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Correlations of switch/sucrose nonfermentable complex mutations with clinical outcomes in advanced non–small cell lung cancer

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Abstract

Background: The switch/sucrose nonfermentable complex mutations (SWI/SNF-mut) are common in non–small cell lung cancer (NSCLC). However, the association of SWI/SNF-mut with the clinical outcomes of immune checkpoint inhibitors (ICIs), particularly of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), has not been established.

Methods: We retrospectively collected data of patients at Cancer Hospital Chinese Academy of Medical Sciences. Patients with advanced NSCLC who received programmed cell death protein-1 or programmed cell death ligand 1 (PD-[L]1) inhibitors were included in cohort 1 and those with EGFR mutations (EGFR-mutant) received EGFR-TKIs monotherapy were included in cohort 2. Two reported Memorial Sloan-Kettering Cancer Center (MSKCC) cohorts received immunotherapy alone used as the validation for cohort 1. We analyzed the relationship between SWI/SNF alterations and clinical outcomes in each cohort.

Results: In total, 1162 patients were included, of which 230 patients (19.8%) were identified as SWI/SNF-mut with the most common genetic alterations being ARID1A (33.4%) and SMARCA4 (28.3%). In cohort 1 ($n = 146$), patients with co-mutations of SWI/SNF and Kirsten rat sarcoma oncogene (KRAS) (SWI/SNFmutKRASmut, $n = 18$) had significantly prolonged progression-free survival (PFS) (8.6 m vs. 1.9 m; hazard ratio [HR], 0.31; 95% confidence intervals [CI], 0.11–0.83; $p = 0.032$) to PD-(L)1 inhibitors monotherapy, which was consistent with the MSKCC cohorts (not reach [NR] vs. 6.3 m; HR, 0.36, 95% CI, 0.15–0.82; $p = 0.016$). In cohort 2 ($n = 205$), ARID1A-mut ($n = 16$) was associated with improved PFS after EGFR-TKIs (20.6 m vs. 11.2 m; HR, 0.47, 95% CI, 0.27–0.94; $p = 0.023$).

Conclusions: In advanced NSCLC, patients with SWI/SNFmutKRASmut seem to benefit more from ICIs. Furthermore, ARID1A-mut may provide a protective effect to EGFR-TKIs in EGFR-mutant patients. However, this is a retrospective single-institution analysis that requires further validation by large prospective studies.

KEYWORDS
epidermal growth factor receptor, immune checkpoint inhibitors, non–small cell lung cancer, SWI/SNF, tyrosine kinase inhibitors

INTRODUCTION

The human switch/sucrose nonfermentable (SWI/SNF), which is a chromatin remodeling complex dependent on adenosine triphosphate (ATP), affects DNA replication and repair by regulating genomic architecture.[1] SWI/SNF encoded by 29 genes belongs to three broad subfamilies: canonical BAF (cBAF), polybromo-associated BAF (PBAF), and non-canonical BAF (ncBAF).[2,3] Genomic abnormalities in SWI/SNF were presented in nearly 20% of non–small cell lung cancer (NSCLC), of which the frequently mutated genes were ARID1A, SMARCA4, ARID2, ARID1B, and PBRM1.[4–6] Previous studies in NSCLC have identified that SWI/SNF mutations (SWI/SNF-mut) were frequently co-mutated with Kirsten rat sarcoma oncogene (KRAS), STK11, KEAP1, and mutually exclusive with current sensitive driver mutations including epidermal growth factor receptor (EGFR), ALK, MET, ROS1, and RET.[7,8]

In NSCLC, ARID1A, and SMARCA4 were the most frequently mutated genes, which occur in 8% to 9% of patients.[8–11] The impact of SWI/SNF gene mutations on the efficacy of immune checkpoint inhibitors (ICIs) in NSCLC has recently drawn considerable attention. A retrospective study among 292 NSCLC patients treated with ICIs found that patients with SMARCA4 alterations had improved overall survival (OS) (hazard ratio [HR], 0.67; $p = 0.01$).[10] However, another retrospective study showed that ICI-treated patients with homozygous truncating SMARCA4-mut presented significantly shortened OS (HR, 1.62; $p = 0.01$), but no statistical difference was observed between patients with non-homozygous truncating SMARCA4-mut and SMARCA4 wild-type (wt).[8] Therefore, most of the previous studies on the relationship between SWI/SNF and ICIs in NSCLC included patients from non-Asian populations and conclusions were inconsistent.

EGFR tyrosine kinase inhibitors (EGFR-TKIs), as the typical targeted inhibitors, have greatly propelled the evolution of precision treatment and prolonged survival for advanced NSCLC patients with EGFR mutations.[12–14] EGFR exon 19 deletions (19del) and exon 21 Leu858Arg (21L858R) mutation represent the prevalent sensitive mutations to EGFR-TKIs.[15] However, there is almost no evidence on the association of SWI/SNF-mut with the clinical outcome to EGFR-TKIs to date. Here, we characterized the clinical characteristics of SWI/SNF-mut and evaluated the relationship between SWI/SNF-mut and clinical outcomes of ICIs and EGFR-TKIs in Chinese patients with NSCLC.

METHODS

Study population

From January 2019 to October 2021, we collected data of patients detected by next-generation sequencing (NGS) in the Cancer Hospital Chinese Academy of Medical Sciences for analysis. Patients with advanced NSCLC were evaluated in two cohorts: cohort 1 included patients who received programmed cell death protein-1 or programmed cell death ligand 1 (PD[L]-1) inhibitors alone (monotherapy) or in combination with chemotherapy (combined therapy), and cohort 2 included those with EGFR 19del or 21L858R mutation (EGFR-mutant) who received EGFR-TKIs monotherapy. Patients underwent PD-L1 inhibitors or EGFR-TKIs as consolidation therapy after concurrent radiotherapy or without assessment after treatment were excluded. Two Memorial Sloan-Kettering Cancer Center (MSKCC) cohorts totaling 109 NSCLC received immunotherapy alone (PD-1 inhibitors or CTLA4 inhibitors) were included as validation for cohort 1.[16,17] The clinical data and whole exome sequencing (WES) data of MSKCC cohorts were downloaded from cBioPortal (http://www.cbioportal.org/). Clinical characteristics, treatment data, and survival information were collected for analysis. The response was determined based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Pathology and gene sequencing results were reviewed by two oncologists independently. This study was approved by the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (NCC21/032-2703). We performed methods according to approved guidelines and obtained comprehensive informed consent from each patient.

Targeted tumor NGS

Genetic alterations were detected by OncoScreen assay,[18] which surveys the following 10 SWI/SNF subunits: ARID1A, SMARCA4, ARID1B, ARID2, PBRM1, SMARCA2, SMARCB1, SMARCD1, BRD7, and BCL11A. SWI/SNF-mut was defined as having a mutation in at least one of these subunits; otherwise, SWI/SNF-wt was defined. Tissue blocks containing at least 20% tumor content were selected to obtain genomic DNA. Single-nucleotide variant mutations were selected without germline and intron mutations from all samples. We classified SWI/SNF gene alterations into three groups: (i) SWI/SNF truncating mutations (SWI/SNF-tm) included frameshift insertion–deletion (indels), nonsense, or splice mutation types; (ii) SWI/SNF non-truncating mutations (SWI/SNF-ntm) included missense, in frameshift indels, or fusions; and (iii) SWI/SNF compound mutations (SWI/SNF-cm) include both truncating alterations and non-truncating alterations. Tumor mutational burden (TMB) was measured as the number of somatic, coding, base substitution, and indel mutations per megabase (Mb).

Immunohistochemistry

The expression of PD-L1 was detected with an anti-PD-L1 antibody (Dako 22C3) according to manufacturer's instructions and tumor proportion score (TPS) was determined as per routine procedure.

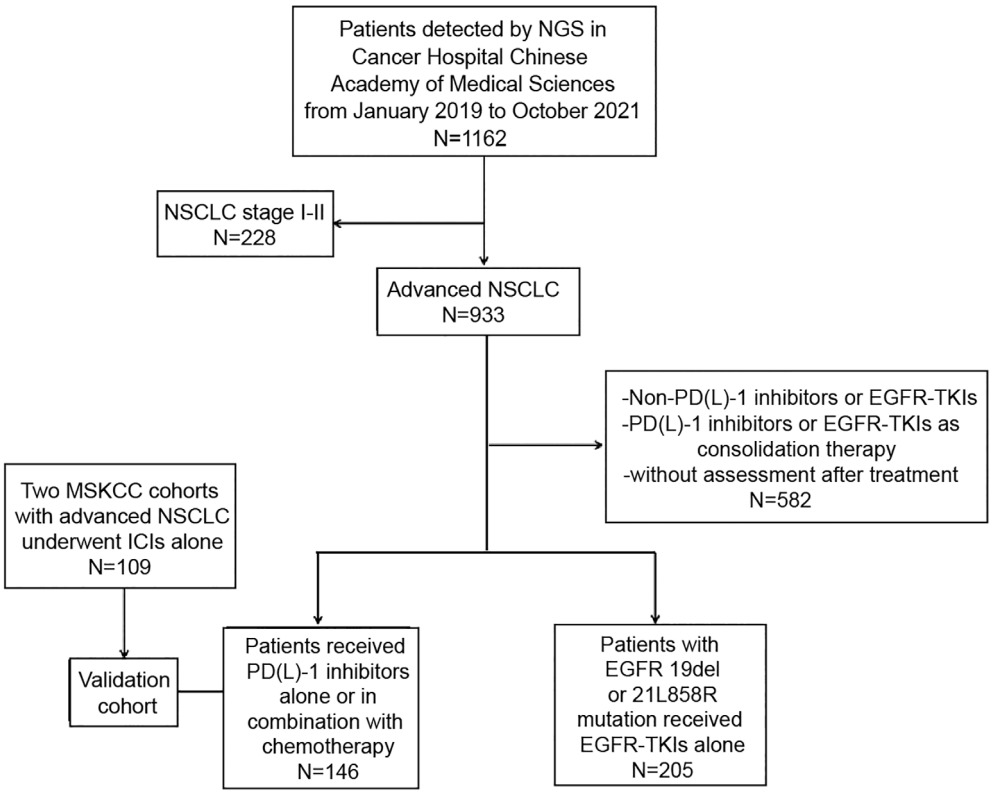

FIGURE 1 Detailed inclusion and exclusion criteria.

Statistical analysis

The overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) was analyzed among patients who underwent PD-L1 inhibitors or EGFR-TKIs. The time from initiation of treatment to progression or death was defined as PFS, if not as censored at the last fellow-up date. We performed statistical analysis by IBM SPSS 26.0, R4.0.3, and Graph Pad Prism 8. Comparison of the clinical characteristics and response rate of each group were evaluated by *t*-test, Wilcoxon test, χ^2 test, or Fisher's exact test, when appropriate. Kaplan–Meier methodology and log-rank tests were used to estimate the distributions and differences in event-time with 95% confidence intervals (CI), respectively. In univariate and multivariate models, HR for PFS was estimated in Cox proportional hazards models and signal of association with $p < 0.1$ were included in multivariate analysis. All analyses were at two-sided level and $p < 0.05$ was predefined statistically significance.

RESULTS

Clinical characteristics

In total, 1162 NSCLC detected by NGS were included (Figure 1), identifying 230 (19.8%) patients with SWI/SNF-mut (Figure 2(a)). Compared with 932 (80.2%) SWI/SNF-wt tumors, those with SWI/SNF-mut were more common in older age ($p = 0.009$), male sex ($p = 0.002$), smokers ($p < 0.001$), positive PD-L1 expression ($p = 0.028$), high TMB (7.2 vs. 3.2 mut/mb, $p = 0.009$, Figure 2b), advanced disease ($p < 0.001$), bone metastasis ($p = 0.018$), and liver metastasis ($p < 0.001$) (Table 1).

Spectrum of SWI/SNF genomic alterations

Of the 230 patients with SWI/SNF-mut, there were 100 (43.5%) truncating alterations, 113 (49.1%) non-truncating alterations, and 17 (7.4%) compound alterations (Figure 2(a)). The frequency of SWI/SNF genomic alterations were ARID1A (33.4%), SMARCA4 (28.3%), ARID2 (15.6%), PBRM1 (14.8%), ARID1B (6.9%), SMARCA2(3.9%), SMARCB1 (3.0%), BRD7 (2.5%), SMARCD1 (0.9%), and BCL11A (0.4%), respectively, among which 8.3% had multiple alterations in SWI/SNF genes (Figure 2(c)). In our cohort, the most commonly co-mutated genes with SWI/SNF were TP53 (52.1%), EGFR (27.3%), KRAS (13.4%), and KEAP1 (11.7%), respectively (Figure 2(d)). The DNA and protein changes of SWI/SNF-mut were listed in Table S1.

Association of SWI/SNF and KRAS co-mutations with clinical outcome to immunotherapy in advanced NSCLC

In total, 146 patients with advanced NSCLC were included in cohort 1 (Table S2). There were 127 (87.0%) patients received combined therapy, whereas the remaining patients received PD-(L)1 inhibitors monotherapy. Although SWI/

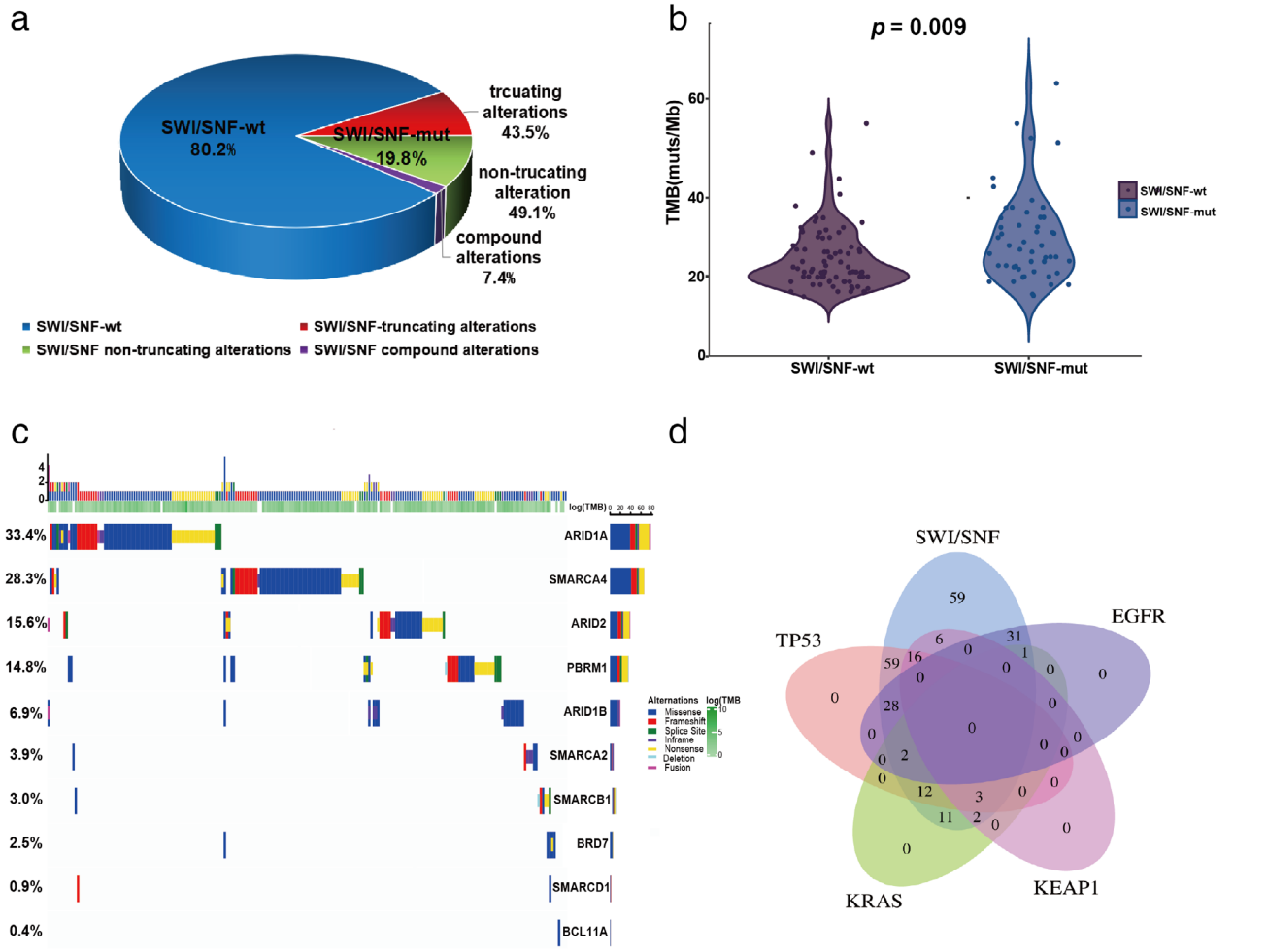

FIGURE 2 (a) Frequency of SWI/SNF genomic alterations among 1162 NSCLC. (b) TMB by SWI/SNF mutation status. Frequency of (c) the full spectrum of SWI/SNF genomic alterations and (d) the co-mutations in SWI/SNF complex. SWI/SNF, switch/sucrose nonfermentable family; NSCLC, non–small cell lung cancer; TMB, tumor mutational burden; wt, wild-type; mut, mutation; Mb, megabase.

SNF-mut tumors had a higher TMB (10.3 vs. 5.0 Mut/mb, $p = 0.005$) than those with SWI/SNF-wt, there were no statistically differences across ORR (40.0% vs. 34.4%, $p = 0.493$) (Figure 3(a)), DCR (77.6% vs. 75.4%, $p = 0.752$) (Figure 3(a)), or PFS (6.5 m vs. 5.0 m; HR, 0.77; 95% CI, 0.51–1.18; $p = 0.231$) (Figure 3(b)) between them. Moreover, neither of the different SWI/SNF-mut types, ARID1A-mut nor SMARCA4-mut, impacted the efficacy to PD-(L)1 inhibitors (Figure S1(a)–(c)). Because published data showed KRAS are frequently co-mutated with SWI/SNF and are associated with the prognosis of ICIs in NSCLC,[11] we further analyze clinical characteristics (Table S4) and efficacy to ICI by KRAS mutation status and found that there were no significant differences between KRAS-wt and KRAS-mut patients for PFS after ICIs (Figure S1(d)). However, patients with concurrent SWI/SNF mutation and KRAS mutation (SWI/SNFmutKRASmut, $n = 18$) had significantly higher TMB (14.0 vs. 7.0 mut/mb, $p = 0.002$) (Figure 3(c)) and conferred longer PFS (8.9 m vs. 4.9 m; HR, 0.53, 95% CI, 0.26–1.06; $p = 0.071$) (Figure 3(d)) to PD-L1 inhibitors than those with non-SWI/SNFmutKRASmut (defined as SWI/SNF wild-type and KRAS wild-type, SWI/SNF wild-type and KRAS mutation, SWI/SNF mutation and KRAS wild-type, $n = 128$), especially for monotherapy treatment (8.6 m vs. 1.9 m; HR, 0.31, 95% CI, 0.11–0.83; $p = 0.032$) (Figure 3(e),(f)).

Because of the number of cases treated with ICIs monotherapy was limited in this cohort, we included two MSKCC cohorts containing totally 109 patients with advanced NSCLC received ICIs alone for validation (Table S3). Consistently, no significant differences of survival were observed either in patients with SWI/SNF-mut and SWI/SNF-wt (Figure S1(e)) or in patients with KRAS-mut and KRAS-wt (Figure S1(f)), whereas SWI/SNFmutKRASmut patients exhibited higher TMB (9.8 vs. 5.7 mut/mb, $p = 0.043$) (Figure 3(g)) and longer PFS to ICIs than non-SWI/SNFmutKRASmut patients (NR vs. 6.3 m; HR, 0.36; 95% CI, 0.15–0.82; $p = 0.016$) (Figure 3(h)).

Association of ARID1A-Mut with clinical survival to EGFR-TKIs in EGFR-mutant NSCLC

There were 205 NSCLC with advanced EGFR-mutant received EGFR-TKIs alone in cohort 2 (Table S5), in which

TABLE 1 Clinical characteristics by SWI/SNF mutation status in the overall cohort of 1162 NSCLC

Characteristics	Total $n = 1162$	SWI/SNF-mut $n = 230$	SWI/SNF-wt $n = 932$	p Value
Age, median (range)	61 (23–87)	63 (33–84)	61 (23–87)	0.009
Sex (%)				0.002
Male	640 (55.1)	148 (64.3)	492 (52.8)	
Female	522 (44.9)	82 (36.7)	440 (47.2)	
Smoking status (%)				<0.001
Current or ever	373 (40.9)	106 (53.0)	267 (37.6)	
Never	538 (59.1)	94 (47.0)	444 (62.4)	
N.A.	251	30	221	
Family history of cancer (%)				0.132
Yes	285 (32.1)	72 (36.5)	213 (30.9)	
No	602 (67.9)	125 (63.5)	477 (69.1)	
N.A.	275	33	242	
Histology (%)				0.800
Adenocarcinoma	963 (82.9)	188 (81.7)	775 (83.2)	
Squamous	124 (10.7)	25 (10.9)	99 (10.6)	
Others[a]	75 (6.4)	17 (7.4)	58 (6.2)	
Stage (%)				
I–II	220 (19.1)	24 (10.6)	196 (21.2)	<0.001
III–IV	933 (80.9)	203 (89.4)	730 (78.8)	
N.A.	9	3	6	
Metastatic sites (%)				
Brain	171 (14.7)	37 (16.1)	134 (14.4)	0.512
Bone	279 (24.0)	69 (30.0)	210 (22.5)	0.018
Liver	69 (5.9)	26 (11.3)	43 (4.6)	<0.001
PD-L1 expression (%)				0.028
<1%	189 (37.4)	33 (30.3)	156 (39.3)	
1%–49%	181 (35.8)	36 (33.0)	145 (36.5)	
≥50%	136 (26.9)	40 (36.7)	96 (24.2)	
N.A.	656	121	535	
TMB, median (mut/mb)	4.0	7.2	3.2	0.009

Abbreviations: Mut, mutation; mut/mb, mutations per megabase; N.A., not available; PD-L1, programmed cell death-ligand 1; SWI/SNF, switch/sucrose nonfermentable; TMB, tumor mutational burden; wt, wild-type.

[a]Adenosquamous carcinomas, sarcomatoid carcinoma, carcinoid, large cell carcinoma, high-grade neuroendocrine carcinoma, and poorly differentiated non-small cell lung carcinomas; not otherwise specified (NOS).

82.9% ($n = 170$) of the patients were treated with first or second-generation TKIs (gefitinib, erlotinib, icotinib, afatinib, or dacomitinib), whereas the remaining patients with third-generation TKIs (osimertinib or almonertinib). Comparing SWI/SNF-wt patients ($n = 164$, 80.0%) with SWI/SNF-mut patients ($n = 41$, 20.0%), there were no significant differences across ORR, DCR, or PFS in the overall group ($n = 205$) (Figure 4(a),(b)) nor in the subgroups of first, second ($n = 170$) (Figure S2(a),(b)), or third generation TKIs treatment ($n = 35$, Figure S2c,d).

In cohort 2, the most frequent SWI/SNF genomic alterations were ARID1A ($n = 16$, 7.8%), and the baseline clinical characteristics were similar between patients with ARID1A-mut and ARID1A-wt (Table S5). However, patients with ARID1A-mut had higher DCR (100.0% vs. 92.6%, $p = 0.541$) (Figure 4(c)) and significantly longer prolonged PFS to EGFR-TKIs than those with ARID1A-wt (20.6 m vs. 11.2 m; HR, 0.47; 95% CI, 0.27–0.94; $p = 0.023$) (Figure 4(d)), which was consistent both in first, second (Figure S2(e)) and third generation EGFR-TKIs subgroups (Figure S2(f)). Conversely, none of the other SWI/SNF gene alterations were associated with efficacy of EGFR-TKIs (Table S6). Importantly, in the multivariable survival analysis adjusted for other variables, ARID1A-mut was still associated with improved survival to EGFR-TKIs (HR, 0.49; 95% CI, 0.25–0.98; $p = 0.047$) (Figure 4(e)).

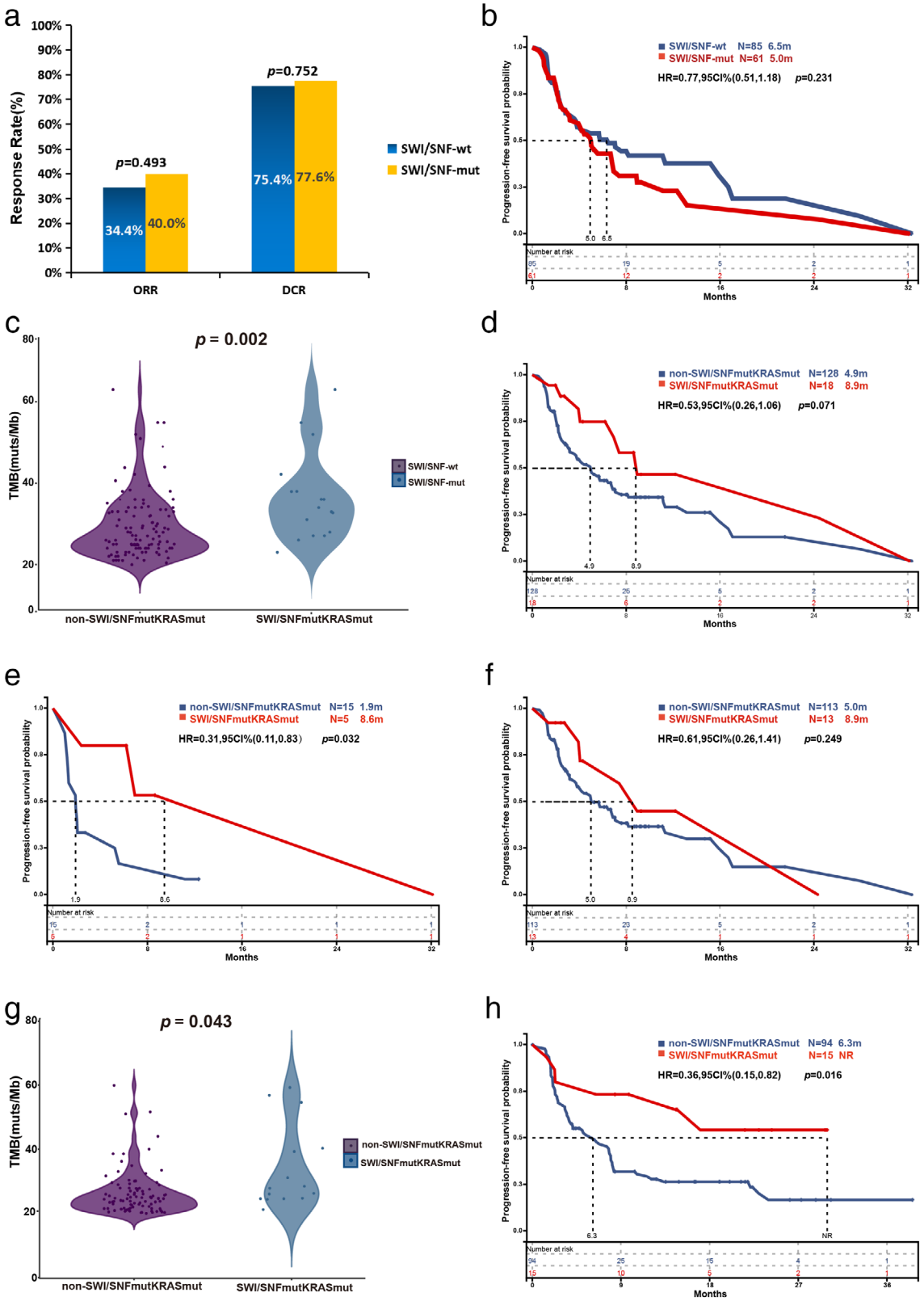

FIGURE 3 (a) Response rate and (b) Kaplan–Meier analysis for PFS to PD-(L)1 inhibitors in patients with SWI/SNF-mut vs. SWI/SNF-wt in cohort 1. (c) Response rate and (d) Kaplan–Meier analysis for PFS to PD-(L)1 inhibitors in patients with SWI/SNFmutKRASmut vs. non-SWI/SNFmutKRASmut in cohort 1. Kaplan–Meier analysis for PFS to (e) PD-(L)1 inhibitors monotherapy and (f) combine therapy in patients with SWI/SNFmutKRASmut vs. non-SWI/SNFmutKRASmut in cohort 1. (g) Response rate and (h) Kaplan–Meier analysis for PFS to ICIs in patients with SWI/SNFmutKRASmut vs. non-SWI/SNFmutKRASmut in MSKCC cohorts. SWI/SNF, switch/sucrose nonfermentable family; wt, wild-type; mut, mutation; Mb, megabase; PFS, progression-free survival; PD-(L)1, programmed cell death ligand 1; HR, hazard ratio; ICIs, immune checkpoint inhibitors.

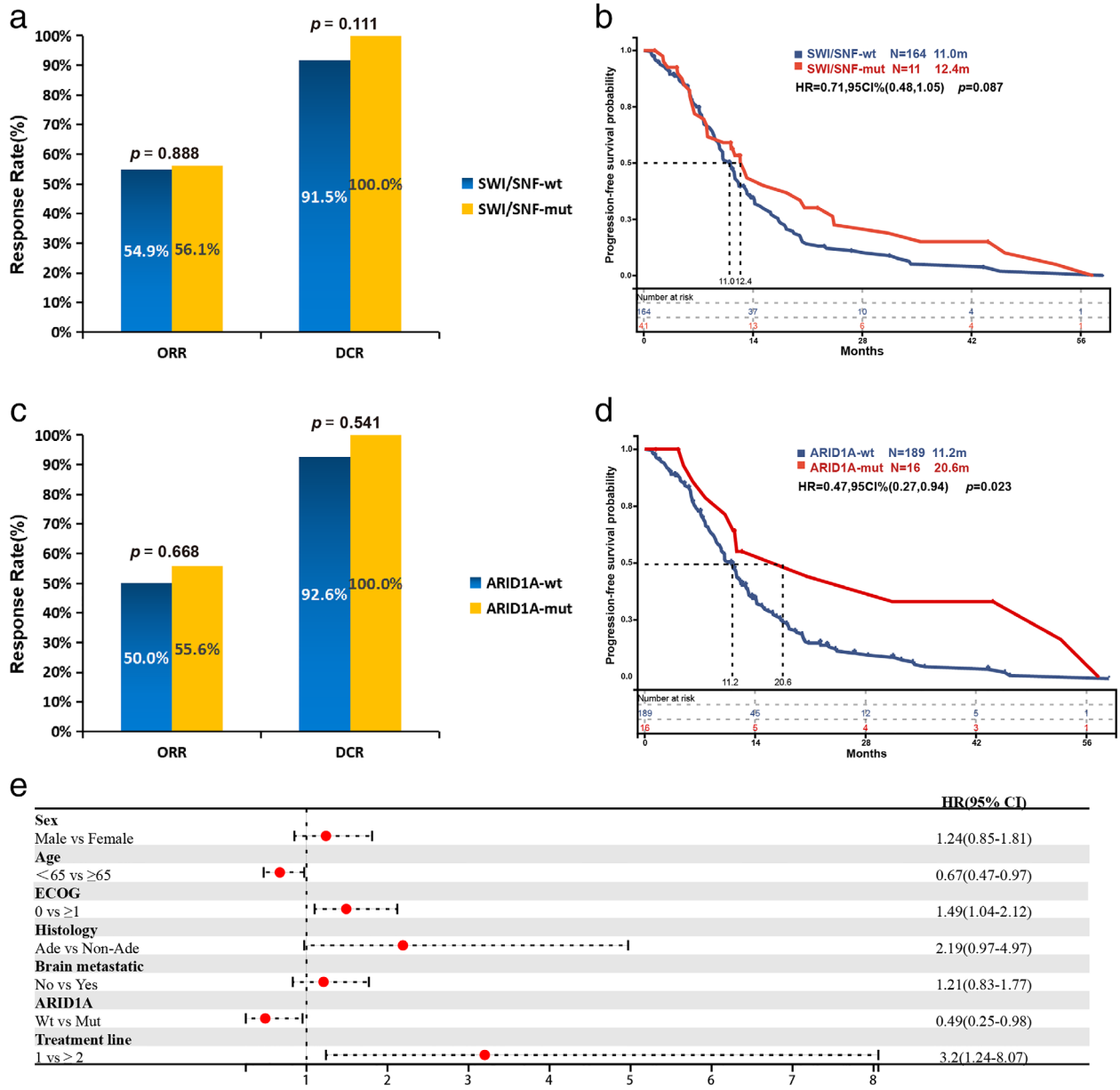

FIGURE 4 (a) Response rate and (b) Kaplan–Meier analysis for PFS to TKIs in patients with SWI/SNF-wt vs. SWI/SNF-mut. (c) Response rate and (d) Kaplan–Meier analysis for PFS to TKI in patients with ARID1A-wt vs. ARID1A-mut. (e) Multivariable survival analysis of clinical factors for PFS to TKIs. SWI/SNF, switch/sucrose nonfermentable family; wt, wild-type; mut, mutation; PFS, progression-free survival; TKIs, tyrosine kinase inhibitors; HR, hazard ratio; CI, confidence interval.

DISCUSSION

In our institutional study of 1162 Chinese patients with NSCLC, we reported a mutational incidence rate of ~20% in SWI/SNF genes. Consistent with previous studies,[9,11,19,20] SWI/SNF-mut was correlated with older age, smoking, male sex, higher TMB, and higher proportion of PD-L1-positive. Moreover, SWI/SNF-mut was more often observed in tumors with advanced disease, bone, and liver metastasis. In advanced NSCLC, neither SWI/SNF-mut nor its common individual gene alterations affected the clinical outcome of ICIs. However, patients with SWI/SNFmutKRASmut had improved clinical outcome to ICIs compared to those with non-SWI/SNFmutKRASmut. Furthermore, our study indicated that ARID1A-mut was associated with prolonged survival to EGFR-TKIs in patients with EGFR-mutant.

Previous studies reported that SWI/SNF genes are frequently co-mutated with KRAS, and patients with SMARCA4 and KRAS co-mutation had poorer survival rates after ICIs.[11,21] However, we found that patients with SWI/SNFmutKRASmut presented higher ORR and DCR and longer PFS to ICIs, especially in those treated with ICIs monotherapy. Similarly, multiple studies have showed that KRAS-mut impacts clinical outcomes of ICIs in NSCLC.[22–26]

A meta-analysis including six randomized clinical trials on ICIs monotherapy or combined therapy as second- or first-line treatment for advanced NSCLC (IMpower-150, Keynote-189 and Keynote-042, Oak, Poplar, and CheckMate-057), demonstrated that ICIs had prolonged PFS and OS in KRAS-mut patients.[26] KRAS-mut was correlated with PD-L1-positive ($p = 0.031$)[27] and has been confirmed to be a potential driver to produce more neoantigens.[23] In our study, the patients harboring SWI/SNFmutKRASmut had significantly higher TMB compared to those without SWI/SNFmutKRASmut. Overall, it is possible that the superior clinical outcome observed in SWI/SNFmutRASmut patients might be because of the increased production of neoantigens and a higher PD-L1 expression, both of which are highly correlated with improved response to ICIs.

EGFR mutation rates were higher in our cohort (27.3%) than that in previous studies (11%–14%),[8,11] which is likely because of the higher prevalence of EGFR mutations in Asian NSCLC (50%–60%) compared to Caucasian NSCLC (10%–20%).[12,13,28] In advanced EGFR-mut NSCLC, we observed a significantly longer PFS after EGFR-TKIs in patients with ARID1A-mut compared to those with ARID1A-wt. As a cBAF-specific subunit, ARID1A protein has been confirmed to be one of the critical components that modify the position of nucleosomes on DNA and is associated with proliferation, migration, invasion, and metastasis of various cancers.[29–34] Recent studies showed that enhanced glutathione metabolism contributes to EGFR-TKIs resistance.[34] Inhibition of glutathione de novo synthesis by targeting AKR1B1 or METTL7B can overcome acquired resistance to both first and third generation EGFR-TKIs in NSCLC.[35,36] ARID1A-inactivating mutations were associated with reduced metabolism of glutathione in ARID1A-deficient cancers,[37] which may be one of the factors affecting sensitivity to EGFR-TKIs. On the contrary, a retrospective study of 19 EGFR-mutant NSCLC patients showed that icotinib treatment had significantly reduced PFS ($p = 0.001$) for patients with ARID1A-mut ($n = 3$).[38] Obviously, the sample size is small and all the patients received first generation EGFR-TKIs, which differs from ours. For the remaining SWI/SNF gene alterations, efficacy of EGFR-TKIs exhibits significant heterogeneity. Further studies with larger sample sizes are needed for validation.

In our study, there were several limitations that should be considered. First, this was a retrospective single-institution analysis with some inherent bias. Second, our assay contained the most common SWI/SNF genes, but did not cover all SWI/SNF genes. Third, the results of this study were descriptive and further research is required to determine the mechanisms of the effect of SWI/SNF gene mutations on the response to ICIs and EGFR-TKIs.

In conclusion, our study represents a comprehensive cohort with SWI/SNF-mut NSCLC in China and provides new knowledge on the genetic contributions of SWI/SNF-mut to response to ICIs and EGFR-TKIs in advanced NSCLC. Although no association was observed between SWI/SNF-mut and clinical outcomes of ICIs or TKIs, SWI/SNF-mut and KRAS-mut co-occurrence appeared to improved clinical survival for patients who received ICI treatment, especially for those who received ICI alone. Furthermore, we demonstrated that ARID1A-mut seems to prolong clinical survival after EGFR-TKIs in EGFR-mutant advanced NSCLC. These findings could lead to improved outcomes for NSCLC by identifying more patient-specific treatments that cater to SWI/SNF genetic alternations. Additional prospective studies with more detailed sequencing of all SWI/SNF genes and larger sample sizes are needed in the future. Meanwhile, further studies to unveil the mechanism by which SWI/SNF affects clinical outcomes is an important issue.

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DISCLOSURE

The authors declare that there are no conflicts of interest.

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REFERENCES

1. Bates SE. Epigenetic therapies for cancer. N Engl J Med. 2020;383:650–63.
2. Michel BC, D'Avino AR, Cassel SH, Mashtalir N, Mckenzie ZM, Mcbride MJ, et al. A non-canonical swi/snf complex is a synthetic lethal target in cancers driven by baf complex perturbation. Nat Cell Biol. 2018;20:1410–20.
3. Mashtalir N, D'Avino AR, Michel BC, Luo J, Pan J, Otto JE, et al. Modular organization and assembly of swi/snf family chromatin remodeling complexes. Cell. 2018;175:1272–88.
4. Ashizawa M, Saito M, Min A, Ujiie D, Saito K, Sato T, et al. Prognostic role of arid1a negative expression in gastric cancer. Sci Rep. 2019;9:6769.
5. Abou AS, Nassar AH, Xie W, Bakouny Z, Berchuck JE, Braun DA, et al. Mammalian swi/snf complex genomic alterations and immune checkpoint blockade in solid tumors. Cancer Immunol Res. 2020;8:1075–84.
6. Helming KC, Wang X, Roberts C. Vulnerabilities of mutant swi/snf complexes in cancer. Cancer Cell. 2014;26:309–17.
7. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014;511:543–50.
8. Fernando TM, Piskol R, Bainer R, Sokol ES, Trabucco SE, Zhang Q, et al. Functional characterization of smarca4 variants identified by targeted exome-sequencing of 131,668 cancer patients. Nat Commun. 2020;11:5551.

9. Zhu G, Shi R, Li Y, Zhang Z, Xu S, Chen C, et al. Arid1a, arid1b, and arid2 mutations serve as potential biomarkers for immune checkpoint blockade in patients with non-small cell lung cancer. Front Immunol. 2021;12:670040.
10. Schoenfeld AJ, Bandlamudi C, Lavery JA, Montecalvo J, Namakydoust A, Rizvi H, et al. The genomic landscape of smarca4 alterations and associations with outcomes in patients with lung cancer. Clin Cancer Res. 2020;26:5701–8.
11. Alessi JV, Ricciuti B, Spurr LF, Gupta H, Li YY, Glass C, et al. Smarca4 and other switch/sucrose nonfermentable family genomic alterations in nsclc: clinicopathologic characteristics and outcomes to immune checkpoint inhibition. J Thorac Oncol. 2021;16: 1176–87.
12. Remon J, Hendriks L. Targeted therapies for unresectable stage iii non-small cell lung cancer. Mediastinum. 2021;5:22.
13. Melosky B, Kambartel K, Hantschel M, Bennetts M, Nickens DJ, Brinkmann J, et al. Worldwide prevalence of epidermal growth factor receptor mutations in non-small cell lung cancer: a meta-analysis. Mol Diagn Ther. 2022;26:7–18.
14. Passaro A, Leighl N, Blackhall F, Popat S, Kerr K, Ahn MJ, et al. Esmo expert consensus statements on the management of egfr mutant non-small-cell lung cancer. Ann Oncol. 2022;33:466–87.
15. Bogershausen N, Wollnik B. Mutational landscapes and phenotypic spectrum of swi/snf-related intellectual disability disorders. Front Mol Neurosci. 2018;11:252.
16. Hellmann MD, Nathanson T, Rizvi H, Creelan BC, Sanchez-Vega F, Ahuja A, et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. Cancer Cell. 2018;33:843–52.
17. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to pd-1 blockade in non-small cell lung cancer. Science. 2015;348:124–8.
18. Wang M, Chen X, Dai Y, Wu D, Liu F, Yang Z, et al. Concordance study of a 520-gene next-generation sequencing-based genomic profiling assay of tissue and plasma samples. Mol Diagn Ther. 2022;26:309–22.
19. Dagogo-Jack I, Schrock AB, Kem M, Jessop N, Lee J, Ali SM, et al. Clinicopathologic characteristics of brg1-deficient nsclc. J Thorac Oncol. 2020;15:766–76.
20. Naito T, Udagawa H, Umemura S, Sakai T, Zenke Y, Kirita K, et al. Non-small cell lung cancer with loss of expression of the swi/snf complex is associated with aggressive clinicopathological features, pd-l1-positive status, and high tumor mutation burden. Lung Cancer. 2019;138:35–42.
21. Liu L, Ahmed T, Petty WJ, Grant S, Ruiz J, Lycan TW, et al. Smarca4 mutations in kras-mutant lung adenocarcinoma: a multi-cohort analysis. Mol Oncol. 2021;15:462–72.
22. Lee J, Tan AC, Zhou S, Yoon S, Liu S, Masuda K, et al. Clinical characteristics and outcomes in advanced kras-mutated nsclc: a multicenter collaboration in asia (atorg-005). JTO Clin Res Rep. 2022;3: 100261.
23. Dong ZY, Zhong WZ, Zhang XC, Su J, Xie Z, Liu SY, et al. Potential predictive value of tp53 and kras mutation status for response to pd-1 blockade immunotherapy in lung adenocarcinoma. Clin Cancer Res. 2017;23:3012–24.
24. Liu C, Zheng S, Jin R, Wang X, Wang F, Zang R, et al. The superior efficacy of anti-pd-1/pd-l1 immunotherapy in kras-mutant non-small cell lung cancer that correlates with an inflammatory phenotype and increased immunogenicity. Cancer Lett. 2020;470:95–105.
25. Kim JH, Kim HS, Kim BJ. Prognostic value of kras mutation in advanced non-small-cell lung cancer treated with immune checkpoint inhibitors: a meta-analysis and review. Oncotarget. 2017;8:48248–52.
26. Landre T, Justeau G, Assie JB, Chouahnia K, Davoine C, Taleb C, et al. Anti-pd-(l)1 for kras-mutant advanced non-small-cell lung cancers: a meta-analysis of randomized-controlled trials. Cancer Immunol Immunother. 2022;71:719–26.
27. Ng TL, Liu Y, Dimou A, Patil T, Aisner DL, Dong Z, et al. Predictive value of oncogenic driver subtype, programmed death-1 ligand (pd-l1) score, and smoking status on the efficacy of pd-1/pd-l1 inhibitors in patients with oncogene-driven non-small cell lung cancer. Cancer. 2019;125:1038–49.
28. Liu L, Xiong X. Clinicopathologic features and molecular biomarkers as predictors of epidermal growth factor receptor gene mutation in non-small cell lung cancer patients. Curr Oncol. 2021;29:77–93.
29. Hu C, Li W, Tian F, Jiang K, Liu X, Cen J, et al. Arid1a regulates response to anti-angiogenic therapy in advanced hepatocellular carcinoma. J Hepatol. 2018;68:465–75.
30. Wilson MR, Reske JJ, Holladay J, Wilber GE, Rhodes M, Koeman J, et al. Arid1a and pi3-kinase pathway mutations in the endometrium drive epithelial transdifferentiation and collective invasion. Nat Commun. 2019;10:3554.
31. Yang F, Xu Y, Liu C, Ma C, Zou S, Xu X, et al. Nf-kappab/mir-223-3p/arid1a axis is involved in helicobacter pylori caga-induced gastric carcinogenesis and progression. Cell Death Dis. 2018;9:12.
32. Wang J, Yan HB, Zhang Q, Liu WY, Jiang YH, Peng G, et al. Enhancement of e-cadherin expression and processing and driving of cancer cell metastasis by arid1a deficiency. Oncogene. 2021;40:5468–81.
33. Guan B, Wang TL, Shih I. Arid1a, a factor that promotes formation of swi/snf-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. Cancer Res. 2011;71:6718–27.
34. Zhang Y, Xu X, Zhang M, Bai X, Li H, Kan L, et al. Arid1a is downregulated in non-small cell lung cancer and regulates cell proliferation and apoptosis. Tumour Biol. 2014;35:5701–7.
35. Zhang KR, Zhang YF, Lei HM, Tang YB, Ma CS, Lv QM, et al. Targeting akr1b1 inhibits glutathione de novo synthesis to overcome acquired resistance to egfr-targeted therapy in lung cancer. Sci Transl Med. 2021;13:g6428.
36. Song H, Liu D, Wang L, Liu K, Chen C, Wang L, et al. Methyltransferase like 7b is a potential therapeutic target for reversing egfr-tkis resistance in lung adenocarcinoma. Mol Cancer. 2022;21:43.
37. Ogiwara H, Takahashi K, Sasaki M, Kuroda T, Yoshida H, Watanabe R, et al. Targeting the vulnerability of glutathione metabolism in arid1a-deficient cancers. Cancer Cell. 2019;35:177–90.
38. Han X, Luo R, Wang L, Zhang L, Wang T, Zhao Y, et al. Potential predictive value of serum targeted metabolites and concurrently mutated genes for egfr-tki therapeutic efficacy in lung adenocarcinoma patients with egfr sensitizing mutations. Am J Cancer Res. 2020;10:4266–86.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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