Review Article

Translational Insights into Focal Adhesion Kinase Inhibition for Non-Small-Cell Lung Cancer

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ABSTRACT

Lung cancer remains the leading cause of cancer mortality globally, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of cases. Focal adhesion kinase (FAK), a non-receptor tyrosine kinase encoded by Protein Tyrosine Kinase 2 (PTK2), integrates signals from integrins and growth-factor receptors to drive cell proliferation, survival, migration, and invasion. Aberrant FAK activation, resulting from gene amplification, overexpression, or crosstalk with receptor tyrosine kinases, contributes to tumor progression and therapeutic resistance. This review synthesizes mechanistic insights into FAK signaling and critically appraises the development of ATP-competitive FAK inhibitors, including defactinib (VS-6063), GSK2256098 (a novel oral FAK), and VS-4718. We examine their pharmacodynamic effects, safety profiles, and preliminary efficacy when combined with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and immune checkpoint blockade. Key challenges and opportunities for clinical translation are addressed, including biomarker development for patient selection, optimization of combination regimens to overcome adaptive resistance, and strategies to integrate FAK-targeted therapies within existing treatment paradigms. By aligning molecular and clinical perspectives with global healthcare realities, this review aims to inform research priorities and facilitate the integration of FAK-targeted therapies into the management of NSCLC worldwide—a graphical abstract illustrated in Figure 1.

Keywords

Metastasis; angiogenesis; proliferation; microenvironment; resistance; invasion; oncogenesis; phosphorylation; Focal adhesion kinase; Non–Non-small-cell lung cancer.

INTRODUCTION

> "*Smoking causes almost 7 of every 10 deaths from lung cancer in men and women across the world.*" [1]

Pulmonary carcinoma is a serious challenge for health professionals since it remains the leading cause of cancer deaths worldwide [2-4]. In 2022, there were approximately 2.5 million new

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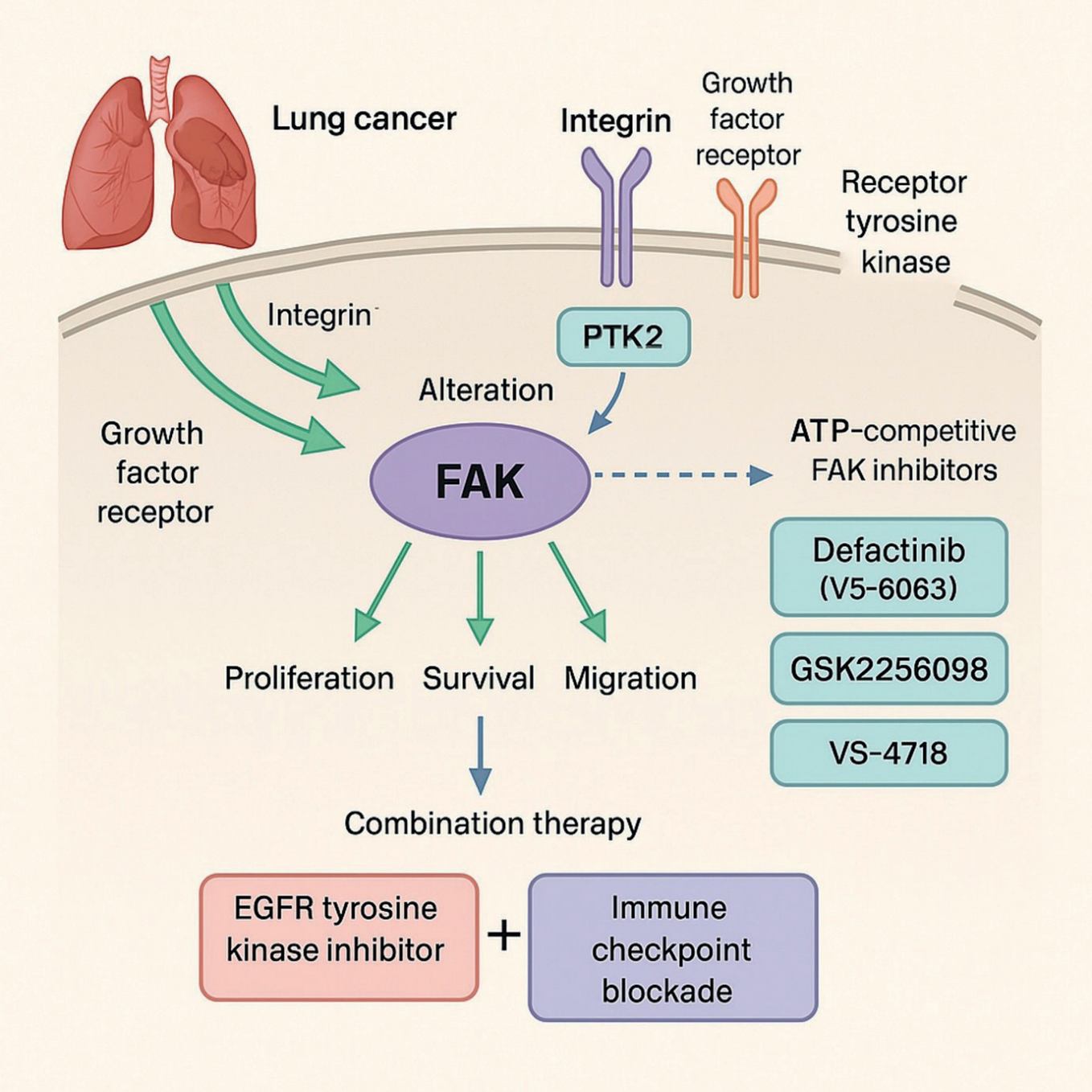

Figure 1: Graphical abstract.
Illustration Credit: Mohit Rana

cases diagnosed and 1.8 million deaths, showing how hazardous this disease was for the world. [1] Principally, there are two subclasses of respiratory system malignant tumors, small-cell lung carcinoma and non-small-cell lung carcinoma (NSCLC), in considering for 15% and 85% of all pulmonary neoplasms, respectively [5,6]. NSCLC is additionally categorized into three types: large-cell carcinoma, adenocarcinoma, and squamous-cell carcinoma [7]. While doctors and researchers have seen substantial improvements in early detection and treatment, most patients with advanced NSCLC have only a low chance of survival. It has been reported that approximately 18-19% of cases of lung malignancy have been observed over the past five years.

Furthermore, it was revealed that life expectancy can be prolonged by 20-30% through early detection and radical surgical and medical management [5-7]. The rate of mortality and morbidity of NSCLC differs because of subtypes and their predisposition for metastasis, and the subsequent development of resistance [8,9]. Conventional platinum-based chemotherapy regimens for NSCLC offer diffident survival assistants [10,11] and tend to cause multiple adverse drug reactions (ADRs), e.g., profound nausea, vomiting, and hematological ADR [12]. Currently, therapeutic intervention regarding NSCLC targeted for the epidermal growth factor receptor (EGFR), [13,14] anaplastic lymphoma kinase (ALK), [15] and ROS (reactive oxygen species) proto-oncogene 1, [16,17] receptor tyrosine kinase (ROS1) [17-19] drivers has substantially changed medical care for these patients. [20-22] Comparably, hindering programmed cell death protein 1 (PD-1) and its ligand PD-L1 with immune checkpoint inhibitors has yielded ongoing benefits in some cases of NSCLC [23,24]. However, these agents tend to lose their effective pharmacodynamic potential eventually because malignant cells gain support in their target kinase, activate other signaling pathways, or evade immune surveillance in the NSCLC-affected area [25,26].

Focal Adhesion Kinase (FAK) is gaining attention as a new therapeutic target in NSCLC pharmacological management because it plays a crucial role in integrin-based and growth factor receptor-based gesticulating trails. [27,28] The non-receptor tyrosine kinase FAK, encoded by the Protein Tyrosine Kinase 2 (PTK2) gene, primarily coordinates key cellular processes that facilitate the initiation, progression, and metastasis of malignant tumors [29,30]. After FAK phosphorylates itself at Phospho-FAK (Tyr397) and attracts Src family kinases (SFKs), it can turn on many downstream pathways such as PI3K (phosphoinositide 3-kinase)–AKT [also known as Protein Kinase B (PKB)], RAS–RAF–MEK–ERK [also called as the MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) itinerary, is an imperative waving outpouring system to intricate in cell growth, proliferation, differentiation, and survival, and Rho GTPase [Guanosine Triphosphate hydrolases (GTPases)]-controlled changes to the cytoskeleton [31,32]. All these signal cascades converge in NSCLC cells to enhance their ability to survive, grow, migrate, and invade [33]. In addition to its role in the cytoplasm, FAK is also found in the nucleus, where it interacts with regulators such as p53 and participates in programs that influence inflammation, angiogenesis, and the behavior of the immune system [34-36]. Apart from its role in tumor cells, FAK helps the nearby stroma and immune cells reorganize the matrix, form new blood vessels, and create an area that hinders the immune response. [37-39] Greater amounts and activity of FAK are associated with higher tumor grade, metastasis to lymph nodes, and poor outcomes in NSCLC cases, indicating that it could be used to both predict outcomes and as a target for treatment. [40,41] Multiple research studies have revealed that antagonizing the activity of the protein FAK makes NSCLC cells more sensitive to chemotherapy, kinase-targeted drugs, and checkpoint blockade agents, thereby justifying further studies in patients [27,28,30,42]. Key findings of this narrative review are depicted in Box 1.

Key Findings of This Narrative Review

1. Respiratory malignant tumors are classified into two subclasses: small-cell lung carcinoma and NSCLC.
2. When Conventional platinum-based chemotherapy regimens are used for NSCLC treatment, there is diffident survival assistance and multiple adverse drug reactions.
3. Malignant cells can overcome the pharmacodynamic effects of therapeutics targeting immune checkpoints in NSCLC by activating alternative signaling pathways and evading immune surveillance in the affected NSCLC area.
8. Defactinib administration alone or in combination in orthotopic pulmonary malignancy decelerated tumor expansion without considerable adverse effects.
9. FAK inhibition using combination therapy, such as pembrolizumab plus platinum-based chemotherapy, in metastatic NSCLC can modify the tumor microenvironment, reduce the presence of cancer-suppressing cells, and increase the number of immune cells attack the malignant respiratory growth.
10. Other combinations for FAK inhibition being researched and used include GSK2256098 plus EGFR-TKIs GSK2256098 plus trametinib, defactinib plus EGFR–TKIs, and defactinib together with pembrolizumab.

Key Findings of This Narrative Review	
4. FAK, a vital component of integrin and growth-factor pathways, coordinates key cellular processes that facilitate the initiation, progression, and metastasis of malignant tumors. It is now being considered as the new therapeutic target	11. Biomarkers explicitly PD-L1 and TMB have been confirmed as prognosticators of NSCLC while using FAK inhibitors.
5. High levels of FAK are associated with higher tumor grade, metastasis to lymph nodes, and poor outcomes in NSCLC cases and may be of prognostic value.	12. Antagonizing FAK in combination with radiotherapy in patients with KRAS-mutant NSCLC exhibits a beneficial effect.
6. FAK antagonizing results in increased response of NSCLC to chemotherapy, kinase-targeted drugs, and checkpoint blockade agents	13. More targeted combination therapies for FAK inhibition are now being sought, as they currently lack strong efficacy.
7. Its clinical translation remains limited by an incomplete understanding of signaling crosstalk, a lack of validated predictive biomarkers, and suboptimal combinatorial strategies.	14. Studies are underway to advance our understanding of the genetic backgrounds and mechanisms used by tumors to bypass receptor tyrosine kinase, with the aim of improving therapy for NSCLC in the future.

Box 1: Key findings of this narrative review are depicted.
Box Credit: Rahnuma Ahmad.

Problem Statement of This Narrative Review

NSCLC remains the leading cause of cancer mortality, with current targeted therapies and immunotherapies often failing due to acquired resistance, intratumoral heterogeneity, and adaptive signaling mechanisms [43]. FAK is emerging as a central node mediating NSCLC cell survival, invasion, and therapeutic failure. Yet, its clinical translation remains limited by an incomplete understanding of signaling crosstalk, a lack of validated predictive biomarkers, and suboptimal combinatorial strategies [44-46]. This narrative review addresses these gaps by synthesizing mechanistic insights into FAK signaling, evaluating the preclinical and clinical progress of ATP-competitive FAK inhibitors, and highlighting the challenges in integrating FAK-targeted therapies into the management of NSCLC.

Objectives of The Study

The great deal of biological challenges posed by NSCLC and FAK's role in driving cancer progression and resistance, this review explains how FAK inhibitors are being tested in patients with NSCLC. This narrative review begins by outlining the key role of FAK in signaling. Then it provides a comprehensive discussion of ATP-competitive FAK inhibitors, including their pharmacological effects and mechanisms of action. Next, we focused on evaluating new findings from clinical trials, discussed the selection of patients using biomarkers, and explored plans to offer drugs in combination to combat resistance. Lastly, we focus on the hurdles and future paths for incorporating FAK-targeted treatments into standard NSCLC care, aiming to enhance precision oncology for these patients. This desktop research are also review the molecular mechanisms by which FAK drives NSCLC pathogenesis while critically evaluating the efficacy, resistance mechanisms, and safety profiles of current FAK inhibitors and to identify emerging predictive biomarkers of FAK-targeted therapy response, explore rational combinatorial strategies with other treatments, and highlight the challenges and future directions for translating FAK-based interventions into clinical practice.

MATERIALS AND METHODS

This review compiles and thoroughly reviews current translational research on FAK inhibition in the context of NSCLC, with a focus on preclinical studies, clinical trials, and combination strategies involving targeted therapies and radiation.

Literature Search Strategy

A comprehensive literature search was performed using the following electronic databases: Google Scholar, PubMed, Web of Science, Scopus, and ResearchGate. The search included articles published from January 2000 to June 2025, using combinations of the following

keywords: "Metastasis", AND "angiogenesis", AND "proliferation", AND "microenvironment", AND "resistance", AND "invasion", AND "oncogenesis", AND "phosphorylation", AND "Focal adhesion kinase", AND "non-small-cell lung cancer", AND "tumor microenvironment", AND "clinical trials". Boolean operators (AND/OR) were used to refine search results.

Inclusion Criteria

- Peer-reviewed original research, preclinical research, and clinical trials.
- Research focused on FAK signaling, FAK inhibitors, or combination therapies involving FAK targeting in NSCLC.
- Articles written in English.
- Studies reporting mechanistic, therapeutic, or translational outcomes.

Exclusion criteria

- Studies unrelated to NSCLC.
- Abstract only articles, editorial, or commentaries without primary data.
- Publications written in languages other than English, and articles lacking full text.

Study Selection and Data Extraction

Titles and abstracts of retrieved articles were screened independently by two reviewers to categorize eligible studies. Full-text articles were then reviewed for final inclusion. Any dissimilarities were fixed through discussion or consultation with a third reviewer (Figure 2).

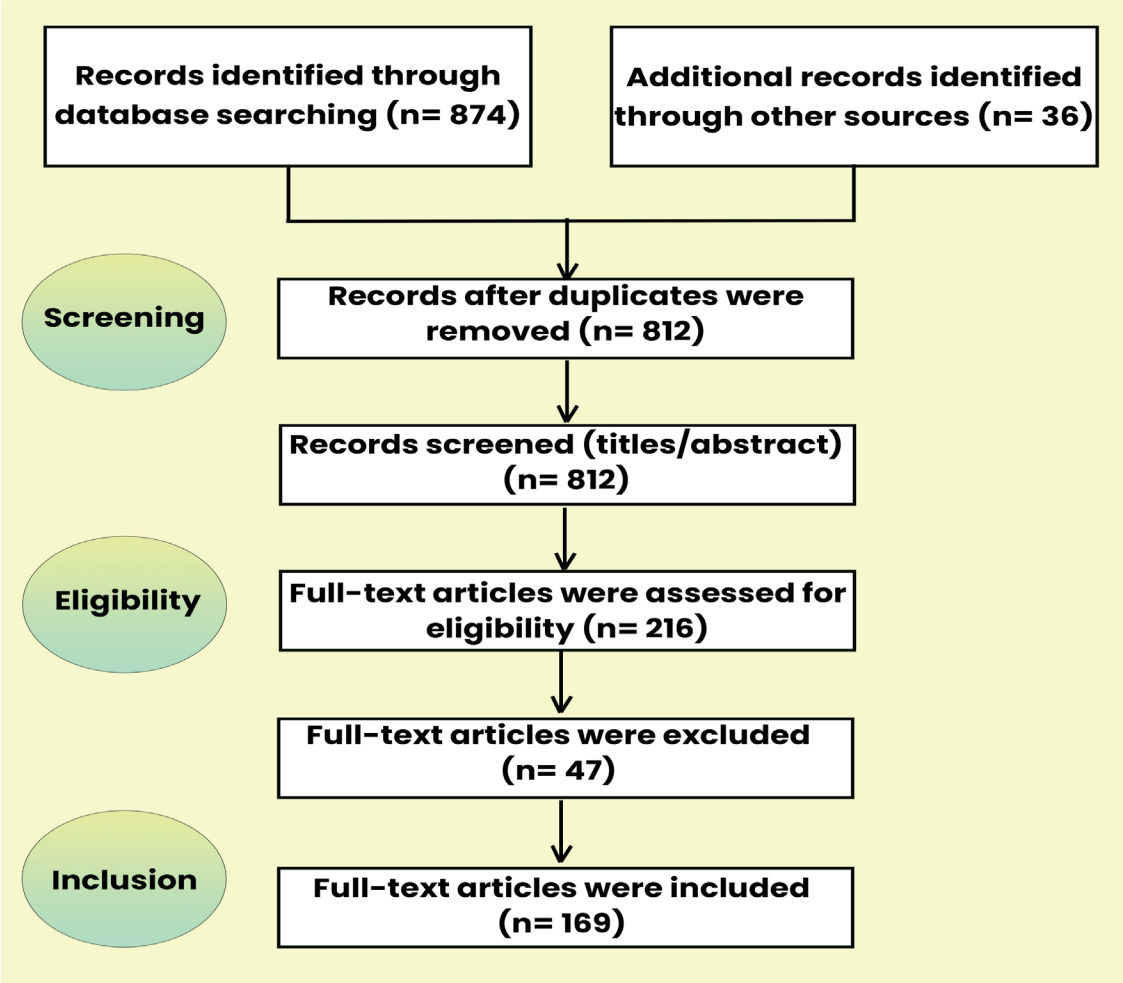

Figure 2: Chart showing the methodology of this review. **Notes:** This figure was drawn using the premium version of Adobe Photoshop.
Illustration Credit: Susmita Sinha.

Review of Literature

Biological Functions of FAK in Lung Cancer

FAK functions as a cytoplasmic non-receptor tyrosine kinase, encoded by the PTK2 gene, and is vital for integrin and growth-factor pathways [47,48]. FAK is organized into three parts: the FERM domain at the N-terminal side links to β-integrins and other receptors, the central region is the kinase domain that powers its function, and the FAT domain at the C-terminus binds paxillin and talin at the sites of focal adhesion [38,49]. Integrins bind with fibronectin or collagen within the extracellular matrix, and FAK phosphorylates Tyr397 and becomes a strong site for Src family kinases to dock. After that, the complex leads to phosphorylation of Tyr576/Tyr577 in the activation loop and Tyr861/Tyr925 in the C-terminus, fully activating FAK's kinase action [38,50,51]. Once activated, FAK uses several ways to pass signals: it associates with p85 (regulatory subunit of the PI3K enzyme) in PI3K (phosphoinositide 3-kinase) to produce PIP3 (phosphatidylinositol-3,4,5-trisphosphate) and start AKT [V-akt murine thymoma viral oncogene homolog or protein kinase B (PKB)] to support cell life; it links with Grb2 (Growth Factor Receptor-Bound Protein 2) and SOS [Sinusoidal Obstruction Syndrome (also known as Veno-occlusive Disease)] at Tyr925 (a specific phosphorylation site on the protein FAK), motivating the RAS/RAF/MEK/ERK (a cellular signaling pathway called the RAS-RAF-MEK-ERK pathway) cascade for increased cell division; and it works with adaptors like p190RhoGAP (p190 Rho GTPase-activating protein) to regulate cytoskeleton movement and cell mobility [52-54].

Studies have found that abnormal FAK function is prevalent in lung malignancies [30,44,38,55,] and this issue is especially true for NSCLC, [56,57,] often leading to larger tumors and a higher likelihood of worse clinical outcomes [58-60]. FAK activation enhances cancer by increasing the growth of malignant tumors [58-60], allowing cells to resist death by upholding cell subsistence and hindering programmed cell fatality [38], inducing an early hard-to-treat form of malignancy, [27,30,58,] improving cancer cell movement, [30,] and supporting colonization at distant sites [61,62]. In addition, FAK connections with receptor tyrosine kinases such as EGFR, MET (mesenchymal-epithelial transition pathway and the hepatocyte growth factor receptor), and ALK mean that cancer cells can evade the effects of tyrosine-kinase-targeted cancer therapy, suggesting that successful treatment of NSCLC may depend on inhibiting both FAK and tyrosine-kinase receptors simultaneously [27,63-65]. FAK kinase works outside the nucleus. FAK scaffolds mediated by its FERM (four-point-one, ezrin, radixin, moesin) and FAT (fat mass and obesity-associated gene) domains bring it into the nucleus, where it associates with regulators like p53 and GATA4 (GATA binding protein 4) and alters inflammation and angiogenesis gene programs. [34,36,66] In the area around the tumor, FAK signaling in stromal and immune cells strengthens an environment that benefits cancer by increasing angiogenesis, attracting regulatory T cells, and changing the matrix around cells [37,67,68].

Higher expression and phosphorylation of FAK in NSCLC tissues, as observed with immunohistochemistry, are associated with worse overall survival. [60,69,70] A greater amount of p-FAK is often detected in the circulating tumor cells (CTCs) of advanced patients compared to those with earlier-stage disease, suggesting a possible role as a dynamic biomarker [71,72]. As a result, scientists have created small-molecule FAK inhibitors, including defactinib, GSK2256098 (a novel oral FAK), and VS-4718 (PND-1186 or V-4718, which is a FAK inhibitor), which fit into the adenosine triphosphate (ATP) binding pocket of FAK and halt signaling [28,73]. Results from preclinical research confirm that blocking FAK in conjunction with platinum chemotherapy, EGFR-TKIs, or immune checkpoint therapy enhances treatment efficacy, providing a strong rationale for exploring these combinations in clinical studies [74-76]. The combined evidence from its molecular roles, patterns of dysregulation, and early clinical work for FAK supports the ongoing development of its use in lung cancer [65,77,78]. It highlights the need for further studies to refine suppression therapies and overcome treatment resistance.

Development and Clinical Evaluation of FAK Inhibitors

Researchers have now found that changes in FAK activity encourage lung cancer development and make it harder to treat. As a result, several drugs have already been developed to block the ATP-binding pocket of the FAK kinase [28,79,80]. Initially, scientists concentrated on developing thienopyridine derivatives for therapeutic intervention in NSCLC, leading to defactinib (VS-6063), one of the first drugs to undergo clinical testing [81,82]. Experiments conducted before clinical trials found that defactinib inhibited Tyr397 (tyrosine 397) phosphorylation in cancer cells, suppressed related PI3K (phosphoinositide 3-kinase)/AKT and RAS (rat sarcoma)/

MAPK (mitogen-activated protein kinase) pathways, and decreased tumor cell proliferation and movement [58,82]. Defactinib administration alone or in combination in orthotopic pulmonary malignancy decelerated tumor expansion without considerable adverse effects, explaining why studies were performed in patients with advanced solid tumors [37,81,83]. While the overall actions of each agent were limited, the highest response recorded was stable disease for roughly 34.5% of the participants, with a 5-year survival rate [84,85].

There were no substantial adverse effects found in the use of defactinib (VS-6063 or PF-04554878), which reached a maximum dose of 400 mg twice daily, in people with several kinds of solid cancer, e.g., NSCLC, experiencing more usual adverse effects like low-intensity tiredness, "nausea (37%), fatigue (33%), vomiting (28%), diarrhea (22%) and headache (22%)"[86] and a transitory rise in hepatic function biomarkers [83,86,87]. Multiple studies identified the recommended Phase II dose, leading to the investigation of combination treatments [88-90]. The orally accessible FAK inhibitor GSK2256098 endured a comparable elaboration course to target-based pharmacological interventions [91,92]. Combining GSK2256098 and EGFR-TKIs (epidermal growth factor receptor tyrosine kinase inhibitors) effectively killed cells in EGFR-mutant NSCLC cell lines, also overcoming the development of resistance to EGFR-TKIs [93,94]. This result led to a Phase II study of GSK2256098 in combination with trametinib for patients with Kirsten rat sarcoma (KRAS)-mutant NSCLC, which revealed limited clinical benefit. [95,96] The combination achieved partial responses in 15% of those who completed the research and disease control in around half. [96]. Signs such as rash and diarrhea were controlled when the dose was adjusted, suggesting that further studies should be conducted. [96].

Building on earlier findings, various studies are testing defactinib alongside other relevant drugs for treating lung cancer [81,97]. Among patients with EGFR-mutant NSCLC who had stopped responding to EGFR-TKIs in first-line treatment, using gefitinib and erlotinib in combination led to a 43.8% objective response rate (ORR) [98]. The "median progression-free survival (PFS) were 8.9, 11.8, and 10.5 months for the EGFR mutation group, EGFR wild type, and the unknown EGFR group (p=0.013 and p=0.042), respectively. [99] Additionally, this study also revealed [99] that "there was no significant difference in overall survival (OS) among the three groups (34.6 months for EGFR mutant group vs. 31.9 months for the EGFR wild type vs. 22.6 months for EGFR unknown group; p=0.792 and p=0.284)" [100-102]. Another study exploring the combination of pembrolizumab and platinum-based chemotherapy in metastatic NSCLC, as previous laboratory experiments have shown that FAK inhibition can modify the tumor microenvironment, reduce the presence of cancer-suppressing cells, and increase the number of attacking immune cells [103].

The clinical use of FAK inhibitors in pulmonary malignancy requires tackling multiple issues. Several biomarkers have been confirmed as prognosticators of immunotherapy in NSCLC; nevertheless, only two have exhibited authenticity and clinical pertinence [28], explicitly "programmed death-ligand 1 (PD-L1) and tumor mutational burden (TMB)" [44]. Furthermore, higher p-FAK levels tend to indicate a poor clinical outcome of NSCLC; [45] their ability to predict treatment with FAK inhibitors remains unclear when given alone. [28,45,104] Biomarkers transported by EVs (extracellular vesicles), e.g., comprising exosomes, transmit a variety of consignments of proteins, nucleic acids, and other molecules, including FAK and cytokine-related markers, which are still being investigated; however, further research is required to develop a consistent method [105,106]. Likewise, the optimal use of existing targeted and immune therapies must be determined to ensure maximum therapeutic benefit in the management of NSCLC. [20,107] Multiple studies have reported that targeted test models in the preclinical phase demonstrate that blocking both FAK and EGFR or checkpoint pathways is an effective therapeutic option; however, further testing is necessary due to shared adverse effects and the risk of resistance [38,65,108-110]. Scientists, medical doctors, and pharmacologists should continue their research endeavors to offer simple tests, such as point-of-care immunoassays, and establish networks for central pathology checking to integrate into healthcare systems with limited diagnostic and observational capabilities.

All in all, testing FAK inhibitors in humans has proven both the potential and the difficulties of targeting adhesion kinase signals in lung cancer [28,51]. Defactinib and GSK2256098 showed no major safety concerns and some promise, predominantly when combined with inhibitors of the EGFR and immune checkpoints [51]. New scientific discoveries can benefit people with the disease, with these strategies (Table 1).

Table 1: FAK inhibitors with their mode of action.

FAK inhibitor	Model	Findings
CT-707	H3122CR and H2228CR NSCLC cell lines	By targeting FAK, it activates the PDPK1-AKT1 pathway.
Timosaponin AIII (TAIII)	A549 cells	Inhibits Src/FAK, ERK1/2, and β-catenin signaling pathways leading to apoptosis induction and cell cycle arrest.
CDCA	A549 cells	Blocking the integrin α5β1 signaling pathway involved in phosphorylation of FAK and production of integrin 1 and 5; upregulated the expression of the tumor suppressor gene p53 that regulates the integrin α5β1/FAK pathway.
Defactinib- PROTAC	A427 cells	Reduced FAK protein levels in KRAS mutant NSCLC A427 cells lead to inhibition of tumor growth.
PROTAC B5	A549 cells	Potent FAK degradation activity, significant antiproliferative effects, and the ability to inhibit cell migration and invasion.
MZ-5-156	A549 cells	Antagonize FAK activity and MMP-9 and MMP-2 expression; suppression of angiogenesis and invasion-associated factors.
Rubus idaeus L. extracts	A549 cells	Up-regulate α-catenin and E-cadherin; down-regulate vimentin, snail-1, fibronectin, and N-cadherin.
Ephemeranthol A	A549 cells	Inhibits the activation of Akt and FAK, reducing the levels of Slug, vimentin, and N-cadherin, which leads to tumor growth inhibition and a decrease in cell invasion and migration.
Deguelin	A549 cells	Inhibit CtsZ activation via FAK/Src/Paxillin signaling, resulting in inhibition of tumor cell movement and invasion.
Xipsxanthone H	Zebrafish models	ROS production and cell cycle arrest, achieved by suppressing FAK and STAT3, result in a reduction in tumor growth, angiogenesis, and metastasis.
XAP	A549 cells	Inhibit the release of CCL5, the CCR5 ligand, and cause reductions in Rho C expression and FAK phosphorylation, resulting in inhibition of tumor cell movement and invasion.
Batatasin III	A549 cells	Decreases the level of phosphorylated p-FAK (Try397), p-AKT, and p-CDC42, resulting in effective suppression of cancer cell growth and migration.
Phoyunnanin E	A549 cells	A reduction in the phosphorylated forms of FAK and AKT, as well as decreased levels of integrin αv and integrin β3, leads to a decrease in metastasis.
β-elemene	H1299 and A549 cells	Inhibiting FAK and Src proteins resulted in reduced motility, as well as decreased invasion and migration capabilities.
APG-2449	A549 cells	Inhibiting the phosphorylation of FAK, ROS1, and ALK results in a reduction in metastasis.

Table Credit: Gaurav Gupta.

Clinical Relevance of Focal Adhesion Kinase in Non–small–cell Lung Cancer

NSCLC development and progression are primarily controlled by focal adhesion kinase (FAK); FAK antagonist also affects how NSCLC responds to treatment [111,112]. Multiple earlier studies have shown that FAK is highly expressed in NSCLC tumors and is strongly phosphorylated at Y397 (a specific tyrosine (Y) residue at position 397 on the FAK protein), which activates pathways that support cell growth, movement, and survival [28,113,114]. Using immunostaining, the research team observed that pY397 (phosphorylated tyrosine 397) FAK is more abundant in primary lung cancer tumors and their metastases than in nearby healthy lung tissue. [113,115] Even with the substantial increase in pY397 FAK in tumor cells, its role in prognosis cannot be easily decided. [45,113] Wang and colleagues 2016 carried out detailed comparisons between pY397 FAK intensity and significant features of NSCLC patients, including tumor size, histologic subtype, degree of differentiation, lymph node metastasis, and survival [113]. Interestingly, analyzing patient groups without specific traits did not reveal a link between high pY397 FAK expression and either

disease aggressiveness or patient outcome. [45,104,113,116-118] This may be caused by how FAK is regulated, as well as the plethora of other genes and environmental factors that enable malignant cells to execute their function in an explicit modus operandi. [119,120]

It is well known that FAK substantially influences the growth, progression, and metastasis of NSCLC tumors and is equivocally reliant on patients' genetic makeup; commonly mutated genes include, e.g., EGFR, *KRAS*, and ALK [121,122] (Figure 3). Multiple studies have reported that antagonizing the FAK protein or RHOA ensures cell death in cases of selectively oncogenic KRAS and INK4A/ARF (inhibitor of cyclin-dependent kinase 4a/alternative reading frame)- mutated or mutated-deficient NSCLC [57,114,123]. Soon after, applying a pharmacologic antagonist of FAK promotes irreparable DNA injury [124], halts the cell cycle [125], and enhances the apoptosis process [126], establishing a synthetic-lethal association between FAK and KRAS's oncogenic action. [127,128] Significantly, NSCLC cells with usual wild-type KRAS could function without FAK, while mutant *KRAS* cells could not, suggesting that FAK is only needed when KRAS (Kirsten rat sarcoma viral oncogene homolog) is mutant [124,129].

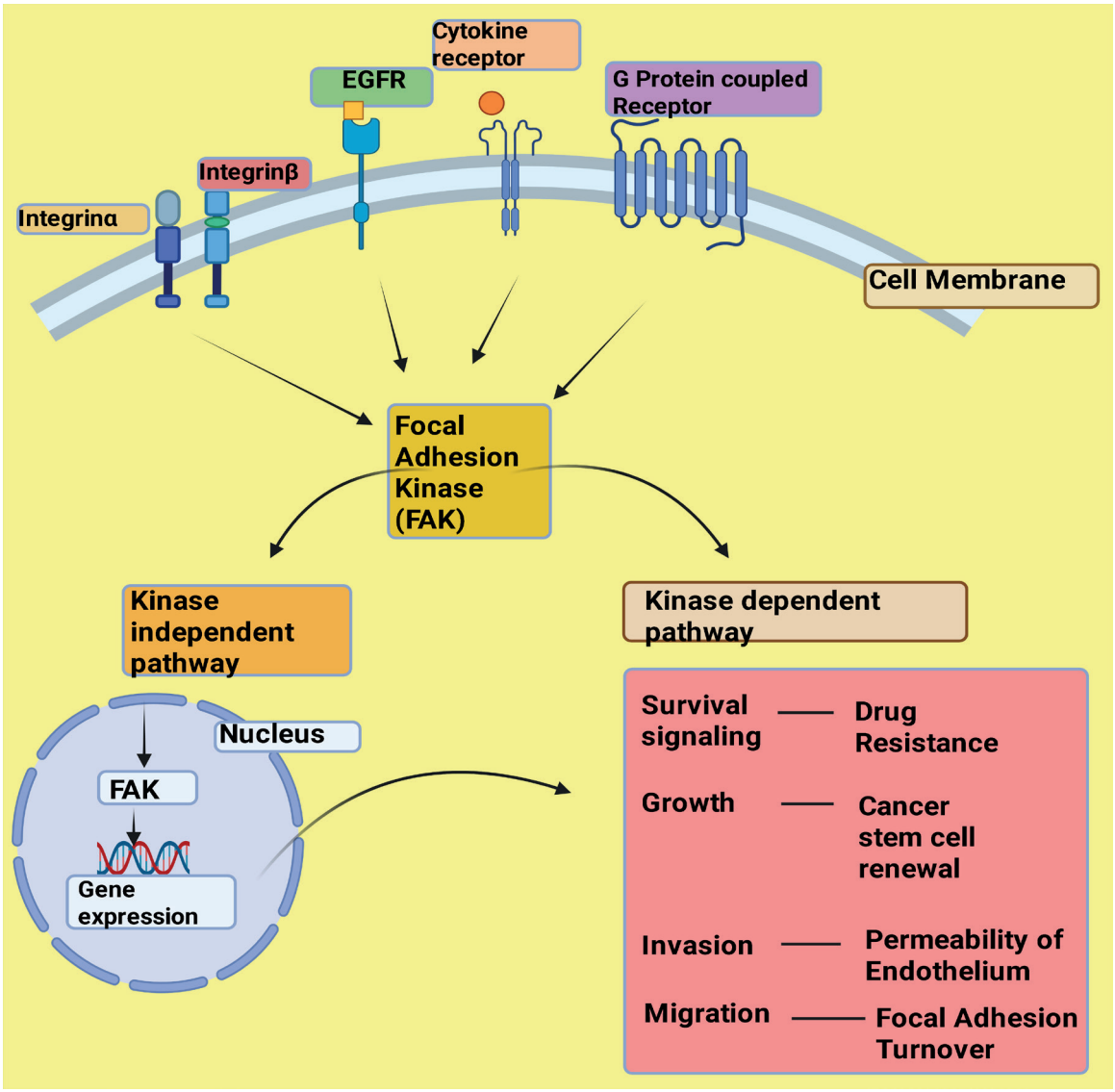

Figure 3: Illustrates the role of Focal Adhesion Kinase in influencing growth, progression, and metastasis of cancer. EGFR: Epidermal Growth Factor Receptor. This figure was created using the premium version of BioRender [130] (https://biorender.com/, accessed July 22nd, 2025), with the license number BY28JGBG7B. **Image Credit:** Rahnuma Ahmad

Multiple studies have observed the beneficial effects of antagonizing FAK in combination with radiotherapy on KRAS-mutant NSCLC in patients. [131,132] FAK antagonist was shown to considerably enhance the cytotoxic pharmacodynamics of radiotherapy by inhibiting its ability to repair DNA double-strand breaks. [133-135] Combining treatments in live animals effectively blocked tumor growth, caused more tumor cells to die, and prolonged the survival times of the animals more than using each therapy alone. [136,137] Overall, these results suggest that FAK inhibitors can act strongly as radiosensitizers in cancers that are genetically or inherently less capable of repairing damage [29,38,51] (Figure 4).

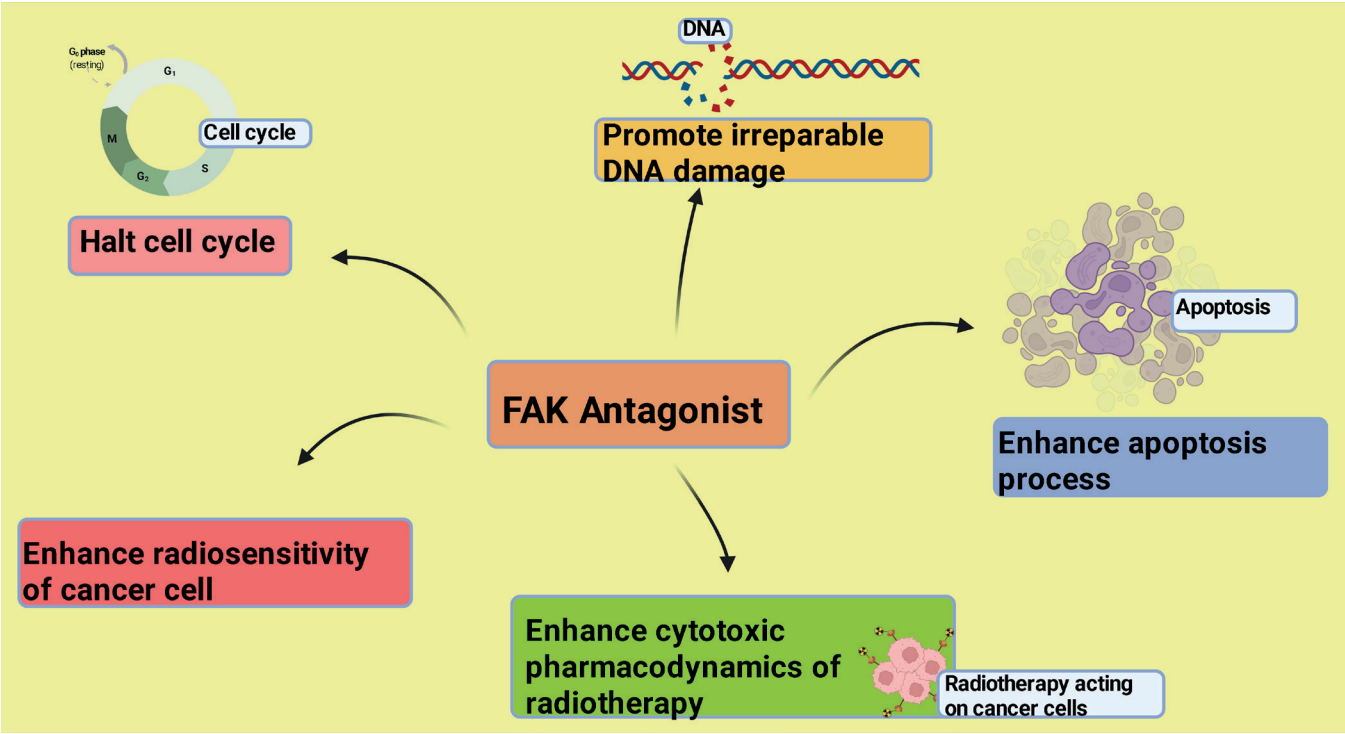

Figure 4: Illustrates the role of Focal Adhesion Kinase Antagonist in promoting cancer cell death. FAK: Focal Adhesion Kinase. This figure was created using the premium version of BioRender [130] (https://biorender.com/, accessed July 22, 2025), with the license number *BD28JGGF32*.
Image Credit: Rahnuma Ahmad

Experiments in living animals have proven that blocking FAK leads to a decrease in tumor size. [30] Administering FAK inhibitors to lung carcinoma with KRAS mutation and loss of INK4A/ARF showed that they stopped tumor growth, improved survival rate, and had only mild adverse effects [81,138]. The positive results in the lab suggest that precision medicine may utilize FAK inhibitors for patients whose cancer cells rely on FAK for survival. [29,30] In essence, research indicates that FAK plays a crucial role in driving the progression of NSCLC and may be a valuable target for specific treatment approaches. [139,140] Although pY397 FAK overexpression is frequent in NSCLC, its clinical significance becomes apparent with specific oncogenic changes, particularly alterations in KRAS and INK4A/ARF. [113,124] The synergy between blocking FAK and KRAS, along with the benefits seen with radiotherapy, makes testing in patients very promising [141,142]. In the future, scientists, pharmacologists, and oncologists should focus separately on each NSCLC patient based on the mutated protein regarding FAK inhibitors alone or in combination with other drugs, thereby helping people with NSCLC cases [143].

Global Clinical Applications and Case Studies

In the past decade, researchers in North America, Europe, and the Asia–Pacific region have investigated FAK inhibition for NSCLC, focusing on three inhibitors: PF-562-271 (a small molecule inhibitor of FAK and Pyk2, a tyrosine kinase), PF-04554878

(defactinib), [87] and GSK2256098 (a selective FAK kinase inhibitor) [87,144,145]. PF-562-271 was first tested in advanced solid tumors, such as NSCLC, at multiple study centers in the United States and Canada. [91] With the dosages tested, these trials reported that people had only grade 1–2 fatigue, nausea, and transient increases in their transaminase levels, which happen naturally. [87,144-146] Even so, the studies found that the drug worked best against lung cancer only when the tumors were not growing too rapidly, with approximately 25% of NSCLC patients seeing their tumors remain stable [147]. Based on the initial data, the recommended phase 2 dose (RP2D) for defactinib was determined in a Phase I European trial, which included a wide range of patients with previously treated NSCLC and those with other solid tumors. [97] When administered at the RP2D, defactinib was tolerated well and stabilized the disease in approximately 20-30% of NSCLC patients. [148] Although pharmacokinetics demonstrated dose-proportional exposure, only a few patients benefited from the treatment [92].

Meanwhile, GSK2256098 was being investigated in additional early-phase studies in Europe and North America, involving diverse solid tumors and NSCLC groups defined by their biology. [96,149] KRAS-mutated NSCLC patients who received GSK2256098 and trametinib experienced a response rate of 15-34% [96,150]. Thereby, GSK2256098 and trametinib pharmacodynamics were found effective when given together, with minimal ADRs, e.g., decreased appetite, nausea, diarrhea, fatigue, rash, pruritus; nonetheless, none were grade 4 ADRs, and it was not active among all highly progressive solid carcinomas. [92,96,149]. Researchers found that, despite inhibiting FAK kinase, EGFR, and MET receptor tyrosine kinases, bypass loops form that allow PI3K and AKT, or RAS and ERK, signaling to occur, thereby reducing the treatment's effectiveness [(92, 150-152)]. As a result of these findings, targeting other known cell signaling pathways in conjunction has become a common approach. [153] Clinical studies are now investigating the combination of defactinib plus EGFR-TKIs for patients with EGFR-mutant NSCLC [94,153,154], as well as defactinib together with pembrolizumab for advanced cancer, to enhance the immune response and overcome resistance.[155-157]

Moving forward, classifying patients based on their receptor tyrosine kinases (RTKs) expression and related genetic alterations will likely impact treatment outcomes. [158,159] Laboratory research indicates that overactivity of MET or EGFR often leads to resistance to FAK inhibitors, as long as these receptors are not addressed simultaneously [160-163]. Additionally, STK11 (serine/threonine kinase 11) and KEAP1 (Kelch-like ECH-associated protein 1) mutations, which are often detected in pulmonary and other malignant tumors, increase the possibility of developing distinctive vulnerabilities that minimize therapeutic selection options through suppressor genes. [164-166] Experiments are underway to develop more effective and selective FAK inhibitors, and clinical trials using basket and umbrella approaches are being conducted to pair the right treatments with the correct molecular subtypes [28, 167-169]. In addition, clinical trials of FAK inhibitors and NSCLC are underway, aiming to determine if these strategies remain effective in individuals from diverse backgrounds [80].

While globally studied FAK inhibitors are considered safe for treating small cell lung cancer (SCLC), they lack strong efficacy. Advances in understanding how RTK bypass occurs, along with insights into the genetic background, have inspired the development of combination treatments and biomarker research, leading to a more targeted use of FAK inhibition in oncology. This integration involves using serial biopsies to identify blood markers and testing pharmacodynamic outcomes, aiming to optimize the dose, reduce drug resistance, and maximize the potential of FAK therapies in NSCLC.

Limitations of the Narrative Review

The available literature on FAK in NSCLC is heavily weighted toward preclinical models, with relatively few clinical trials exploring the efficacy of inhibitors, which limits the ability to generalize findings to patient populations. Existing studies vary widely in their experimental designs, and differences in cell lines, animal models, and dosing regimens introduce heterogeneity that complicates the synthesis of results. Biomarker data remain sparse and often rely on small cohort analyses, which hinders the validation of predictive signatures across diverse patient groups. Moreover, many reports focus on single-arm or early-phase trials without long-term follow-up, making it challenging to assess sustained responses or resistance patterns over time. The review's narrative scope also encounters gaps where emerging pathways intersecting with FAK are incompletely characterized, resulting in potential oversight of relevant crosstalk mechanisms. Additionally, variability in how DOIs, journal

formatting, and citation conventions are reported across sources can introduce inconsistencies when collating reference data. Finally, rapidly evolving fields such as immuno-oncology may render some conclusions outdated shortly after publication, emphasizing the provisional nature of this synthesis.

Recommendations for Future Research

Future investigations should prioritize large-scale clinical trials to validate the safety and efficacy of novel FAK inhibitors in diverse NSCLC cohorts, integrating standardized biomarker assessments to predict response and resistance to treatment. Detailed mechanistic studies using patient-derived xenografts and three-dimensional organoid models are needed to elucidate FAK's interactions with immune pathways and metastatic niches. Research should explore rational combinatorial regimens that co-target compensatory signaling axes, such as the PI3K/AKT pathway or immune checkpoints, with comprehensive longitudinal monitoring to assess the dynamics of resistance. Additionally, the incorporation of multi-omics profiling and clinical validation pipelines will facilitate the identification of predictive signatures, enable personalized FAK-targeted therapies, and optimize the translational potential.

CONCLUSION

In NSCLC, FAK is positioned at a critical point in signaling networks that involve integrins, receptor tyrosine kinases, and the extracellular matrix, regulating cell survival, movement, and the environment formed by tumor cells. Already, early results show that inhibitors of FAK, including defactinib and GSK2256098, are safe to use in combination with EGFR drugs and MD-targeted therapies. However, the limited results indicated that more precise patient selection and combination of treatments are necessary. Many avenues need urgent attention in the future. Projects must initially be set up to group patients based on whether their FAK signaling is active, the presence of KRAS, INK4A/ARF, STK11, and KEAP1 oncogenic changes, and their varying expression of RTKs. These three methods must be fully validated to support the prediction of response and monitoring of pharmacological effects.

Next, combining strategies can be optimized more effectively using mechanistic knowledge of resistance. Blocking FAK and RTKs or combining FAK inhibitors with therapies that induce DNA damage appears promising for enhancing the management of tumors. Furthermore, research is identifying new roles of FAK in the immune system, including its effect on the polarization of macrophages and the number of T-cells, which makes combining FAK inhibitors with PD-1/PD-L1 inhibitors more promising. Thirdly, innovative frameworks such as umbrella and adaptive platform trials speed up testing numerous FAK-based regimens in groups defined by their molecular features. These designs require serial biopsies and instant biomarker results, enabling early decisions on whether to proceed with the trial or adjust the dose.

Working together worldwide through academic consortia, partnerships with industry, and regulators is necessary for equal access to FAK-targeted treatments. The results of pharmacoeconomic analyses can guide the strategy for reimbursement, mainly in areas with limited resources. As a result, when the right molecules, complementary treatments, and fast clinical studies are combined, patients with NSCLC may have better hope due to FAK inhibition.

Consent for Publication

The author has reviewed and approved the final version and agrees to be accountable for all aspects of the work, including any accuracy or integrity issues.

Disclosure

Mainul Haque works as an editorial team member of the Bangladesh Journal of Medical Science, Bangladesh. The remaining authors declare that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to the subject matter or materials presented in this review paper.

Data Availability

Information for this review paper is taken from freely available sources.

Authorship Contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, or interpretation of data, or all these areas. They also participated in the drafting, revision, and critical review of the paper, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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