang B, You H, Ye D, Yi Y, Liu Y, Qing B, Wang C, Liu J, Zhang J, Wang N, Wan P, Shen L, Xu Z. A retrospective study of the efficacy and safety of immune checkpoint inhibitors combined with chemotherapy for the treatment of SMARCA4-deficient thoracic tumors. Transl Lung Cancer Res 2024;13(12):3460-3472. doi: 10.21037/tlcr-24-691