Review Article

New driver alterations in non-small cell lung cancer: a narrative review

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Objective: This review aims to provide an up-to-date snapshot on the state of development of novel biomarker-driven treatments in non-small cell lung cancer (NSCLC).

Background: The introduction of immune checkpoint inhibitors and target therapies has revolutionized the natural history of many NSCLCs, allowing for lasting and profound responses. In particular, mutations in the epidermal growth factor receptor (EGFR), rearrangements of the anaplastic lymphoma kinase (ALK), or oncogene c-Ros 1 (ROS1) have marked a paradigm shift in the treatment of NSCLC. Furthermore, new inhibitors for B-Raf proto-oncogene (BRAF), rearranged during transfection (RET), mesenchymal-to-epithelial transition factor (MET), or neurotrophic tyrosine kinase (NTRK) 1–3 have revealed fascinating data, obtaining accelerated approvals from the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Today, the extensive use of next-generation sequencing (NGS) techniques has shown a broad molecular heterogeneity of NSCLC. Many of the mutations identified are considered potential therapeutic targets, and numerous studies are currently evaluating the efficacy of selective inhibitors.

Methods: We carried out an extensive review of the literature on PubMed, Web of Science, and Scopus databases and the congress abstracts presented at the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC) in the last 5 years. Our analysis considered works regarding new inhibitors for alterations of Kirsten rat sarcoma viral oncogene homolog (KRAS), PIK3CA, neuregulin-1 (NRG-1), human epidermal growth factor receptor 2 (HER2), fibroblast growth factor receptor (FGFR), genes that have recently become no longer undruggable.

Conclusions: Precision oncology is revolutionizing the natural history of NSCLC. Several alterations have been identified as possible treatment targets, and numerous inhibitors show promising results in ongoing clinical trials.

Keywords: Driver mutations; precision oncology; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the leading cause of cancer deaths worldwide. Histologically, lung cancer is divided into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximately 80–85% of cases are diagnosed as NSCLC, and about 70% of patients have locally advanced or metastatic disease at the time of diagnosis (1). The overall 5-year survival rate is only 14–17% (2), mainly due to poor detection of lung cancer in its early stages and ineffective treatment for advanced settings. However, in recent years, the introduction of immune checkpoint inhibitors (ICIs) and target therapies has revolutionized the natural history of many NSCLC, allowing for lasting and profound responses. In particular, mutations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and oncogene c-Ros 1 (ROS1) rearrangements marked a paradigm shift in the treatment of this disease. More recently, the possibility of extensive molecular profiling has revealed the extensive molecular heterogeneity of NSCLC, stimulating a new phase in drug development. New selective inhibitors for mutations affecting B-Raf proto-oncogene (BRAF), rearranged during transfection (RET), mesenchymal-to-epithelial transition factor (MET) and neurotrophic tyrosine kinase (NTRK) 1–3 genes have shown their effectiveness, obtaining accelerated approvals from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in a few years. Many other identified mutations are now candidates as potential therapeutic targets, and numerous studies are currently evaluating the efficacy of novel selective inhibitors. We, therefore, conducted a systematic review of clinical trials investigating new possible targets in NSCLC to provide an updated snapshot of current drug development. PubMed, Web of Science, and Scopus databases were explored to identify works published between January 2016 and June 2021. The following main search terms were used in our search strategy: (non-small-cell-lung-cancer) OR (lung cancer) AND (basket protocol) OR (umbrella protocol) OR (biomarker-driven) OR (precision-medicine) OR (precision-oncology) OR (molecular profiling) OR (genomic profiling) NOT (retrospective). Furthermore, we also reviewed relevant abstracts presented in major conferences, including the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) congress, and World Conference on Lung Cancer (WCLC). We present the following article using a Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-19/rc).

Kirsten rat sarcoma viral oncogene homolog (*KRAS*)

Histological and molecular characteristics

KRAS mutation is one of the most prevalent in NSCLC (3). It is more widely represented in adenocarcinoma, with a prevalence of 20–40% in Caucasian patients and 2–10% in Asian patients, in contrast to the opposite frequency trend of EGFR-mutations in the two populations (4). *KRAS*-mutant lung cancers are marked by defined clinicopathological features; they are typically associated with invasive mucinous adenocarcinoma (IMA), more commonly with a pure mucinous pattern than mixed mucinous/non-mucinous pattern. They also occur in lung adenocarcinoma (LUAC) with a solid pattern. Additional somatic mutations in other genes are frequently detected in KRAS mutated LUAC. RNA-sequencing studies identified three subgroups according to the dominant co-occurring mutated gene and the biological and immune properties that characterize them (5). Inactivating mutations in the serine/threonine kinase 11 (*STK11*)/liver kinase B1 (*LKB1*) gene differentiate the STK11/LKB1 subgroup (KL subgroup), which shows functional inactivation of the LKB1-AMP activated protein kinase (AMPK) axis and adaptation to oxidative, proteotoxic, and energetic stress. Kelch-like ECH-associated protein 1 (*KEAP1*) mutations were also enriched in this cluster. The KL group shows a low T cell infiltrate and a reduced expression of the programmed death-1 ligand (PD-L1), indicating a relative lack of immune system engagement.

On the contrary, the TP53 co-mutation subgroup KP is characterized by a denser $CD8^+$ T cell infiltrate and higher expression of PD-L1 with consequent enrichment in the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inflammation pathway and the immune tolerance/escape gene sets. Both groups are more frequent in smokers, where *KRAS*-mutant tumors are genomically more complex and present a higher mutational burden than tumors from never smokers (6). The third group KC carries a bi-allelic loss of cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*), with no immunohistochemical staining for the thyroid transcription factor-1 (TTF-1), mostly mucinous histology and activation of gastrointestinal differentiation programs (5). Similarly, Jurmeister *et al.* have shown that LUAC with intestinal morphological and immunohistochemical features have a distinct molecular

Table 1 Available clinical trials of *KRAS*^{G12C} inhibitors in NSCLC

Drug	Phase	No. of patients	Setting	Results (if available)
Sotorasib (12)	I	59	Metastatic NSCLC; pretreated patients	88.1% DCR; 32.2% PR or CR; mPFS 6.3 months
Sotorasib (13)	II	126	Metastatic NSCLC; pretreated patients (at least two treatment)	37% ORR; 81% DCR; DoR 11.1 months; mPFS 6.8 months; mOS 12.5 months
Sotorasib *vs.* docetaxel (14)	III	Enrolling	Metastatic NSCLC; second line of treatment	N/A (ongoing)
MRTX849 (adagrasib) (15)	I/II	79	Advanced/metastatic NSCLC; pretreated patients with chemotherapy and anti-PD-1/ PD-L1	43% ORR; 96% DCR
MRTX849 (adagrasib) + pembrolizumab (16)	II	Enrolling	Unresectable or metastatic NSCLC; first line	N/A (ongoing)

CR, complete response; DCR, disease control rate; DoR, duration of response; mOS, median OS; mPFS, median PFS; N/A, not available; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

signature (7). IMA, pulmonary enteric adenocarcinomas (PEAD), and pulmonary colloid adenocarcinomas (CAD) were analyzed in their report. *KRAS* mutation was found as the most frequent genetic alteration in IMA, followed by CD74-NRG-1 translocations. PEAD seems to occur more frequently in heavy smokers showing the highest tumor mutational burden. *TP53* and adenomatous polyposis coli (*APC*) mutations were more common in PEAD than in IMA or CAD, whereas MYC amplifications frequently occur in CAD. The majority of mutations occur in codons 12 and 13. The most common mutation is the *KRAS*^{G12C} (8–13%), followed by *KRAS*^{G12V} (7%) and *KRAS*^{G12D} (8). The *KRAS*^{G12C} mutation is commonly found in smokers; in contrast, *KRAS*^{G12D} is more frequent in non-smokers.

Drugs development and clinical trials

Many studies tried to target *KRAS* mutations or their downstream pathways in recent years, with disappointing results. Many of them evaluated genes involved in the KRAS pathway, including *MEK*, *MET*, *epiregulin*, *WT1*, *GATA2*, or *NF-kb* as possible targets, but none of these achieved satisfactory results (9,10). In the context of *KRAS*-mutated NSCLC, the attention is currently placed on the *KRAS*^{G12C} mutation (11). A complete view of trials investigating *KRAS*^{G12C} inhibitors is available in *Table 1*. In particular, Sotorasib and MRTX849 have shown early promising results regarding response rate (RR) and disease control rate (DCR) (12,17). *KRAS*^{G12C} can actively circulate between GDP and GTP forms, maintaining interaction with its downstream effectors. The mutated cysteine locates next to a pocket (P2) of the switch II region. The P2 pocket is present only in the inactive GDP-bound conformation of KRAS. Sotorasib (AMG510) is a small molecule that irreversibly targets *KRAS*^{G12C}, locking KRAS in its idle GDP-bound state. By targeting the mutated cysteine residue, this mechanism allows to specifically inhibit the protein by blocking it in its inactive conformation. The results of the phase I study, involving patients with pretreated *KRAS* mutated solid tumors, were presented for the first time at the International Association for the Study of Lung Cancer (IASLC)'s World Conference on Lung Cancer (WCLC) in Barcellona 2019; the results of the phase I study were published in 2020 (12). In the lung group, 32% of patients had a disease response, and 88% had a disease control with a progression-free survival (PFS) of 6.3 months. Phase II data were recently submitted to the 2021 IASLC World Conference; 126 patients with *KRAS*^{G12C} mutated NSCLC were included (13). Patients must have already received at least two treatment lines for metastatic disease. The overall response rate (ORR) was 37%, with a DCR of 81%. The median duration of response was 10.0 months, and the median PFS was 6.8 months. Phase III study "Codebreak 200" is currently enrolling, comparing Sotorasib versus docetaxel in the second-line setting (14). MRTX849 (adagrasib), another *KRAS*^{G12C} irreversible inhibitor, also showed activity in a recent phase I/II study, achieving a 43% ORR and a 96% DCR (15). The phase II KRYSTAL-7 trial is ongoing to evaluate adagrasib in

combination with Pembrolizumab for mutant *KRAS*^{G12C} NSCLC, while the phase III KRYSTAL-12 study is comparing adagrasib with docetaxel in pretreated patients (16,18). These studies highlighted the complexity of targeting *KRAS*-mutated cancer. The difficulty arises from many different aberrations and co-mutations that probably modulate tumor biology and response to therapy. Recently data from a series of 38 patients who developed resistance to adagrasib highlighted some of the main escape mechanisms (19). Of the 38 patients analyzed, 27 had lung cancer, 10 had colorectal cancer, and one had appendix cancer. Some of the main resistance mechanisms identified were MET amplification, mutations in *NRAS*, *BRAF*, mitogen-activated protein kinase kinase 1 (*MAP2K1*), RET, fusions involving *ALK*, *RET*, *BRAF*, *RAF1*, and fibroblast growth factor receptor (*FGFR*)-3, and loss-of-function mutations in neurofibromatosis type 1 (*NF1*) and phosphatase and tensin homolog (*PTEN*). In addition, two patients with LUAC showed a histological transformation into squamous cell lung cancer (SqCC) without identifying other resistance mechanisms.

PIK3CA

Histological and molecular characteristics

The phosphoinositide 3-kinase (PI3K) family is part of a complex intracellular signaling pathway involving protein kinase B (PKB), also known as AKT, and mechanistic target of rapamycin (mTOR), named the PI3K/AKT/mTOR pathway. It has a crucial role in intracellular signaling, and it is involved in many cellular processes, such as growth, metabolism, and cell cycle progression. Thus, somatic mutations affecting this pathway can be responsible for deregulated proliferation and cancer (20). PI3K comprises a regulatory (p85) and a catalytic (p110) subunit. Three genes, namely *PIK3CA*, *PIK3CB*, and *PIK3CD*, encoded the catalytic portion, with the first one most frequently mutated in various types of cancer (21). *PIK3CA* mutations account for up to 2–7% of NSCLC, more often in squamous cell carcinoma and Asian population (22,23), so its association with a smoking history is not unusual. Notably, in a systematic review and meta-analysis of 3,908 patients, only lymph node metastasis status was positively related to *PIK3CA* mutation (24). The impact of such mutations on survival parameters is still unclear, although many authors suggested poorer prognoses in this subtype of patients (24,25). Interestingly, in preclinical models, *PIK3CA* mutations alone do not have the power to initiate and promote tumorigenesis, even when PTEN, a negative regulator of the PI3K/AKT/mTOR pathway, is mutated. *In vitro* and *in vivo* data suggested that cooperation with other oncogenic drivers, such as *BRAF*^{V600E}, *KRAS*^{G12D}, and *TP53* silencing, is necessary to achieve tumor maintenance and progression. Only a combination therapy results in a response improvement (26,27). This observation reflects clinical practice, where additional oncogenic driver aberrations ranged from 57% to more than 75% in tissue specimens collected from NSCLC patients (28).

Drugs development and clinical trials

To date, available data on early phase clinical trials have not provided satisfying results, and mainly investigated the impact of single or dual PI3K/AKT/mTOR pathway inhibitors, often combined with standard of care treatments (29). Pictilisib, a pan-class I PI3K inhibitor, has been evaluated in phase IA/IB trials either alone or in combination with chemotherapy, with encouraging results not confirmed in a phase II study (30). Data regarding phase I/II trials involving other pan-class inhibitors, such as PX-866 and buparlisib (BKM120), had likewise failed to demonstrate an improvement in survival parameters (31-33). The efficacy of a selective PI3K p110α, p110γ, and p110δ isoforms inhibitor, namely Taselisib (GDC-0032), was investigated in phase II LUNG-MAP study on a population of 21 patients with mutated *PIK3CA* and failed to meet its primary endpoint. The study was closed for futility after an interim analysis (34). A phase I basket study showed limited efficacy of Taselisib in a selected *PIK3CA*-mutated population with various types of cancers (35). Also, AKT inhibitors were tested in phase I/II trials. Perifosine was first evaluated in a phase I trial, with one unconfirmed partial response (PR) and two stable diseases (SDs) on a total of 15 patients. Results of a subsequent phase II trial are not yet available (36). The efficacy of another compound, namely MK-2206, was investigated in combination with erlotinib in patients previously progressing on the EGFR inhibitor treatment, with a median PFS of 4.6 months in EGFR wild-type patients and 4.4 months in EGFR-mutated patients (37). Proceeding through the pathway, also mTOR inhibitors were tested in patients with NSCLC. Many phase I/II trials were conducted based on the already demonstrated efficacy in different types of tumors, such as renal cell carcinoma and breast cancer. Everolimus, a mTOR complex 1 (mTORC1) inhibitor, was evaluated alone or with chemotherapy/targeted therapies with modest

results and did not proceed to phase III trials (38-41). Sirolimus showed a potential benefit when combined with pemetrexed in recurrent, metastatic NSCLC (42). Temsirolimus displayed limited efficacy in an *ERBB2* mutated cohort of lung cancer patients when combined with Neratinib, an oral ERBB2 inhibitor (43). Also, inhibitors of both mTORC1 and mTORC2 complexes were developed. Vistusertib (AZD2014), in combination with paclitaxel, showed activity and an impressive RR (33%) in previously treated patients with squamous NSCLC (44). A complete view of trials investigating the PI3K/AKT/mTOR pathway is available in *Table 2*. Notably, none of these agents have received approval for the treatment of NSCLC yet, and the lack of efficacy has markedly slowed down. The reasons why a selective inhibition of the PI3K/AKT/mTOR pathway failed to improve ORR and survival are still not fully understood. As mentioned, PI3K mutations seem to occur later in the multi-step carcinogenesis process. This could promote intratumor heterogeneity by developing resistant subclones among different tumor regions that present a higher mutational burden and different survival pathways (28). Further studies are therefore needed to define the best strategy to target neoplasms with emerging *PIK3CA* mutated clones.

Neuregulin-1 (NRG-1)

Histological and molecular characteristics

NRG-1 is part of a large family of growth factors that presents an EGF-like consensus sequence in their structure, which favors their binding to ERBB transmembrane receptor tyrosine kinases (RTKs) (45). ERBB receptors retain an essential role in cell proliferation, development, and differentiation and are constitutively expressed in epithelial, neuronal, and cardiovascular systems (46). The family is subdivided into four members: ERBB1 (also known as EGFR), ERBB2 (also known as HER2), ERBB3, and ERBB4, which are slightly different for structure and type of activation (47). These are composed of an extracellular ligand-binding domain, a juxtamembrane domain, and an intracellular kinase domain, which permits signaling through different pathways, like RAS/RAF/mitogen-activated protein kinase (MAPK) or the already mentioned ones PI3K/AKT/mTOR (48,49). Therefore, aberrant activation of these receptors could lead to unregulated cell growth and cancer development (50). After ligand binding, these receptors form homo and heterodimers to proceed with kinase signaling, and only ERBB1 and ERBB4 are autonomous. ERBB2 cannot bind ligands, and ERBB3 displays deficient kinase activity (51,52). Complete functional activation of these proteins relies on heterodimerization with other family members. Curiously, the couple ERBB2-ERBB3 is considered the most transforming and mitogenic one (53,54). NRG-1 is encoded by the homonymous gene, generating six proteins (I–VI) and at least 31 isoforms (55). Among these, type III NRG-1 presents a membrane-anchored epidermal growth factor (EGF)-like domain, which could act in an autocrine and paracrine manner (55). Recent researches suggested that NRG-1 overexpression and, therefore, ERBB3 aberrant signaling could be responsible for cancer development and maintenance in preclinical models (56-58). Moreover, NRG-1 binding to ERBB3 can induce ERBB2-ERBB3 heterodimerization (59). Rearrangements involving the *NRG-1* gene are described in LUAC, especially in the mucinous subtype, with a reported frequency of 0.14–1.7%, with prevalence in non-smoking female patients. Multiple partner genes, such as *CD74*, *SDC4*, *SLC3A2*, and *VAMP2*, have been described in LUAC, with *CD74* being the most frequent one. The only one squamous cell carcinoma of the lung reported in the literature harbored *SMAD4-NRG-1* fusion (60). *NRG-1* fusions result in aberrant expression of the EGF-like the domain of NRG-1, which serves as a ligand for ERBB3 (HER3) producing ErbB2/ErbB3 heterodimerization and ErbB3 phosphorylation, with consequent continuous stimulation of the downstream PI3K/AKT pathway. All mucinous adenocarcinoma with CD74-NRG-1 fusion expressed phosphorylated ErbB3 protein (pErbB3). Therefore, immunohistochemistry for pErbB3 has been proposed as a screening test to suspect *NRG-1* fusion (61). Among LUAC histotypes, *NRG-1* gene fusions seem to occur predominantly in 8–32% of IMA (62).

Drugs development and clinical trials

Due to these molecular features, many ERBB receptor inhibitors were tested both in preclinical and clinical settings. Human lung cancer cells with *CD74-NRG-1* fusion protein were exposed to Afatinib, a pan-ERBB inhibitor, and Lapatinib, an EGFR, and HER2 inhibitor, with decreased signaling and cell growth in preclinical models (63). In xenograft models, both the anti-ERBB3 GSK2849330 and the pan-ERBB inhibitor, Tarloxotinib, displayed antitumor activity (64,65). Other potential *NRG-1* fusion-targeted agents were developed, such as Seribantumab (MM-121), AV-203, 9F7-F11, and LJM716, but data are limited to

Table 2 Available clinical trials of PI3K/AKT/mTOR pathway inhibitors in NSCLC

Drug	Phase	No. of patients	Setting	Results (if available)
Pictilisib (30) (paclitaxel + carboplatin or pemetrexed + cisplatin, ± bevacizumab)	I	66	First-line therapy for NSCLC	PR in 29 (43.9%) patients; SD in 20 (30.9%) patients
Pictilisib (paclitaxel + carboplatin, ± bevacizumab)	II	501	First line therapy for NSCLC	N/A
Docetaxel ± PX-866 (31) (arm A standard; arm B experimental)	II	95	Second-, third-line therapy for NSCLC	PFS 2.0 months arm A; PFS 2.9 months arm B; OS 7.0 months arm A; OS 9.2 months arm B; ORR 6% arm A; ORR 0% arm B
Carboplatin + paclitaxel, ± buparlisib (32)	I/II	63	Previously treated squamous NSCLC with PI3K activation	Terminated due to DLTs/AEs safety profile considered challenging; stage II was not initiated
Taselisib (34)	II	26	Previously treated squamous NSCLC with PI3K activation	Closed for futility at interim analysis; median PFS 2.9 months; median OS 5.9 months
Perifosine (36)	I/II	20	Previously treated NSCLC	N/A
MK-2206 (37) (+ erlotinib; arm 1 EGFR mutant; arm 2 *EGFR* WT)	II	80	NSCLC previously treated with erlotinib	Median PFS arm 1: 4.4 months; median PFS arm 2: 4.6 months; DCR arm 1: 40%; DCR arm 2: 47%
Everolimus (38) (arm 1 pretreated with PB-chemotherapy; arm 2 pretreated with chemotherapy and EGFR inhibitors)	II	85	Previously treated NSCLC	Median PFS arm 1: 2.6 months; median PFS arm 2: 2.7 months; ORR arm 1: 7.1%; ORR arm 2: 2.3%
Everolimus (39) (+ pemetrexed)	I	24	Previously treated NSCLC	3 PR observed with MTD
Erlotinib (40) (± everolimus; arm A + everolimus; arm B + placebo)	II	133	Previously treated NSCLC	Median PFS arm A: 2.9 months; median PFS arm B: 2.0 months. DCR 3 months arm A: 39.4%; DCR 3 months arm B: 28.4%. Grade 3–4 AEs arm A: 72.7%; grade 3–4 AEs arm B: 31.8%
Everolimus (41) (+ gefitinib; arm A previously untreated NSCLC; arm B previously treated NSCLC)	II	62	Previously untreated/ treated NSCLC	ORR 13% among the two groups taken together
Sirolimus (42) (pemetrexed)	I/II	42	Previously treated NSCLC	27 patients treated with MTD, among those: PR in 6 (22.2%) patients; SD in 12 (44.4%) patients; median PFS 18.4 weeks
Neratinib ± temsirolimus (43) (arm A with placebo; arm B with temsirolimus)	II	62	HER-2 mutated NSCLC	ORR arm A: 0%; ORR arm B: 8%. Median PFS arm A: 3.0 months; median PFS arm B: 4.1 months. Median OS arm A: 10.0 months; median OS arm B: 15.8 months
Vistusertib (AZD2014) (44) (+ paclitaxel)	II	32	Previously treated squamous NSCLC	ORR 33%

AEs, adverse events; AKT, protein kinase B; DCR, disease control rate; DLTs, dose-limiting toxicities; MTD, maximum-tolerated dose; mTOR, mechanistic target of rapamycin; N/A, not available; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PB, platinum-based; PFS, progression-free survival; PR, partial response; SD, stable disease; WT, wild-type.

Table 3 Available clinical trials and case reports of NRG-1 inhibitors in NSCLC

Drug	No. of patients	Setting	Results (if available)
Afatinib (68)	12	Stage IV NSCLC	55% PD; 18% PR; 18% SD; median PFS was 3.5 months
Afatinib (64)	3	Advanced NSCLC	1 SD (33%); 2 PD (66%)
GSK2849330 (64)	1	Advanced NSCLC	1 PR for 19 months
Afatinib (69)	1	Pre-treated NSCLC	1 PR for 12 months
Afatinib (69)	1	Previously untreated NSCLC	1 PR for 10 months
Lumretuzumab (70) (RG7116)	2	Pre-treated NSCLC	2 SD for 4 months
Zenocutuzumab (71) (MCLA-128)	1	Advanced NSCLC	1 PR for 4.5 months, ongoing

NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

preclinical and phase I settings (66,67). The most widely studied compound used in clinical practice is Afatinib. Data highlighting its potential activity are mainly extracted from case reports of patients with IMA, NSCLC, ovarian cancer, and pancreatic ductal adenocarcinoma. A global registry of *NRG-1* fusion-positive NSCLC has been created, with an accrual of 80 patients (68). Among these, 12 were treated with Afatinib, with an ORR of 18%, a DCR of 36%, and a median PFS of 3.5 months. In the work of Drilon *et al.* (63), four patients experienced a progression of the disease quickly after starting treatment. This emphasizes our need to understand possible primary resistance mechanisms in this intricate scenario. Conversely, Gay *et al.* (69) presented a cohort of 404 NSCLC patients, in which two patients had *NRG-1* fusion-positive cancers (0.5%). One harbored the *SLC3A2-NRG-1* fusion and had a PFS of 12 months, while the second displayed the more frequent *CD74-NRG-1*, with a PFS of 10 months. In these cases, Afatinib was effective both in pretreated (first case) and treatment-naïve (second case) patients, suggesting a potential and concrete survival benefit. Notably, other ERBB inhibitors achieved acceptable results. Lumretuzumab (RG7116), an anti-ERBB3 antibody, was tested in two previously treated patients with *SLC3A2-NRG-1* fusion. SD was the best response in both cases, and the PFS was 4 months (70). Zenocutuzumab (MCLA-128), a bispecific anti-HER2/ERBB3 antibody, is currently being tested in a phase II basket trial for cancers with *NRG-1* fusion (NCT02912949). A patient with NSCLC is experiencing a PR, with an ongoing 4.5 months PFS (71). A complete view of trials and case reports regarding NRG-1 inhibitors is available in *Table 3*.

Due to the emerging need for targeted therapies for less common gene signatures, the Drug Rediscovery Protocol Trial (DRUP, NCT02925234) aims to assign an already available treatment to a potentially actionable specific genomic alteration to a patient. Similarly, the Targeted Agent and Profiling Utilization Registry Study (TAPUR, NCT02693535) predicts to enroll over 3,300 patients with a selection of 13 gene signatures. Understanding mechanisms that underlie acquired resistance to ERBB inhibitors, either alone or combined, is another ambitious challenge to face today. Still, recent advances in tumor molecular profiling could help overcome this gap and satisfy the unmet need for tailored therapies.

ERBB2

Histological and molecular characteristics

ERBB2 alterations are found in a small subgroup of NSCLCs. They can be detected as oncogenic drivers or emerge as resistance mutations. Altered ERBB2 NSCLC typically has lower RRs to standard chemotherapy treatments and shorter overall survival (OS). In general, HER2 alterations can be divided into three subgroups: mutation, amplification, and protein overexpression. Typically, most cases of ERBB2 overexpression are due to gene amplification, but this can also occur due to transcriptional mechanisms or post-transcriptional regulation, such as increased protein stability. *ERBB2* mutations can be detected both in the extracellular (exons 5–8) and the transmembrane (exon 17) domains, but they are much more common in the tyrosine kinase domain (TKD = exons 18–24), as is also the case for EGFR. Similar to *EGFR* mutations, the mutants in the TKD can be substitutions, ex19dels, and in-frame ex20ins or duplications. In-frame insertions in exon 20 are the most common and reported in 2–10% of LUACs (72-74). The

mutation is frequent in women, with a mean age of 60, in non-smokers and the Asian population (75). *ERBB2* mutated LUACs are moderate- or poorly differentiated (76). Coexisting *ERBB2* mutation and amplification have been documented in a variable proportion of *ERBB2* mutated LUAC. However, only a minority of the samples with *HER2* mutation show significant immunohistochemical overexpression of ERBB2 protein, indicating that mutation alone does not seem to be associated with increased protein expression. Among all NSCLC, ERBB2 copy number gains have been reported in 2–5% of adenocarcinomas, 2–7% of large-cell carcinomas, and 1% of squamous cell carcinomas (77).

As mentioned, EGFR and ERBB2 belong to the same family of receptors and have a very similar conformation and mechanism of action. Their exon 20 consists of one region, the α-C helix, and the loop following the α-C helix (78). The C-helix of the protein could have an inactive or active conformation, and the activation status of EGFR and ERBB2 depends on it. When exon 20 insertions occur, the C-helix changes to a permanent active conformation, resulting in enhanced survival, invasiveness, and tumorigenicity of the cells harboring these mutants. Most insertions have from 3 to 12 bp and are located in the proximal region of the exon, between codons 775 and 881. The most frequent insertion is p.A775_G776insYVMA, in which the insertion of 12 bp results in the duplication of amino acids YVMA at codon 775 (79,80), and D770-N771insX is the most frequent of *EGFR* exon 20 mutations (81). These alterations do not increase the affinity for EGFR TKIs, because they do not concern the ATP-binding pocket (82). On the contrary, they force the αC-helix into the αC-in position causing constitutive dimerization and activation.

Drugs development and clinical trials

Alteration of ERBB2 in NSCLC has been described both as pre-existing and acquired after target therapy. Their prevalence increases after treatment with EGFR TKI in patients with a sensitizing *EGFR* mutation. Recent studies suggested an ERBB2 alteration in about 10–15% of patients that develop resistance to EGFR-TKIs (83). Different TKI and anti-ERBB2 drugs have been evaluated in *ERBB2* mutant lung cancers, with contrasting results. First, second-generation EGFR inhibitors (Afatinib, Dacomitinib, and Neratinib) irreversibly bind to EGFR and ERBB2 (81). Afatinib showed a limited control on *ERBB2* mutant NSCLC patients in the Niche trial (84). Furthermore, Afatinib is modestly active in patients with ERBB2-mutant LUACs, also after ERBB2 targeted therapies, in a recently published retrospective multicenter study where the median duration of response was 6 months (85).

Dacomitinib presents comparable results in *EGFR* and *ERBB2* mutant NSCLC compared to other TKIs. In a phase II study, Dacomitinib showed a PR in a phase II study on 3 of 26 patients with *ERBB2* mutations or amplifications (86). Neratinib was studied in combination with an mTOR inhibitor, temsirolimus, in a preclinical setting and then in a phase II study, showing a moderate efficacy in patients with NSCLC with ERBB2 mutations (87). A retrospective study identified a cohort of 101 NSCLC patients with ERBB2 mutations in various European centers. Among these 65 received ERBB2 target therapy, notably including trastuzumab (n=57), trastuzumab emtansine (T-DM1, n=1), neratinib (n=14), afatinib (n=11), and lapatinib (n=5). Different responses were observed depending on the agent used; in trastuzumab-based (trastuzumab and T-DM1), treated patients achieved an RR of 50.9% and a PFS of 4.8 months [95% confidence interval (CI): 3.4–6.5]. Conversely, all five patients treated with lapatinib had progressive disease as the best response (88).

Mobocertinib (TAK-788) selectively inhibits *EGFR* and *ERBB2* mutated exon 20. Its efficacy has been studied *in vitro* and *in vivo* (89). Recently, fascinating data have been presented in pretreated *EGFR* exon 20 insertion NSCLC patients (90), which led to FDA approval.

Poziotinib shows the most solid activity against *ERBB2* exon 20 mutations compared to other TKIs *in vitro* studies, probably due to its small size and flexibility. Poziotinib effectively inhibited the growth of cells with EGFR or ERBB2 exon 20 mutations *in vitro*. Moreover, it has been tested in clinical trials with promising results in NSCLC heavily pretreated patients. In a phase II study evaluating this setting, the ORR was 27% (95% CI: 12–46%), with a median PFS of 5.0 months [95% CI: 4.0 months–not evaluable (NE)], and a median OS of 15 months (95% CI: 9.0 months–NE). The rate of adverse events was the main problem with the drug. In total, G3 skin toxicities were reported in 47% of cases, G3 diarrhea, and G3 paronychia in 20% (91).

The efficacy of poziotinib was also demonstrated in the ZENITH20-1 study; the same promising results were found in the ZENITH20-2 trial that enrolled 90 patients with *ERBB2* exon 20 insertions (92) with an ORR of 27.8% (95% CI: 18.9–38.2%). Those trials reached their primary endpoint with manageable TKI related toxicities.

Pyrotinib is a multi-target TKI that blocks ERBB1,

ERBB2, and ERBB4 activity. Data from a phase II study conducted on pretreated *ERBB2* exon 20-mutated advanced NSCLC patients showed 8 (53.3%) PRs and 3 (20.0%) SDs, with a median PFS of 6.4 months (95% CI: 1.60–11.20 months) (93).

Anti-ERBB2 drugs have become the standard of care in patients with amplified ERBB2 breast cancer and are routinely used in gastric and colon cancer harboring ERBB2 alterations. Their efficacy against NSCLC harboring ERBB2 aberrations has been evaluated in preclinical and clinical studies. A recent phase II basket trial evaluated trastuzumab emtansine (T-DM1) in *ERBB2* mutated LUAC. Results showed an ORR of 44% [8/18] and a median PFS of 5 months (95% CI: 3–9 months). T-DM1 presented activity in both exon 20 insertion, point mutations, and ERBB2 amplification (94).

Trastuzumab deruxtecan (DS-8201a) is an anti-ERBB2 antibody bound to a topoisomerase I inhibitor, Exatecan derivative, whose activity against mutated ERBB2 cells has been evaluated *in vitro* and *in vivo* studies (95). Recently, trastuzumab deruxtecan was tested in phase I clinical trial that recruited patients with cancers harboring ERBB2 alterations (96). The *ERBB2* mutated NSCLC cohort showed exciting data with a median duration of treatment of 5.5 months (range, 0.69–14.19 months) (97). The updated results of phase II study DESTINY-Lung01 have recently been published. Trastuzumab deruxtecan had an ORR of 55% (95% CI: 44–65%) with a median PFS of 8.2 months (95% CI: 6.0–11.9 months) and median OS of 17.8 months (95% CI: 13.8–22.1 months) (97,98).

Tarloxotinib is a prodrug that exploits tumor hypoxia to generate high levels of downstream effector, the covalent pan-ERBB tyrosine kinase inhibitor, Tarloxotinib-E, within the tumor microenvironment (99). In preclinical studies, Tarloxotinib exhibited promising activity *in vitro* in patient-derived cell lines and xenografts that carried *EGFR* ex20ins or *HER2* ex20ins or HER2 amplification or *NRG-1* fusions (99). In the RAIN trial, Tarloxotinib showed promising antitumor activity and a tolerable safety profile in patients with NSCLC harboring ERBB2 activating mutations, obtaining an ORR of 22% and a DCR of 67% (100). *Table 4* summarizes trials currently investigating anti-ERBB2 therapies for ERBB2 positive NSCLC.

Indeed, data obtained with TKI and anti-ERBB2 drugs, although promising, are not entirely satisfying. Efforts are needed to characterize better the different ERBB2 aberrations, such as point mutations, receptor insertions, amplification and overexpression, and the different responses of each mutation class to different treatments.

FGFR

Histological and molecular characteristics

FGFR-1/2/3 alterations occur in 0.2–6% of NSCLC (101,102) as amplification, point mutation, or translocation. These alterations predominate in males and smokers with a median age diagnosis of 67.5 years (range, 36–89 years). *FGFR-1* amplification (8p12) has been reported in 9–22% of squamous cell carcinomas (LUSC) (103,104). Weiss *et al.* analyzed, by high-resolution genomic profiles, 77 LUACs, and 155 squamous cell carcinomas and identified amplifications of FGFR-1 exclusively in Caucasian's LUSC (105). Examination of an independent series by fluorescence *in situ* hybridization (FISH) revealed *FGFR-1* amplification in 22% of SqCC samples. The incidence of *FGFR-1* amplification was also associated with smoking status suggesting the possibility of smoking-induced amplification. Concerning FGFR-2 and FGFR-3 alteration, Helsten *et al.* describe *FGFR-2*, *3* mutation in 3% of LUSC and any abnormalities of FGFR in 4% of LUAC (106). In Hibi *et al.* NSCLC series *FGFR* mutations occurs in 2.7% on *FGFR-1*, 2.7% of *FGFR-2*, 0% of *FGFR-3* and 5.3% of *FGFR-4* (107).

Drugs development and clinical trials

Alterations in FGFR are a promising therapeutic target in many cancers. FGFR tyrosine kinases are encoded by four genes (*FGFR-1*, *FGFR-2*, *FGFR-3*, *FGFR-4*) and are involved in cell proliferation, motility, angiogenesis, and epithelial-mesenchymal transition. FGFR inhibitors have shown efficacy in various *in vitro* studies; Preclinical cell line and patient-derived squamous NSCLC xenograft models with *FGFR* mutations indicate potential sensitivity to FGFR inhibitors. Several targeted molecules have been developed to block FGFR: monoclonal antibodies (e.g., MFGR1877S), ligand traps (e.g., FP1039/GSK305223042), non-selective TKIs, and selective TKIs (108-110). Several non-selective TKIs inhibitors such as Dovitinib, Nintedanib, Cediranib, Ponatinib, Lucitanib and Pazopanib have been studied in the context of *FGFR* mutations. However, all these drugs are limited by toxicity, potentially due to their non-selectivity and mainly dependent on the VEGF/VEGFR

Table 4 Available clinical trials of HER-2 pathway inhibitors in NSCLC

Drug	Phase	No. of patients	Setting	Results (if available)
Afatinib (84)	II	13	Pretreated patients with advanced NSCLC harboring *HER-2* exon 20 mutations	Median PFS 15.9 weeks; median OS 56.0 weeks
Dacomitinib (86)	II	26	Stage IIIB/IV lung cancers with *HER-2* mutations or amplification	Median OS 9 months patients with *HER-2* mutations; median OS 8 months patients with amplifications
Neratinib ± temsirolimus (87) (arm A with placebo; arm B with temsirolimus)	II	62	Metastatic NSCLC *HER-2* mutated	ORR arm A: 0%; ORR arm B: 8%. Median PFS arm A: 3.0 months; median PFS arm B: 4.1 months. Median OS arm A: 10.0 months; median OS arm B: 15.8 months
Mobocertinib (90)	II	28	Metastatic NSCLC *EGFR* ex20ins	ORR 43%; median DOR 13.9 months; DCR 86%; median PFS 7.3 months
Poziotinib (91)	II	50	Metastatic NSCLC *HER-2* exon 20 mutated	ORR 27%; median PFS 5.0 months; median OS 15 months
ZENITH20-2 (92) (poziotinib)	II	20	Metastatic NSCLC *HER-2* exon 20 mutated	ORR 27.8%; DCR 70%; median PFS 5.5 months
Pyrotinib (93)	II	15	pretreated *HER-2* exon 20-mutated advanced NSCLC patients	ORR 53.3%; median PFS 6.4 months
TDM-1 (94)	II	18	Advanced NSCLC *HER-2* mutated	ORR 44%; median PFS 5 months
Trastuzumab deruxtecan (96)	I	12	Advanced NSCLC *HER-2* mutated	median DOR 11.5 months
DESTINY-Lung01 (98) (trastuzumab; deruxtecan)	II	Recruiting (42 patients until now)	Advanced NSCLC *HER-2* mutated	ORR 55%; median PFS 8.2 months; median OS 17.8 months
RAIN-701 (100) (tarloxotinib)	II	Recruiting (23 patients until now)	Stage IIIB/IV lung cancers with EGFR exon 20, *HER-2* mutations, ERBB and *NRG-1* fusions	Preliminary data; ORR 22%; DCR 67%

DCR, disease control rate; DOR, duration of response; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PR, partial response; ORR, objective response rate; OS, overall survival.

pathway inhibition.

In contrast to non-selective inhibitors, selective TKIs such LY2874455, BGJ398, BAY1163877, and JNJ42756493, exhibit a better toxicity profile, especially limited to hyperphosphatemia as the main event. The GSK3052230 inhibitor was studied in a phase IB study in combination with carboplatin or docetaxel. Treatment was well tolerated in association with chemotherapy, and specific adverse events such as hyperphosphatemia, nail and skin toxicity were not observed (111). AZD4547 is an inhibitor of FGFR-1/2/3 and, despite the good results obtained *in vitro* and in a phase I study, it has not demonstrated the expected efficacy. The molecule was evaluated in the phase II sub-study of Lung Map SWOGS1400D, which included patients with *FGFR* mutated SqCC after failure of platinum-based therapy (112). Only two patients showed a response to the treatment. An ongoing phase II study with Erdafitinib, recently approved by the FDA for *FGFR*-mutated urothelial cancer, is enrolling patients with *FGFR-1* mutations and/or translocations (113). Pemigatinib is currently being tested in various malignancies alone or combined with chemotherapy or ICIs after proven efficacy in preclinical data (114). *Table 5* summarizes trials currently investigating anti-FGFR inhibitors for FGFR-altered NSCLC. The panorama of FGFR inhibition shows modest results in the absence of molecules that, at present, could provide meaningful clinical benefit. The main obstacle is the variable sensitivity that tumors with varying FGFR alterations have for FGFR inhibitors. Preclinical studies showed significantly different responses depending on the

Table 5 Available clinical trials of FGFR inhibitors in NSCLC

Drug	Phase	No. of patients	Setting	Results (if available)
Dovitinib (110)	II	26	Advanced/metastatic SCC; pretreated	11.5% ORR; 50% DCR; OS 5 months; PFS 2.9 months
GSK3052230 (111) [+ paclitaxel and carboplatin (arm A) or docetaxel (arm B)]	Ib	29	Metastatic NSCLC; first line (arm A), second line (arm B)	47% ORR; PFS 5.5 months (arm A); 0% ORR PFS 4.6 months (arm B)
AZD4547 (112)	II	92	Metastatic SCC; previously treated	PFS 2.7 months; OS 7.5 months
Erdafitinib (113)	II	Enrolling	Stage IIIB/IV NSCLC, pretreated	N/A (ongoing)
Pemigatinib (arm B) or pemigatinib + other drug (arm B) (114)	I/II	Enrolling	Metastatic SCC; pretreated	N/A (ongoing)

SqCC, squamous cell lung cancer; ORR, overall response rate; DCR, disease control rate; N/A, not available; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

genetic alteration and the FGFR inhibitor used. Focusing on the diverse and peculiar molecular mechanisms of FGFR alterations could be the key to making this subgroup of alterations druggable.

Discussion

In the era of personalized medicine, tailoring therapies around a single patient could be the right choice to get better outcomes and lower toxicities (115,116). Lung cancer can be considered a model of this innovative approach. The discovery of driver mutations and the adoption of specific inhibitor sequences made it possible to achieve median survivals in a subgroup of patients with actionable mutations that were unthinkable until a few years. A paradigmatic example of this incredible transformation is the natural history of ALK-positive NSCLC, where median survival moved from 12 months of the chemotherapy era to over seven years reached with the advent of the new second- and third generation ALK inhibitors (117). Unfortunately, only a minor proportion of NSCLC have druggable mutations for which target treatments are approved (118). However, the increasingly routine use of comprehensive genomic profiling methods has revealed lung neoplasms' extensive molecular heterogeneity, highlighting other possible therapeutic targets. In a few years, with the advent of selective inhibitors, mutations historically considered undruggable, such as *KRAS* mutations, have aroused renewed interest. Other mutations, instead, such as *PI3CKA* and *FGFR* mutations, while showing their full potential, have not achieved satisfactory results yet. The next few years' goals will be to build a solid and replicable model of precision oncology that can provide solid evidence from preclinical studies to translate in the most advanced phases of clinical trials. On the contrary, the risk is having a high number of molecules and an inadequate supply of evidence (119).

Our review aims to highlight the latest discovery in "unconventional" NSCLC gene alterations, listing already available results and ongoing clinical trials. In the broad mutational landscape of this complex and heterogeneous tumor, finding these alterations and building a new model of patient-centered precision oncology could radically change the natural history of NSCLC.

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