Lung Cancer 205 (2025) 108594

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review article

ARID1A mutational status in non-small cell lung cancer: from molecular pathology to clinical implications with a focus on the relationships with *EGFR*

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ARTICLE INFO

Keywords:
ARID1A
SWI/SNF
Chromatin remodeling
EGFR
NSCLC

ABSTRACT

Lung cancer is the most frequently diagnosed malignancy worldwide and remains the leading cause of cancer-related mortality. Non-small-cell lung cancer (NSCLC) is the most prevalent type of lung cancer, with epidermal growth factor receptor (*EGFR*) gene mutations being among the most frequently reported. ARID1A (AT-Rich Interactive Domain 1A), a key component of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex, has emerged as a tumor suppressor in multiple cancers and is mutated in approximately 8 % of lung cancers, primarily as a loss-of-function (LOF) alteration, which allows the gene to be considered a potential molecular marker, predictive of poor NSCLC prognosis. Co-occurrence of *ARID1A* LOF mutations and *EGFR* alterations presents complex biological and therapeutic challenges. *ARID1A* LOF mutations negatively affect the efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) via several molecular mechanisms, including the aberrant activation of the phosphoinositide 3-kinase/serine-threonine kinase (PI3K/AKT) signaling pathway. This leads to decreased apoptosis, increased tumor angiogenesis, enhanced proliferation, and greater metastatic potential. On the other hand, *ARID1A* LOF mutations have emerged as promising predictive biomarkers for favorable responses to immune checkpoint inhibitors (ICIs). The underlying mechanisms include modulation of epithelial-to-mesenchymal transition (EMT), alterations in the tumor immune microenvironment (TIME), impaired mismatch repair (MMR) function, increased tumor mutation burden (TMB), enhanced neoantigen presentation, and upregulation of programmed death ligand 1 (PD-L1) and type I interferon (IFN-I) expression. These findings highlight the dual role of *ARID1A* mutations as prognostic and predictive biomarkers, underscoring the need for further investigation into their complex biological and therapeutic implications.

1. Introduction

Lung cancer is the most frequently diagnosed cancer (accounting for 12.4 % of all new cases globally) and the leading cause of cancer deaths (18.7 %) [1,2]. It is a heterogeneous disease broadly divided into two categories: non-small-cell lung cancer (NSCLC), the most common,

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https://doi.org/10.1016/j.lungcan.2025.108594
Received 1 April 2025; Received in revised form 3 May 2025; Accepted 25 May 2025
Available online 1 June 2025

accounting for 85 % of all cases, and small-cell lung cancer (SCLC), which account for 15 %. The most common NSCLC subtype is pulmonary adenocarcinoma (40 % of all lung cancer cases) [3].

Chemotherapy has long been the standard of care for advanced lung cancer, but over the past two decades, the discovery of predictive biomarkers has led to the development of targeted therapies [3]. NSCLC can be categorized according to the presence or absence of oncogenic driver alterations [3], which are present in approximately 50 % of lung adenocarcinomas and define several molecular subtypes of NSCLC [4]. Targeted therapies matched to these oncogenic drivers are associated with improved survival and quality of life and are recommended by the main clinical guidelines, including the European Society for Medical Oncology (ESMO) [5].

The National Comprehensive Cancer Network (NCCN), as well as the ESMO Guidelines recommend molecular testing for *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*ex14 skipping, *RET*, and *ERBB2* (*HER2*) alterations in all patients with advanced or metastatic non-squamous NSCLC, and NSCLC not otherwise specified [5,6]. Despite the effectiveness of targeted therapies, treatment-induced resistance can occur via multiple mechanisms. Epigenetic processes may mediate resistance to targeted therapies and represent novel therapeutic targets themselves, especially in tumors that lack clear genetic mechanisms of resistance [7]. Chromatin remodeling is an integral aspect of epigenetic changes and a prominent epigenetic regulator [8]. Chromatin structure is regulated by two general classes of complexes: those that covalently modify histone tails and ATP-dependent chromatin remodelers. The latter include switching defective/sucrose non-fermenting (SWI/SNF) complexes, which represent a link between chromatin remodeling and tumor suppression, as evidenced by recurrent mutations in subunits of the complex identified in various human cancers [9].

Dysregulation of ATP-dependent chromatin remodeling complexes is implicated in a variety of cancers [10,11]. These complexes utilize ATP hydroxylation energy to reposition, eject, or exchange nucleosomes, thereby modulating DNA accessibility to other cellular machinery involved in transcription, replication, methylation, and repair [12]. *ARID1A* encodes a homonymous protein, which is a subunit of the SWI/SNF complex. The *ARID1A* gene is located on chromosome 1p36 and is involved in the regulation of many cellular processes, including proliferation, DNA repair, development, differentiation, and tumor suppression. Most of the *ARID1A* mutations inactivate and lead to the LOF of *ARID1A* [13,14]. ARID1A is the most frequently altered subunit of the SWI/SNF complex and is aberrant in approximately 6 % of all cancers, including 8 % of lung cancer [15,16]. These findings support a major tumor-suppressive role of *ARID1A* [16,17].

This review summarizes the main scientific evidence of the role of *ARID1A* as a tumor suppressor gene, the biological consequences of its downregulation, and its potential clinical and pharmacological applications in NSCLC, with a particular focus on those *EGFR* mutated (Fig. 1).

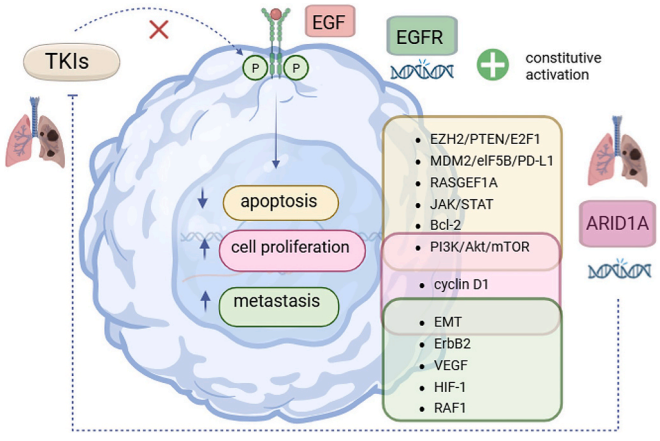

Fig. 1. Summarizing figure of the different biological functions regulated by *ARID1A*. TKIs: tyrosine kinase inhibitors. (Created with BioRender.com)

2. Overview of ARID1A and EGFR: characteristics and functions

The mammalian SWI/SNF complex comprises three subfamilies, of which the BRG1/BRM-associated factor (BAF) is the most crucial chromatin remodeling factor in humans [18]. BAF complexes are composed of one of the two mutually exclusive ATPase subunits (SMARCA2 and SMARCA4) and a set of core subunits, including the AT-rich interacting domain (ARID) and SMARCB1 [12]. The structural core of BAF consists of ARID1A, with SMARCC and SMARCD serving as regulatory subunits. The BAF complex can be further subdivided by the presence of mutually exclusive accessory subunits that generate several hundred possible subunit combinations in SWI/SNF complexes that regulate chromatin accessibility to several related molecules, including those involved in transcription, DNA replication and DNA repair process proteins, as well as DNA-binding proteins, cofactors, and regulators, allowing a single gene to serve a multitude of functions based on its expression pattern [15,18,19]. ARID1A, which has a crucial function in DNA repair and stabilization, can be dysregulated in malignancies and is associated with histological differentiation [20], metastasis, and poor prognosis [14,20,21,22,23], but not with tumor size or histological type [24].

Comprehensive molecular profiling of lung adenocarcinoma has identified genetic alterations in the *ARID1A* gene at a frequency of approximately 8 %, most of which are single nucleotide substitutions [25]. LOF alterations in *ARID1A*, including nonsense mutations, frameshift mutations, splice-site mutations, structural rearrangements, and truncating mutations are common in NSCLC [20]. Missense mutations are present in approximately 42 % of cases, with two or more different types of *ARID1A* mutations frequently occurring in the same patient. These mutations can be found anywhere in the *ARID1A* gene, as is typical of tumor suppressor genes [19].

EGFR is a transmembrane tyrosine kinase receptor that plays a pivotal role in signaling pathways governing cell survival, growth, and proliferation [26]. Upon binding with its ligands, EGFR modifies its auto-inhibited monomeric conformation and undergoes dimerization and autophosphorylation, initiating a cascade of downstream signaling pathways, including the RAS-RAF-MEK-ERK and PI3K-AKT pathways, that are integral for regulating gene expression, cell cycle progression, and survival mechanisms in epithelial cells [27,28]. EGFR tyrosine kinase domain (TKD)-activating mutations occur in approximately 10–40 % of NSCLC, with a higher prevalence in Asians (reaching up to 40–60 %) than in Caucasians (10–30 %) and an incidence about three times higher in non-smokers than in smokers and in women than in men. The entire TKD is encoded by exons 18–24 [29]. The common *EGFR* mutations, together accounting for 80–85 % of *EGFR* gene alterations, are: I) the "gain-of-function" mutations (~45 % of *EGFR* mutations) occurring as short in-frame deletions in exon 19 (Ex19Del), and II) the point mutations in exon 21 (~40 %), mainly resulting in arginine replacing leucine at codon 858 (L858R) [30,31]. Both mutations result in constitutive receptor activation, promoting uncontrolled cell proliferation and survival and contributing to oncogenesis and tumor progression [27].

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) are the treatment of choice in patients with advanced NSCLC with sensitive *EGFR* mutations. [5,32]. However, despite the efficacy of EGFR-TKIs, most patients eventually develop resistance, either de novo (primary resistance) or after an initial response (acquired resistance), highlighting the need for further research into resistance mechanisms [33,34]. Osimertinib, for instance, is currently among the standard first-line treatments for *EGFR*-mutated NSCLC patients [35]. It is a third-generation EGFR-TKI that offers several advantages compared to first- and second-generation ones: it targets the resistance-associated T790M mutation, along with the activating mutations L858R and exon 19 deletion, while sparing wild-type *EGFR* [36,37,38]. Moreover, it

crosses the blood–brain barrier and shows significant efficacy in treating central nervous system metastases [38,39]. However, despite achieving a durable response, drug resistance is inevitable [40].

In NSCLC, ARID1A loss has been correlated with resistance to both first- and third-generation EGFR-TKIs. Among 57 lung adenocarcinoma (LUAD) patients harboring sensitizing *EGFR* mutations (exon 19 deletion in 24 patients and exon 21 L858R in 33 patients) treated with first-line, first-generation EGFR TKIs (icotinib, erlotinib, gefitinib), those with high ARID1A expression exhibited a significantly longer progression-free survival (PFS) than those with low expression (14.6 vs 9.6 months, P = 0.0015) [23]. Interestingly, *ARID1A* expression was observed in 57.1 % of T790M-negative cases versus 42.9 % of T790M-positive cases, suggesting that *ARID1A* deficiency may contribute particularly to EGFR-TKI resistance in T790M-negative patients [23]. In vitro multi-omics analyses have revealed several potential mechanisms underlying resistance to EGFR-TKIs in the context of *ARID1A* loss, including bypass activation of the ErbB and VEGF signaling pathways [23]. Furthermore, screening of the NCI-60 database has identified various small-molecule inhibitors with potential efficacy in *ARID1A*-deficient NSCLC. These include PI3K/Akt/mTOR pathway inhibitors such as dactolisib (a pan-class I PI3K and mTOR inhibitor), GDC-0068 (a pan-Akt inhibitor), and rapamycin (an mTOR inhibitor), as well as multitarget agents like axitinib, which inhibits VEGFR1, VEGFR2, VEGFR3, and PDGFR-β [23]. Sun et al. analyzed 77 *EGFR*-mutant LUAD patients treated with Osimertinib (38 with exon 19 deletion and 39 with exon 21 L858R; 70.13 % T790M-positive) and found that low ARID1A expression was significantly associated with shorter PFS (6.2 vs 11.2 months, P = 0.0183) compared to patients with high ARID1A expression [41]. Mechanistically, *ARID1A* deficiency was shown to promote osimertinib resistance by inhibiting programmed cell death via multiple pathways: the EZH2/PTEN/E2F1 axis, MDM2-mediated p53 degradation, disruption of the MDM2/eIF5B/PD-L1 pathway, and upregulation of RASGEF1A, leading to enhanced Ras signaling [41]. Based on these findings, Simvastatin (a E2F1 inhibitor) and Amlodipine (an autophagy promoter that facilitates PD-L1 degradation), either as monotherapy or in combination with osimertinib, appear promising in restoring apoptosis and may serve as potential therapeutic options in *ARID1A*-deficient LUAD [41]. Additionally, Sun et al. demonstrated a synergistic antitumor effect from combining osimertinib with lipid nanoparticles delivering siRNA targeting PD-L1. This strategy effectively inhibited the transcription and translation of nuclear PD-L1, MDM2, and eIF5B, as well as suppressed mTOR pathway activity [41].

3. Mechanisms of ARID1A-mediated resistance to EGFR TKIs

Table 1 and Table 2 summarize the main ARID1A-mediated mechanisms of resistance to EGFR TKIs and the immunological modulations. Many of the mechanisms that cause resistance to EGFR-TKI treatment in patients with NSCLC lead to abnormal continuous activation of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway [23,42,43], which involves multiple mechanisms responsible for cancer progression [44]. PI3K/AKT upregulates phosphorylation levels of downstream molecules of the EGFR signaling pathway, endowing cancer cells with the ability to escape from the inhibition of proliferation induced by EGFR-TKIs, resulting in the evasion of apoptosis [33]. *ARID1A* mutations are believed to be crucial triggers for the activation of the PI3K/AKT signaling pathway [44,45,46].

These processes occur mainly via somatic mutation of specific components of signal transduction and activation of tyrosine kinase receptors, such as loss of the cancer-suppressor gene PTEN (phosphatase and tensin homolog) and activating mutation of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA) [47]. Aberrant expression of these genes leads to uncontrolled AKT activation and consequent constitutive activation of the PI3K/AKT signaling pathway. Guan et al. [48] investigated the effect of ARID1A on the PI3K/AKT pathway by comparing *ARID1A* knockout mice and *ARID1A/PTEN*

Table 1
ARID1A-mediated mechanisms regarding EGFR TKIs resistance in NSCLC.

ARID1A AND EGFR TKIs RESISTANCE IN NSCLC			
Pathway involved and function	**Molecular mechanism**	**Experimental Setting**	**Reference**
Activation of PI3K/Akt/mTOR pathway:	Cyclin D1, Bcl-2, p-Akt upregulation	ARID1A-KD NSCLC cell lines	Zhang et al [49]
	p-Akt upregulation	ARID1A-KD LUAD cell lines (including a cell line harboring EGFR mut) and ARID1A-KD mNSCLC xenograft murine models	Sun et al [14]
- Upregulates phosphorylation levels of downstream molecules of the EGFR signaling pathway;			
- Increased proliferation and metastasis;	p-Akt2 upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [23]
- Reduced apoptosis.			
	p-Akt and p-mTOR upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [41]
Activation of JAK/STAT signaling pathway:	p-STAT3 upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [41]
- Downstream pathway of activated EGFR signaling;			
- Mediator of the oncogenic effects of somatic EGFR mutations.			
RAS signaling pathway:	RASGEF1A upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [41]
- Promotes the growth and progression of cancer cells.			
MAPK signaling pathway:	pMAPK upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [23]
- Regulating cell proliferation, differentiation, survival and apoptosis.			
Activation of RB-E2F pathway:	p-E2F2 and p-E2F8 upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [23]
- Increased proliferation.			
Activation of EZH2/PTEN/E2F1 axis:	Increased E2F1 level, decreased PTEN level, decreased P53 transcription, increased MDM2 expression	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [41]
- Inhibited autophagy and attenuated MDM2/P53-primed apoptosis.			
Bypass activation of the ErbB pathway and activation of the VEGF HIF-1, and RAF1 pathway:	p-EGFR, HER-2, HER-3 and HER-4 upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [23]
- Tumor progression and metastasis.			
Epithelial-Mesenchymal Transition (EMT):	p-HGF, p-Vimentin and p-ZEB1 upregulation	ARID1A-KD LUAD cell lines with a sensitive EGFR mut	Sun et al [23]

(*continued on next page*)

Table 1 (*continued*)

ARID1A AND EGFR TKIs RESISTANCE IN NSCLC			
Pathway involved and function	**Molecular mechanism**	**Experimental Setting**	**Reference**
- Increasing invasiveness and metastasis of cancer cells.	Impaired MGT#1 expression	ARID1A-KD LUAD cell lines	Serresi et al [53]

OTHER POSSIBLE MECHANISM WITH EVIDENCE IN OTHER SOLID CANCERS		
Pathway	**Evidence**	**Reference**
NF-κB signaling pathway:	ARID1A KD HCC mouse models: ARID1A expression loss could activate the NF-κB signaling pathway	Fang et al [54]
- Tumorigenesis and development of malignancies.		
- Associated with the resistance to EGFR-TKIs.	ARID1A KD OCCC cell line: NF-κB pathway inhibitors could reverse chemoresistance and suppress cell proliferation induced by ARID1A loss	Kim et al [55]

Abbreviations: PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin kinase; Bcl-2, Bcl2 apoptosis regulator; p-Akt, phosphorylated-Akt; p-mTOR, phosphorylated-mTOR; JAK, janus kinase; STAT, signal transducer and activator of transcription; p-STAT3, phosphorylated-signal transducer and activator of transcription 3; ARID1A-KD, ARID1A knockdown; NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; mNSCLC, metastatic NSCLC; RAS; Rat sarcoma viral oncogene homolog; RASGEF1A, RAS Guanine Nucleotide Exchange Factor 1A; MAPK, Mitogen-Activated Protein Kinase; p-MAPK, phosphorylated-MAPK; RB, retinoblastoma protein; E2F, E2F transcription factor; p-E2F2, phosphorylated-E2F transcription factor 2; p-E2F8, phosphorylated-E2F transcription factor 8; EZH2, enhancer of zeste homolog 2; PTEN, phosphatase and tensin homolog; E2F1, E2F transcription factor 1; MDM2, mouse double minute 2; P53, tumor protein P53 ErbB, erythroblastic leukemia viral oncogene homolog; VEGF; vascular endothelial growth factor; HIF-1, hypoxia-inducible factor 1; RAF1, rapidly accelerated fibrosarcoma 1; p-EGFR, phosphorylated-epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2, HER-3, human epidermal growth factor receptor 3, HER-4, human epidermal growth factor receptor 4, p-HGF, phosphorylated-hepatocyte growth factor, p-Vimentin, phosphorylated-vimentin; p-ZEB1, phosphorylated zinc finger E-box binding homeobox 1; MGT#1, mesenchymal genetic tracing vector #1; HCC, hepatocellular carcinoma; OCCC, ovarian clear cell carcinoma; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa B.

double-knockout mice. Among the *ARID1A/PTEN* double knockout mice, 60 % developed poorly differentiated ovarian carcinoma with intraperitoneal dissemination and ascites, and the other 40 % showed hyperplasia of the ovarian surface epithelium. In contrast, *ARID1A* knockout mice did not develop discernable histopathological changes, which suggests that mutation of *ARID1A* alone does not cause the development and progression of cancer but that a combination of *ARID1A* inactivation and a PI3K/AKT pathway aberration is required to initiate tumorigenesis [14,46,47].

About NSCLC, additional studies documented an increase in Akt phosphorylation induced by loss of ARID1A expression in vitro and in vivo [14,49]. Similarly, as demonstrated by Zhang et al. [49], the Akt signaling pathway was found to be significantly activated after ARID1A depletion. Akt regulates cell apoptosis and survival through the phosphorylation of the pro-apoptotic protein BAD and activation of pro-survival genes. Akt activation has also been shown to overcome cell cycle arrest at the G1 phase. In this study, Zhang et al. [49] deepened the understanding of the role of ARID1A in several apoptosis- and proliferation-related proteins and found that ARID1A depletion

Table 2
Summarizing table on available data on ARID1A-induced immunological modulation in NSCLC.

Reference	Population	Sample size (N)	ARID1A-mediated immunological modulation
Zhu et al. [75]	ARID1A-mut cancer pts (including NSCLC)	192	**↑TMB*↑PD-L1 expression*TIME modulation:**↑CD4+ T lymphocytes and CD8+ T lymphocytes
Sun et al. [22]	ARID1A-KD EGFR-mut LUAD cells	NA	**↑EGFR/PI3K/Akt/mTOR↓Autophagy↑ Rig-I-like receptor pathway activity and type I interferon production.**
Sun et al. [22]	EGFR-mut LUAD pts with low ARID1A expression	64 (TCGA) 22 (study)	**↑TMBTIME modulation:**↑ activated CD4-positive T cells and effector memory CD4-positive T cells↑ CD8+ cytotoxic T lymphocytes
Duran et al. [76]	ARID1A-mut advanced LUAD pt	1	**Sporadic MSI due to somatic MLH1 gene promoter methylation and MLH1 gene mutation***
Zhu et al. [77]	ARID1A-mut advanced NSCLC pts	238	**↑TMBTIME modulation****:**↑** macrophage M1 and T-cell follicular helper cell.↓ monocytes, activated mDCs and CD4+ memory resting T cells.↓ CCL17, CXCL17, CXCL16, CXCR2, CXCR1, CCR2, BTLA, CD244, HAVCR2, LGALS9, NT5E and TMIGD2
Alessi et al. [78]	ARID1A-mut NSCLC pts	156	**↑TMB**
Sun et al [21]	LUAD and LUSC samples	517 (LUAD) 501 (LUSC)	As ARID1A expression decreases:**↑TMB↑PD-L1 expressionTIME modulation↑** activated CD8+ T cells and activated DCs
Hung et al. [20]	ARID1A-mut NSCLC pts	184	**↑TMB in ARID1A-mutdMMR enriched in ARID1A diffuse loss**
Okamura et al. [79]	ARID1A-mut NSCLC pts	21	**↑TMB↑ MSI-high**
Jiang et al. [80]	ARID1A-mut cancers pts	266 (NSCLC)	**↑TMB***
Naito et al. [81]	BAF-Loss NSCLC pts	13	**↑TMB**
Wei et al. [82]	NSCLC pts ARID1A-mut	97	**↑TMB**

Abbreviations: ARID1A-mut, ARID1A mutated; pts, patients; NSCLC, non-small cell lung cancer; TMB, tumor mutation burden; PD-L1, programmed death-ligand 1; TIME, tumor immune microenvironment; SWI/SNF-mut, SWI/SNF-mutated; CD4+ T lymphocytes, cluster of differentiation 4 positive T lymphocytes; CD8+ T lymphocytes, cluster of differentiation 8 positive T lymphocytes; LUAD, lung adenocarcinoma; MSI, microsatellite instability; MLH1, MutL homolog 1; mDCs, myeloid Dendritic Cells; DCs, Dendritic Cells; CCL17, C-C motif chemokine ligand 17; CXCL17, C-X-C motif chemokine ligand 17; CXCL16, C-X-C motif chemokine ligand 16; CXCR2, C-X-C motif chemokine receptor 2; CXCR1, C-X-C motif chemokine receptor 1; CCR2, C-C motif chemokine receptor 2; BTLA, B and T lymphocyte attenuator; CD244, Cluster of differentiation 244; HAVCR2, Hepatitis A virus cellular receptor 2; LGALS9, Galectin-9; NT5E, 5′-nucleotidase ecto; TMIGD2, Transmembrane and immunoglobulin domain containing 2; dMMR, deficient mismatch repair; BAF, BRG1-associated factor.
*No specific data for NSCLC.
**No specific data for ARID1A-mut.
***ARID1A interacts with MMR MutS protein homolog 2 (MSH2), recruiting MSH2 to chromatin during Deoxy- riboNucleic Acid (DNA) replication, and promoting MMR. By contrast, ARID1A inactivation impairs MMR machinery leading to an increased mutation burden that correlates with MSI.
****in a subset of NSCLC ARID1A, ARID1B, or ARID2-mut for whom both RNA-seq and DNA-seq data were available.

upregulates cyclin D1 and Bcl-2 expression (Table 1). Cyclin D1 is overexpressed in lung cancers and facilitates cancer cell proliferation and cell cycle progression at the G1-S checkpoint [50,51]. Bcl-2 is an anti-apoptotic protein in several cancers, and its upregulation prevents cell death [52]. These results confirm the role of ARID1A as a regulator of the Akt signaling pathway, suggesting that ARID1A downregulation enhances cell proliferation and inhibits apoptosis in NSCLC through the modulation of cyclin D1 and Bcl-2, demonstrating that Akt is a promising target for cancer therapy.

4. Other mechanisms that may be implicated in TKI resistance, tumor proliferation, and metastasis

A recent study conducted by Sun et al. [23] confirmed the role of *ARID1A* as an essential tumor suppressor in *EGFR*-mutant NSCLC, shedding new light on the role of ARID1A loss of expression in altering multiple oncogenic pathways. The results suggest that ARID1A expression loss leads to RB1 phosphorylation, releases the inhibition of the E2F family, and initiates preparation for cell division, as well as the upregulation of cell cycle-related proteins, increasing the activity of CDKs, which accelerates cell division. Among the various mechanisms that contribute to resistance to EGFR-TKIs, the multi-omics analysis conducted in this study highlights the importance of bypass activation of the ErbB and VEGF pathways (Table 1). Finally, based on previous studies that investigated the relationship between the loss of ARID1A and JAK/STAT signaling pathway activation in several tumors [54,56], a recent review proposed that JAK/STAT (via the activation of STAT3 signaling) plays an important role in the impairment of NSCLC apoptosis [57], tumorigenesis, and resistance to EGFR-TKIs [14].

Recently, ARID1A deficiency demonstrated to induce resistance to osimertinib by hindering programmed cell death through the enhancer of zeste homolog 2/phosphatase and tensin homolog/E2F transcription factor 1 (EZH2/PTEN/E2F1) axis. This altered axis influences PD-L1 transcription through E2F1-mediated promoter activation and PD-L1 translation via the mouse double minute 2/eukaryotic translation initiation factor 5B/programmed death-ligand 1(MDM2/eIF5B/PD-L1) axis. Subsequently, ARID1A deficiency resulted in increased expression of eIF5B and Importin-β1, promoting PD-L1 nuclear-translocation. The nuclear PD-L1 (nPD-L1) interacts with Cluster of Differentiation 44 (CD44), leading to nPD-L1 complex formation, activation of the Ras guanine nucleotide exchange factor 1A (RASGEF1A) promoter, initiation of the Ras pathway, and contributing to osimertinib resistance [58].

4.1. Role of ARID1A in NSCLC metastasis

Zhang et al. [49] demonstrated that ARID1A protein expression is decreased in NSCLC tissues and is significantly correlated with lymph node metastasis and pTNM stage. They hypothesized the implications of Akt-mediated cyclin D1 and Bcl-2 regulation, although admitting the need for further investigation of the molecular mechanism. As clarified by Sun [14], ARID1A downregulation promotes lung metastasis by activating the Akt signaling pathway through Akt phosphorylation, which is one of the downstream signaling pathways of EGFR. These results were verified in cell lines with either wt-*EGFR* or mt-*EGFR*, indicating that the loss of ARID1A expression enhances oncogenic functions by directly activating the downstream signaling pathway.

Loss of ARID1A expression was recently shown to trigger various pathways related to tumor progression and metastasis, including the ErbB, VEGF, HIF-1, and RAF1 pathways [23]. In particular, using cell lines of lung adenocarcinoma, the authors showed that members of the ErbB family, including phosphorylated EGFR, ERBB2, and ERBB3, were all upregulated in *ARID1A*-knockdown cells. Along this line, phosphorylated RAF1, AKT2, and several MAPK factors were upregulated in *ARID1A*-knockdown cells. As highlighted by another study, activating these and other pathways enables cancer cells to metastasize to distant sites and adapt to new target organs [14]. In particular, this study showed that loss of *ARID1A* LOF mutations promoted tumor metastasis by the activation of the Akt signaling pathway; of note, the effect of *ARID1A* knockdown on influencing NSCLC metastasization was verified in vivo [14]. Another investigation used NGS-based liquid biopsy in a cohort of patients affected by NSCLC and identified 10 genes, including *ARID1A*, whose mutational status was positively correlated to the presence of brain metastasis [59]. The authors defined them as "deleterious genes" creating a score of brain metastasis risk (called initial brain metastasis velocity, iBMV) associated with their mutational status. In addition to *ARID1A*, the genes considered for iBMV included *BRAF*, *CDK4*, *GNAQ*, *MLH1*, *MSH6*, *PALB2*, *RAD51D*, *RB1*, and *TSC1*.

4.2. Possible role of ARID1A in epithelial to mesenchymal transition (EMT)

EMT is a reversible process used by cancer cells to modulate proliferation, migration, and stress responses [53]. As a dynamic process, it can undergo mesenchymal-epithelial transition (MET) and partial transitions between phenotypes [60]. When an early tumor stage is converted to an invasive stage, epithelial cells transform into mesenchymal stem cells by losing their intercellular adhesion and polarity, gaining migratory and invasive properties [19,61,62]. Notably, stable epithelial and mesenchymal states are less malignant than quasi-states, and the ability of carcinomas to readily cross between both states has been termed epithelial-mesenchymal plasticity (EMP) [63], which is implicated as a driving force promoting tumor growth, metastasis, and multi-drug resistance. EMP involves an elaborate network of transcription and regulatory factors that limit the development of targeted therapies against EMT [53,64]. The correlation between *ARID1A* alterations and EMT has been described as associated processes in previous studies [33], demonstrating through in vitro and in vivo experiments that *ARID1A* alterations may play a role in modulating EMT and the expression of related biomarkers [65,66].

In lung cancer, ARID1A loss induces epithelial transdifferentiation in quasi-mesenchymal cells but has a neutral effect in quasi-epithelial cells [53]. The main characteristics of EMT include a decrease in the expression of cell adhesion molecules (such as E-cadherin) and the formation of a vimentin-based cytoskeleton [67]. Loss of E-cadherin and gain of vimentin are also clinical biomarkers of poor prognosis in several types of cancer [60]. Based on evidence that the loss of ARID1A leads to the upregulation of vimentin and downregulation of cytokeratin-19 and E-cadherin [23,66], a review [33] proposed that EMT may participate in resistance to EGFR-TKIs induced by *ARID1A* alterations, aiding the transformation of the tumor cell phenotype to a mesenchymal cell type characterized by the loss of cell polarity and changes in cell morphology.

5. Immune checkpoint inhibitors and ARID1A

Cancer immunotherapy using immune checkpoint inhibitors (ICIs) has crucially implemented the treatment regimens for NSCLC over the past decade [68,69,70,71,72]. However, most patients with oncogene-addicted NSCLC, including those with EGFR mutations, do not respond adequately to ICIs, with only 20 % benefiting from immunotherapy, either due to primary or acquired resistance [73]. Efforts are underway to identify the molecular mechanisms that enhance ICI efficacy in cancer therapy, such as *ARID1A* mutations, which have been linked to immunogenicity and improved response to immune checkpoint blockade (Table 2) [74,75–83].

ICIs are cancer immunotherapies that increase anti-cancer immune responses by targeting immunologic receptors on the surface of T-lymphocytes [84] and can be divided into two main categories: antibodies targeting the programmed cell death 1(PD-1)/programmed death ligand 1(PD-L1) axis, which mainly act on the immune effector phase, and antibodies targeting cytotoxic T lymphocyte antigen 4 (CTLA-4), which act on the immune-priming phase [85,86]. The co-inhibitory receptors, PD-1/PD-L1 and CTLA-4 are expressed on the surface of T cells to

negatively regulate T cell-mediated immune responses and maintain immune tolerance; however, tumor cells exploit these inhibitory molecules to induce tumor tolerance and T cell exhaustion [86]. Accordingly, ICIs can attach to these co-inhibitory receptors, thereby reactivating the immune response against tumor cells [87]. Several studies have demonstrated a significant correlation between *ARID1A* mutations and increased PD-L1 expression in various tumors, such as melanoma and ovarian, gastric, and kidney cancers, compared to ARID1A wild-type tumors [13,85,88]. Moreover, results from a recent study indicated that patients with SWI/SNF-mutated NSCLC who received first-line chemoimmunotherapy had better survival outcomes than those who received chemotherapy alone, suggesting that immunotherapy may be more beneficial than chemotherapy for patients with SWI/SNF mutations [89]. The study further highlighted that, as modulators of the tumor immune microenvironment (TIME), specific co-occurring mutations could serve as stratification factors to guide patient selection and facilitate individualized ICI therapy in patients with advanced NSCLC with SWI/SNF mutations. Indeed, the co-occurrence of SWI/SNF alterations and *TP53* mutations was associated with higher PD-L1 expression, increased tumor mutational burden (TMB), and an active immune microenvironment due to increased cytokine expression and stronger infiltration of CD8+ T cells and M1 macrophages, showing an exceptional first-line immunotherapy efficacy. In these cases, regulatory T-cell and monocyte abundance significantly shrunk [89]. In contrast, the co-mutation of *SWI/SNF* genes and *STK11/KEAP1* was linked to a poor immunotherapy response, characterized by a high abundance of regulatory T cells and downregulation of genes involved in antigen presentation and immune stimulation, indicating an immune-suppressive microenvironment [89].

Studies have revealed the function of ARID1A mutations in impaired mismatch repair (MMR), enhancing the expression of PD-L1, increasing TMB and neoantigen load [78], and predicting good prognosis for cancer immunotherapy in vivo [13] (Table 2). In fact, as increased TMB is associated with an increased neo-antigen load, it is usually associated with greater immunogenicity and a stronger immune response [90]. *ARID1A* mutation or ARID1A expression loss contributes to the remodeling of the TIME, leading to enhanced ICI sensitivity in gastric [90] and ovarian cancers [90,91,92]. Various studies have been conducted in recent years to find new strategies to overcome the insensitivity of NSCLC to ICI treatment.

Recently, Sun et al. confirmed the implication of the ARID1 subunit in the functions mentioned above [21]. Their findings emphasized the need for further research exploring the mechanisms underlying these correlations and encouraging the ongoing use of ARID1A and ARID1B (the other subunit of ARID1) as biomarkers for prognosis and sensitivity to ICI treatment in advanced NSCLC (Table 2). Further in vitro experiments suggested that *ARID1A* knockdown (*ARID1A*-KD) activates the EGFR/PI3K/Akt/mTOR pathway and inhibits tumor cell autophagy, which attenuates the inhibition of the Rig-I-like receptor pathway and the production of type I interferon (IFN) in *EGFR*-mutant lung adenocarcinoma cells [22]. Ultimately, *ARID1A*-KD enhances the production of type I IFN, which increases immune cell infiltration, remodels the immune phenotype, and reverses responses to immunotherapy [22].

6. Future perspective and potential clinical application of ARID1A

ARID1A regulates chromatin accessibility to a variety of related molecules, including those involved in transcription, DNA replication, and DNA repair, as well as to DNA-binding proteins and cofactors. *ARID1A*-KD significantly correlates with lung cancer, histological differentiation, lymph node, distant metastasis, and TNM stage and is an independent risk factor for poor prognosis in NSCLC, aggravating tumor cell proliferation and metastasis. Recently, an association between ARID1A deficiency and ICIs therapy has been reported. ARID1A deficiency contributes to a high microsatellite instability phenotype, increases TMB, elevates PD-L1 expression, and modulates the immune microenvironment, supporting the view that ARID1A loss may serve as a predictive biomarker for ICIs [93]. Thus, although EGFR-TKIs have impaired efficacy in *EGFR*-mutant lung cancer with concomitant *ARID1A* mutations, ARID1A loss seems to be predictive of ICI sensitivity in lung cancer. These findings suggest that the tumor suppressor gene ARID1A is a potential therapeutic target [19]. In addition, Sun et al. [23] support the use of ARID1A as a novel biomarker for the response to EGFR-TKIs, as it showed robust efficiency in predicting the progression-free survival (PFS) of patients after first-generation EGFR-TKI treatment, making it valuable in risk evaluation before EGFR-TKI administration. In the same study, a series of small-molecule inhibitors were found to be effective as a potential therapeutic strategy to overcome disease progression in patients with NSCLC with ARID1A deficiency.

Interestingly, since it has been shown that ARID1A facilitated efficient processing of double-strand breaks to single-strand ends, sustaining DNA damage signaling, it has been suggested that ARID1A deficiency sensitized cancer cells to poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. This hypothesis has been verified with promising results in vitro and in vivo [94,95]. Such findings suggested a potential therapeutic strategy based on PARP inhibitors for patients with *ARID1A*-mutant tumors, including NSCLC and colorectal cancer [94–96], which further studies in this field should explored. Beyond PARP inhibitors, other potential synthetic lethal targets include EZH2, PI3K/AKT, and HDAC6 inhibitors, as well as targeting residual SWI/SNF complex activity [95]. Along this line, mutations in one SWI/SNF subunit can lead to a specific dependence on other subunits for complex activity. For example, mutations in *ARID1A* may create a vulnerability to targeting *ARID1B*, its mutually exclusive subunit, as a synthetic lethal [97].

Another crucial topic that should be considered in this area is drug resistance. Notably, with the development of emerging technologies such as single-cell sequencing, spatial transcriptomics, and organoid models, new perspectives and methodologies have been provided for the study of tumor drug resistance. Single-cell sequencing permits the investigation at the cellular level of not only the neoplastic elements but also the entire tumor microenvironment. This approach has already provided useful indications for better identifying patients affected by NSCLC who will benefit from immunotherapy, and may also be applied in the future by integrating the *ARID1A* mutational status. For example, a recent investigation showed that single-cell RNA sequencing of NSCLC tumors from patients treated with PD-L1 inhibitor reported that the co-presence of B and plasma cells in tertiary lymphoid structure could predict the patient's overall response to ICIs, independently of CD8+ T cell density and PD-1 expression [98]. Interestingly, spatial transcriptomics can be even more specific since it integrates data regarding the steric distribution of the various cell populations in the tumor microenvironment. Along this line, a recent study clarified the pivotal role of cancer-associated fibroblasts in mediating primary resistance to ICIs in a cohort of patients affected by NSCLC [99]. For a better understanding of tumor drug resistance, it is also important to acknowledge the growing role of organoid models. Indeed, they can reproduce the pathological and genomic profiles of cancer samples, maintaining driver gene mutations (including *ARID1A*). Furthermore, they also preserve the cytological features of malignant tumor cells, showing a highly correlated in vitro drug screening response with the mutation spectrum in primary tumors [100]. Integrating multi-omic analyses with patient-derived organoid models will provide novel insights into the complex field of tumor drug resistance.

Another fascinating field that should be explored in this area is *ARID1A* mutation heterogeneity in terms of intratumor and tumor-metastasis heterogeneity. The presence of intratumor heterogeneity and cancer cell subclones with different molecular profiles have already been described as a potential source for developing drug resistance. Along this line, and as already well-known, *EGFR* T790M mutation in exon 20 is the most common acquired resistance mechanism to first and

second generations of EGFR-TKIs [101]. Notably, it has also been detected on pretreatment tumor samples (at least in a subset of patients), thus indicating the existence of sub-clones with this specific mutation before the beginning of treatment and highlighting the presence of clinically relevant intratumor heterogeneity [101]. Notably, regarding *ARID1A* mutations, a recent investigation showed that metastatic lesions can acquire novel *ARID1A* alterations not present in matched primary tumors [102,103]. Such differences between primary and metastatic tumors represent another fundamental biological mechanism that future investigations regarding precision oncology in lung cancer should consider.

Although numerous drug candidates are being tested in clinical trials, no breakthroughs have been made. However, the broad molecular consequences of *ARID1A* mutations, such as metabolic reprogramming and changes in important oncogenic signaling pathways, are likely to have therapeutic implications of *ARID1A* mutations in lung cancer [19]. Furthermore, *ARID1A* mutations probably have divergent effects depending on the cell and tumor types in which they are present and on the mutational landscape in different cancer types. As a result, functional studies of ARID1A present a substantial scientific challenge [44,104]. However, its crucial roles in the biology of lung cancer suggest intensifying further research in this significant oncological area.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Michele Milella received honoraria for consulting or advisory role from AstraZeneca, MSD Oncology, Ipsen, Hippocrates, Viatris, Servier and Janssen Oncology; research funding from Roche and other relationship (participation to protocol Steering Committees and Independent Data Monitoring Committee) with Novartis and OncoSil; Aldo Scarpa received honoraria from MSD, Incyte, and Medica s.r.l. (consulting and speaker bureau); Sara Pilotto received honoraria or speakers' fees from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Merck, Takeda, Amgen, Novartis, and Roche, outside the submitted manuscript. Lorenzo Belluomini received speakers' fees from AstraZeneca, Merck Sharp & Dohme, and Roche, outside the submitted manuscript, travel fees from Takeda. Claudio Luchini received honoraria or speakers' fees from Bayer, Astellas, and MSD. The other authors did not report conflict of interest.

Acknowledgments/Funding sources

This research did not receive any specific grant from funding agencies in the public or not-profit sectors.

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