REVIEW ARTICLE

Molecular Diagnostic and Precision Medicine in Non-Small Cell Lung Cancer. An Update on the Treatment of the Most Important Actionable Oncogenic Driver Alterations.

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ABSTRACT

Due to groundbreaking developments and continuous progress, the treatment of stage IV non-small cell lung cancer (NSCLC) has become an exciting but increasingly challenging task. This applies in particular to the subgroup of NSCLC with oncogenic driver alterations. While the treatment of epidermal growth factor receptor (EGFR)-mutated and anaplastic lymphoma kinase (ALK)-rearranged NSCLC with different tyrosine kinase inhibitors (TKI) is well established, new targets have been identified in the last years, and new TKI introduced in clinical practice. Even for *KRAS* mutations, considered for a long time as an "untargetable" alteration, promising new drugs are emerging. The detection and in-depth molecular analysis of resistance mechanisms have further fueled the development of new therapeutic strategies. The objective of this review is to give an overview on the current landscape of targetable oncogenes in NSCLC.

Keywords: *NSCLC, oncogenic alterations, precision oncology, targeted therapy*

INTRODUCTION

Globally, lung cancer is the most commonly diagnosed cancer (11.6% of total cases) and the leading cause of cancer death for both sexes combined (18.4% of total cancer deaths).[1] In Switzerland, lung cancer accounts for 11.8% of all cancer cases diagnosed in men and 8.5% in women and is the most common cause of cancer death in men (22.3% of all cancer deaths) and the second most common cause of cancer death in women (14.9%).[2] Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers and is further subdivided into adenocarcinoma (AC), squamous cell carcinoma (SCC), and large cell neuroendocrine carcinoma (LCNEC).[3] This purely morphological taxonomy has been challenged in the past decades as it has been recognized that somatic oncogenetic alterations can further molecularly subdivide these NSCLC subtypes. Genotype-driven therapy ("targeted therapy") is nowadays standard of care for a significant subgroup of NSCLC patients with advanced/metastatic disease. There is significant variability in the incidence of oncogenic driver alterations with a higher incidence in AC compared to SCC and higher number in Asian populations.[4]

NSCLC WITH ACTIONABLE ONCOGENIC DRIVERS

Genotype-driven treatment with rationally targeted therapies has led to unprecedented outcome improvements. Historically, the estimated median overall survival (mOS) for patients with advanced/metastatic NSCLC (stage IV disease) was 10 to 12 months. The discovery of activating epidermal growth factor receptor (EGFR) mutations as predictors of response to EGFR-tyrosine kinase inhibitor (TKI) therapy profoundly changed the therapeutic landscape of lung AC.[5,6] Treatment of EGFR-mutated NSCLC can be seen as a model for a biomarker- based therapy and the establishment of a predictive molecular marker for personalized therapy in the treatment of solid tumors. Since the discovery of EGFR

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mutations as a targetable oncogenic alteration, several other molecular targets have been identified. This led to the development of very effective new drugs, and thus to relevant progress in the treatment of oncogene-addicted NSCLC.

The hallmarks of NSCLC with actionable oncogenic drivers are the following:

- High objective response rates (ORR) to small-molecule receptor TKIs. The ORR to TKIs generally ranges between 50% and 90%, as described in the following sections. The presence of an oncogenic alteration, therefore, has predictive value.
- Randomized studies have shown improved overall survival using a targeted treatment approach compared to conventional chemotherapy.
- The OS of patients with actionable oncogenic mutations is often longer compared to patients without actionable drivers or tumor suppressor mutations. The presence of an actionable oncogenic target has thus a prognostic value.
- In most cases, there is mutual exclusivity of oncogenic alterations.
- The emergence of resistance to targeted therapy usually occurs within 12–24 months. A better characterization of these resistance mechanisms led to the establishment of new therapeutic options for various molecular subtypes.

All these characteristics are based on a model of a single genomic driver event. There is, however, growing evidence about heterogeneity in terms of response to targeted therapy and clinical outcome within oncogenic driver mutations. In this context, the role of co-occurring genomic alterations has been highlighted in a recent review.[7]

The present review focuses on the subset of NSCLC (mainly AC) with actionable oncogenic driver alterations and targeted therapy in the metastatic setting. Molecular changes, their frequency, and targeted therapies are summarized in **Table 1**. We will not address the interesting and highly discussed topic of immune checkpoint inhibitor therapy in the subset of patients with oncogenic driver alterations.

Table 1. Summary of oncogenic driver alterations and targeted therapies in non-small-cell lung cancer. AC: adenocarcinoma; SCC: squamous cell carcinoma; EGFRi: EGFR inhibitor; BRAFi: BRAF inhibitor; MEKi: MEK inhibitor; ChT: chemotherapy.

Genomic alterations	Most common subtype	Frequency #	Investigated targeted agents and approval by Swissmedic
***KRAS* mutations**	G12C, G12V, G12D	AC: 20–25% SCC: 4%	Binimetinib (MEKi)
		KRAS G12C: 13%	KRAS G12C inhibitors: - AMG510 - MRTX849
***EGFR* mutations**	del19p, L858R	12–15%	1st generation EGFRi - Erlotinib* - Gefitinib* 2nd generation EGFRi - Afatinib* - Dacomitinib* 3rd generation EGFRi - Osimertinib*
***ALK* gene rearrangements**	EML4-ALK fusion	2–8%	Crizotinib* Ceritinib* Alectinib* Brigatinib Lorlatinib* Entrectinib
***BRAF* mutations**	V600E	1–5% (50% V600E)	Dabrafenib (BRAFi) Vemurafenib (MEKi) Dabrafenib + Trametinib*
***HER2* alterations**	HER2 amplification	2–4%	HER2 antibodies + ChT Afatinib Neratinib + Temsirolimus T-DM1 Trastuzumab deruxtecan
	HER2 Exon 20 mutation	1–2%	HER2 Exon 20 inhibitors: - Mobocertinib - Poziotinib
***ROS1* gene rearrangements**	Different fusion partners	0.7–1.7%	Crizotinib* Ceritinib Repotrectinib Taletrectinib
***RET* gene rearrangements**	RET-KIF5B	1–2%	Selpercatinib (LOXO-292) BLU-667
***MET* alterations**	MET amplification Exon 14 skipping mutations	4–5% 2–4%	Crizotinib Capmatinib Tepotinib
***NTRK* gene fusions**	NTRK 1, 2, 3 with different fusion partners	0.2%	Entrectinib Larotrectinib*

References to the frequencies of the genomic alterations can be found in the text. The frequencies vary greatly. The values given here refer to a Caucasian population. *Approval by Swissmedic (as of August 2020) for first- and/or further line treatment. For the exact approval text and conditions for reimbursement, we refer to the published scientific information (specialty list).

MOST COMMON GENOMIC ALTERATIONS WITH ONCOGENIC CHARACTER

The prerequisite for discussion of the best possible therapy option for patients with stage IV NSCLC, ideally performed at a multidisciplinary round or precision medicine conference, is the availability of molecular and immune biomarkers provided by molecular pathology. Testing for molecular markers should be performed in appropriate patients. Testing for molecular markers (gene mutations, translocations, and fusions) uses broad molecular profiling systems. These systems, particularly next-generation sequencing, are not subject of this review and have been described elsewhere.[8,9] The prevalence of genomic alterations depends on clinical variables (e.g., sex, race, smoking status) and tumor-associated factors such as histology (e.g., AC) and stage (e.g., early-stage vs advanced/metastatic stage).[4,10] The most important oncogenic alterations discussed in this review are KRAS, EGFR, BRAF, and HER2 mutations, ALK, ROS1, and RET gene rearrangements, MET alterations including MET amplifications and MET exon 14 skipping mutations and NTRK gene fusions. While *KRAS* mutations are the most prevalent oncogenic alterations in advanced/metastatic AC (up to 30%), the incidence of *EGFR* mutations is highly dependent on the tested population.[7,11] Both *BRAF* mutations and *ALK* rearrangements account for approximately 5% of all oncogenic alterations in AC. Other oncogenic alterations are rare to very rare.[12]

KRAS MUTATIONS

KRAS (Kirsten rat sarcoma viral oncogene homolog) oncoprotein is a GTPase and an essential mediator of intercellular signaling pathways, including the RAF-MEK-ERK (MAPK) pathway, involved in cell growth and survival.[13,14] *KRAS* mutations are detected in approximately 20-25% of AC and 4% of SCC.[4,12] Contrary to most of the other oncogenic driver mutations, *KRAS* is more often found in smokers and is detected at a lower frequency in East Asian patients.[15,16] *KRAS* mutations most often occur in codons 12 and 13 and with a lower frequency in codon 61.[4] The most predominant mutations being *KRAS* G12C, G12V, and G12D.[17] The *KRAS* G12C mutation is present in approximately 13% of NSCLC.[18] *KRAS* mutations do generally not overlap with other oncogenic mutations. Increasing evidence is showing that *KRAS*-mutated NSCLC does not represent a homogeneous group. In smokers, there are co-occurring mutations in *TP53* and *STK11*.[19]

Although various attempts inhibiting *KRAS* have been made, there is no established therapy for this large patient subpopulation. So far, the most promising approach was the combination of MEK-inhibitors with chemotherapy.[20–22] However, a randomized phase III study combining selumetinib with docetaxel did not confirm the positive phase 2 data.[23] Within the Swiss Group for Clinical Cancer Research (SAKK) network, we have investigated the combination of the MEK-inhibitor binimetinib with cisplatin/pemetrexed as first-line therapy in a phase I/II study (NCT02964689). This study has completed accrual, and results are pending.

Very recently, encouraging signs of efficacy based on preclinical evidence have been observed for two newly developed specific *KRAS* G12C inhibitors. The first molecule, AMG 510 (sotorasib), has shown promising activity and an acceptable safety profile in the phase I trial in pretreated patients with *KRAS* G12C mutated solid tumors.[24] Early clinical trial results from a subset of 34 patients with NSCLC were presented at the International Association for the Study of Lung Cancer (IASLC) 2019 World Conference on Lung Cancer (WCLC).[25] Among the 13 patients who received the established target dose of 960 mg and were evaluable for efficacy analysis, seven (54%) achieved a partial response, and six (46%) a stable disease. There were no dose-limiting toxicities or adverse events leading to discontinuation in the 34 enrolled patients. The second KRAS G12C inhibitor that is currently studied in a phase I/II trial (NCT03785249) is MRTX849. Recently published results showed that MRTX849 induced promising tumor regression in xenograft models from multiple tumor types. Early clinical findings suggest activity in patients with NSCLC and colorectal cancer with KRAS G12C mutations.[26]

Numerous clinical trials with these new KRAS-inhibitors are ongoing. The CodeBreak 200 study (NCT03600883) is a randomized phase III trial comparing AMG 510 to docetaxel in previously treated patients with NSCLC harboring a KRAS G12C mutation. This study is currently recruiting in several centers in Switzerland. As KRAS mutations are the most common oncogenic alterations in NSCLC, the results of these trials are eagerly awaited. An effective therapeutic approach for this subset of tumors would have a significant impact on patients. So far, targeted therapies for KRAS mutations are not available outside of clinical trials. Referral of patients to study sites is therefore highly recommended.

EGFR MUTATIONS

Epidermal growth factor receptor (EGFR) is the best known and established oncogenic target in advanced/metastatic NSCLC.[5,6] Different EGFR-TKIs have been developed, demonstrating high activity in patients with NSCLC bearing sensitizing EGFR mutations. Efficacy has been shown for the first-generation TKIs erlotinib[27,28] and gefitinib,[5,6,29,30] and the second-generation TKIs afatinib[31] and dacomitinib.[32] Results from the phase III FLAURA study have established osimertinib

as the new standard first-line therapy.[33,34] The FLAURA study included previously untreated patients with locally advanced or metastatic NSCLC harboring a sensitizing *EGFR* mutation. Patients were randomized 1:1 to receive either osimertinib or the first-generation TKIs erlotinib or gefitinib. Patients with disease progression under standard TKI were allowed to cross-over to osimertinib. The primary endpoint, progression-free survival (PFS), was significantly improved (median PFS 18.9 vs 10.2 months).[33] Both ORR (80% vs 76%) and the median duration of response (17.2 vs 8.5 months) were higher with osimertinib. The final OS analysis was presented at the 2019 European Society of Medical Oncology (ESMO) congress, where median OS improved in the osimertinib arm (38.6 months) compared to older generation EGFR-TKIs (31.8 months). Patients remained longer on osimertinib therapy (70% vs 47% after 12 months), and time to first subsequent treatment was significantly prolonged with osimertinib (25.4 vs 13.7 months). Importantly, 30% of patients in both treatment arms received no subsequent anti-cancer therapy. Finally, 30% of patients in the comparator arm crossed over to osimertinib.

A comprehensive review on *EGFR*-mutated NSCLC highlighting the current state-of-the-art treatment and unsolved questions has been recently published in this journal.[35]

ALK GENE REARRANGEMENTS

Anaplastic lymphoma kinase (ALK) is a transmembrane tyrosine kinase receptor that is expressed in neural tissue, the small intestine, and the testes and plays a crucial role in the development of the central nervous system.[36] The ALK receptor is activated after ligand binding to the extracellular receptor domain and dimerization.[37] The *EML4-ALK* fusion gene arises from an inversion on the short arm of chromosome 2. Several variants of *EML4-ALK* have been described that encode the same cytoplasmic tyrosine kinase domain of ALK with different truncations of *EML4*.[38,39] Aberrant ALK activation leads to an activation of multiple downstream signaling pathways, primarily the PI3K/mTOR and RAS/RAF/MAPK cascade.[40–42] *EML4-ALK* rearrangement in patients with NSCLC is a relatively rare event, is present in approximately 2–8% of NSCLCs,[37,43,44] and is most commonly seen in younger patients with AC histology and no or light smoking history. *ALK* rearrangements and other oncogenic drivers, such as mutant *EGFR* and oncogenic *RAS*, are generally mutually exclusive, consistent with the notion that *ALK* rearrangement defines a unique molecular subset of NSCLC.[45]

Crizotinib

The ALK-TKI, crizotinib, was the first targeted drug showing clinical activity in this patient population with response rates similar to what has been seen in *EGFR* mutant NSCLC with EGFR-TKIs.[46] The PROFILE 1007 trial was the first randomized phase III trial for *ALK*-positive patients.[47] Here, 347 patients with *ALK*-positive NSCLC, previously treated with chemotherapy, were randomized between crizotinib and chemotherapy (pemetrexed or docetaxel). ORR for crizotinib was 65% compared to 20% in the chemotherapy group. The primary endpoint of PFS was prolonged from 3 months with chemotherapy to 7.7 months for patients treated with crizotinib. Furthermore, the PROFILE 1014 trial included 343 chemotherapy-naïve *ALK*-positive patients randomized to crizotinib or platinum-based chemotherapy.[48] PFS was significantly longer with crizotinib (10.9 vs 7.0 months), however, cross-over in this trial was allowed which likely explains the lack of OS benefit observed for crizotinib (not reached vs 47.5 months, HR 0.76, p=0.0978).[49]

Despite the high response rate of crizotinib, most patients eventually relapse. To overcome crizotinib-resistance, newer, more specific ALK-inhibitors have been developed, including ceritinib, alectinib, brigatinib, and lorlatinib.

Ceritinib

Ceritinib, an oral TKI against ALK and ROS1, demonstrated activity in patients with *ALK*-rearranged NSCLC who had progressed on crizotinib. In the phase II ASCEND-2 trial, patients who have been previously treated with at least one platinum-based chemotherapy and progressed on crizotinib achieved an ORR of 38.6%.[50] The duration of response was 9.7 months, and common adverse events included nausea (81.4%), diarrhea (80.0%), and vomiting (62.9%). In the ASCEND-4 trial, ceritinib was compared to platinum-based chemotherapy as first-line therapy,[51], which improved PFS (16.6 months vs 8.1 months, respectively). The ASCEND-8 trial assessed whether a lower dose of ceritinib (450 mg or 600 mg, taken with a low-fat meal) improved gastrointestinal tolerability compared to the standard dosing.[52,53] The ORR in the three arms (450mg fed/600mg fed/750mg fasted) were comparable (72-78%), however, while the gastrointestinal toxicity was the lowest in the 450mg-arm, the frequency remained high (75.9%). Finally, ceritinib has not been compared to other ALK-TKIs.

Alectinib

Three randomized phase III studies compared alectinib to crizotinib. J-ALEX randomized 207 Japanese treatment-naïve *ALK*-positive NSCLC patients to alectinib in a lower than the standard dose of 300 mg bid vs crizotinib and showed a median PFS of 34.8 months vs 10.9 months.[54] In this study, cross-over was allowed. HR for OS was 0.80. ALEX, an international

phase 3 randomized trial, assessed first-line therapy with alectinib (600 mg bid) versus crizotinib in 303 patients with untreated ALK-positive NSCLC.[55] PFS, the primary endpoint of the trial, was found to be significantly higher with alectinib compared to crizotinib (HR 0.47). Updated results confirmed the significant improvement in PFS.[56] Median PFS with alectinib was 34.8 months, compared to 10.9 months with crizotinib. The median OS with alectinib treatment was still not reached in an updated analysis in 2020.[57] Fewer patients receiving alectinib had CNS progression compared to crizotinib (12% vs 45%), and objective responses were achieved in 83% of patients in the alectinib group, versus 76% in those with crizotinib treatment. The safety profile was more favorable with alectinib compared to crizotinib (41% vs 50% grade 3 to 5 adverse, respectively). These results were confirmed in the Asian ALESIA study with a significant overall survival benefit.[58]

Brigatinib

In the phase II ALTA study, 222 pretreated *ALK*-positive patients received brigatinib at two-dose levels.[59] Objective response was observed in 53% of patients with a disease control rate (DCR) of 92% and a high intracranial response rate, median PFS was 15.6 months, and 80% 1-year-OS. The phase III ALTA-1L trial assessed brigatinib versus crizotinib as first-line therapy for patients with *ALK*-positive NSCLC.[60] Objective responses were achieved in 71% of patients with brigatinib and in 60% with crizotinib. The intracranial response was also increased with brigatinib (78%) compared to crizotinib (29%). The rate of PFS at 12 months was higher with brigatinib (67%) than for patients receiving crizotinib (43%).

Lorlatinib

Lorlatinib has shown activity in ALK-TKI pretreated patients with a significant response for brain metastases.[61] In this phase II trial, patients have received at least one previous ALK inhibitor; lorlatinib led to an ORR of 47%. In patients with measurable baseline CNS metastases, an objective intracranial response of 63% was achieved with grade 3 to 4 adverse events, including hypercholesterolemia (16%), hypertriglyceridemia (16%) and central nervous system affection (cognitive effects, 1%). Lorlatinib, in a randomized phase III study, is currently being investigated in the first-line setting compared to crizotinib (CROWN, NCT03052608). Recently, Pfizer announced that the primary endpoint of the study was met.[62] The results have not yet been published.

Entrectinib

Entrectinib is an inhibitor of ALK, ROS1, and pan-TRK and has shown activity in *ALK*-positive NSCLC in early phase studies.[63] Entrectinib is currently investigated in a randomized study versus crizotinib in the first-line treatment setting of *ALK*-positive NSCLC (NCT02767804).

Among the above-mentioned ALK-inhibitor, there has been Swissmedic-approval for crizotinib[64], ceritinib,[65] alectinib[66] and newly also for lorlatinib.[67]

BRAF MUTATIONS

v-Raf murine sarcoma viral oncogene homolog B (BRAF) is a serine/threonine kinase that is part of the MAP/ERK signaling pathway. Activating point mutations in *BRAF* result in unregulated signaling via the MAP/ERK pathway. *BRAF* mutations have initially been described in malignant melanoma, where 40–60% of tumors harbor an activating *BRAF* V600E mutation (64). Subsequently, *BRAF* mutations have also been detected in colorectal cancer, papillary thyroid cancer, and other solid tumors.[68–70] *BRAF* mutations are found in 1–5% of lung AC, half of them harboring the classical V600E mutation.[71,72] Other mutations occur within exons 11, and 15.[72] *BRAF* V600E mutations are associated with light/never smoker status, micropapillary histology, and occur more frequently in female patients. On the contrary, non-V600E mutations are more frequent in former or current smokers and are associated with poorer outcomes.[72,73] The presence of the *BRAF* V600E mutation is associated with response to BRAF- as well as combined BRAF- and MEK-inhibitors.

Single-agent dabrafenib was initially tested in *BRAF* V600E mutated NSCLC.[74] The ORR was 33% with a disease control rate (DCR) of 57% in the pretreated group of patients, and median PFS was 5.5 months. Another BRAF-inhibitor, vemurafenib was tested as a monotherapy in a basket study of *BRAF* V600E non-melanoma cancers.[75] Twenty patients with *BRAF* V600E mutated NSCLC were included in this study, in which ORR was 42% and median PFS 7.3 months. The efficacy of combined treatment with the BRAF-inhibitor dabrafenib and the MEK 1/2-inhibitor trametinib has been demonstrated in two pivotal phase II trials.[76,77] In a previously untreated population, ORR for the combination treatment was 64%, while reaching an ORR of 63% as a subsequent treatment line. The median PFS was 10.9 months (untreated patients) and 9.7 months (pretreated). Considerable toxicity was reported: serious adverse events (grade 3–4) occurred in 69% and 56% of patients, respectively, including pyrexia (11–16%), hypertension (11%), and elevated liver enzymes (11%).

The combination treatment has been approved for the treatment of patients with *BRAF* V600E mutation-positive advanced or metastatic NSCLC. No data exists to support the use of BRAF/MEK inhibitors for non-V600E mutations, and chemotherapy or immunotherapy remain the preferred

options. In contrast to other NSCLC with oncogenic driver alterations, immune checkpoint inhibitors appear to be active in patients with *BRAF* mutated NSCLC.[78]

HER2 ALTERATIONS

Human epidermal growth factor receptor 2 (HER2), also known as ERBB2, is a member of the ERBB receptor tyrosine kinase family that is activated by homo- or heterodimerization. In breast cancer, *HER2* amplification occurs in about 20% of patients and is a predictive marker for anti-HER2 antibodies and TKIs.[79–81] In NSCLC, amplification of *HER2*, detected by fluorescence in situ hybridization (FISH), is found in 2–4% of patients. HER2 overexpression by immunohistochemistry is detected in 13–20% of NSCLC patients, although strong expression is only found in 2–4%.[82,83] *HER2* aberrations are more prevalent in AC histology, and, as shown in a meta-analysis, amplification is a negative prognostic marker.[84] Although about 1–2% of AC patients harbor mutations in exon 20 of *HER2*,[85–87] these mutations are not clearly associated with *HER2* amplification.

Anti-HER2 therapies have not shown efficacy in HER2-amplified NSCLC.[88–90] However, in the European cohort study EUHER, AC with HER2 mutations were shown to be responsive to HER2-targeted therapies with an ORR of 50% and a DCR of 83%.[91] In patients treated with chemotherapy in combination with an anti-HER2 therapy, DCR was 93%, and median PFS was 5.1 months. Trastuzumab in combination with paclitaxel has shown activity in EGFR mutated NSCLC that express HER2 after progression on EGFR TKI treatment.[92] Afatinib, a TKI with activity against ERBB family members is approved for *EGFR*-mutated AC and has shown clinical activity in lung cancer patients harboring a *HER2*-mutation even after failure of other EGFR- or HER2-targeting therapies.[91,93] Neratinib is an irreversible pan-HER inhibitor showing clinical activity in *HER2*-mutated NSCLC patients in a phase I trial combined with the mTOR inhibitor temsirolimus.[94]
Better clinical activity in patients with *HER2*-mutated NSCLC has been shown with HER2-directed antibody-drug conjugates. While trastuzumab emtansine has only shown limited activity in NSCLC,[95] there have been better results with ado-trastuzumab emtansine (T-DM1), resulting in an ORR of 44% and a median PFS of 5 months in a study of 18 NSCLC patients with *HER2* mutations.[96] Recently presented data on the novel antibody-drug conjugate trastuzumab deruxtecan have demonstrated an even better clinical activity.[97] Treatment with trastuzumab deruxtecan led to an ORR of 61.9% and a PFS of 14 months.

Interesting results are expected from TKIs that selectively target both *EGFR* exon 20 insertions and *HER2* exon 20 mutations. A first agent, mobocertinib, has been tested in a phase I/II trial (NCT02716116), including a cohort of patients with *HER2* exon 20 mutations. For patients with an *EGFR* exon 20 insertion mutation, mobocertinib produced an ORR of 43%.[98] However, poziotinib, another TKI targeting *EGFR*, and *HER2* exon 20 mutation has shown disappointing results (ORR 15%) in patients with NSCLC with *EGFR* exon 20 insertions.[99] Currently, there are no approved HER2-directed agents in clinical practice.

ROS1 GENE REARRANGEMENTS

The c-ros oncogene 1 (*ROS1*) encodes a tyrosine kinase receptor from the insulin receptor family. A rearrangement of *ROS1* has initially been described in glioblastoma.[100–102] In 2007, *ROS1* rearrangement was found in NSCLC cell lines and primary tumors.[103] *ROS1* fusion partners include *SLC34A2, CD74, TPM3, SDC4, EZR, LRIG3, KDELR2*, and *CCDC6*.[39] A *ROS1* rearrangement has been described in 0.7–1.7% of NSCLC patients.[39,104,105] Similar to previously described oncogenic aberrations in lung cancer, *ROS1* translocation is predominantly found in younger patients with AC histology who are either never, or former light, smokers. The phase I PROFILE 1001 study investigated crizotinib, a tyrosine kinase inhibitor of ALK, ROS1, and MET, against platinum-based chemotherapy in patients with *ALK*-positive NSCLC.[48] An expansion cohort of this trial included patients with *ROS1* rearranged NSCLC (102). Crizotinib demonstrated a very effective and durable anti-tumor activity.[106] Updated results reported an ORR of 72%, a DCR of 90%, a median PFS of 19.3 months,[107] and mOS of 51.4 months. The robust anti-tumor activity has been confirmed in two prospective phase II studies (ORR 70% and 69%, respectively)[108,109] and in the retrospective EUROS1 study (ORR 80%).[110]

Ceritinib, an ALK and ROS1 inhibitor, was investigated in a Korean phase II study, where 32 patients with *ROS1*-rearranged advanced NSCLC were treated.[111] The ORR reached 62% in the 28 patients with response-evaluable disease. The median PFS was 9.3 months for all patients and 19.3 months for crizotinib-naïve patients. For entrectinib, a multikinase inhibitor, pooled analysis from three trials (STARTRK-2, STARTRK-1, and ALKA-372-001) showed an ORR of 77%[112] and grade 3 to 4 adverse events were seen in 34% of patients. Activity against ROS1 has also been described for lorlatinib.[113] In *ROS1*-positive patients, including seven crizotinib-pretreated patients, an objective response was achieved by 6 of 12 patients (ORR 50%).

Two newer inhibitors have been evaluated in phase I studies for *ROS1*-positive NSCLC. In the TRIDENT-1 study,

repotrectinib was investigated in 29 *ROS1*-positive NSCLC patients, ORR was 70% among TKI-naïve patients, and 11% among TKI-refractory patients.[114] Taletrectinib is an orally available and potent selective small-molecule inhibitor of ROS1 and NTRK and has also shown activity in NSCLC patients with *ROS1* fusion.[115,116] In Switzerland, the only approved TKI for *ROS1*-rearranged NSCLC is crizotinib.

RET GENE REARRANGEMENTS

Rearranged during transfection (*RET*) is a receptor tyrosine kinase and a known oncogene in thyroid cancer, where translocations, as well as activating mutations, have been detected.[117,118] The most common *RET* alterations in NSCLC are gene rearrangements (fusions) between the *RET* gene and other partners, the most common being kinesin family 5B (KIF5B).[119] They are found in 1–2% of lung cancers (mostly AC) and are mutually exclusive with other oncogenic drivers.[120] Patients with *RET*-rearranged NSCLC are commonly never- or light-smokers.[121]

Different non-selective RET-inhibitors have been assessed retrospectively in a large international registry of patients with NSCLC harboring *RET*-fusions.[122] In this trial, the response rates for cabozantinib, vandetanib, and sunitinib were 37%, 18%, and 22%, respectively. The limited clinical activity was confirmed for cabozantinib[123,124] and vandetanib[125] in prospective clinical trials leading to an ORR of 28% and 18%, respectively. Both multikinase inhibitors were associated with a high rate of adverse events requiring dose reductions.

Greater efficacy and a better safety profile have been demonstrated with two new selective RET-inhibitors: selpercatinib (LOXO-292) and BLU-667. Selpercatinib, has been investigated in phase I/II Libretto-001 study, with a cohort of patients with *RET* fusion-positive NSCLC (n=247).[126,127] Among the primary analysis set of patients with prior platinum-based treatment, the ORR of selpercatinib was 70%, whereas treatment-naïve patients had an ORR of 88%. Only 3 of 247 patients (1.2%) discontinued treatment for adverse events. Selpercatinib showed a high intracranial response (81.8%), where the median duration of intracranial response was 9.4 months.[128] Selpercatinib is currently investigated in a randomized phase III study versus standard first-line chemoimmunotherapy (LIBRETTO-431, NCT04194944).

BLU-667 is currently being investigated in the phase I/II trial, ARROW (NCT03037385), which enrolled patients with *RET* fusion-positive NSCLC. The first results were presented at the 2019 American Society of Clinical Oncology (ASCO) annual meeting.[129] Of the 57 response-evaluable patients with measurable disease, and at least one follow-up disease assessment, the ORR of BLU-667 was 56%. Furthermore, the response rate was 60% among 30 patients with prior platinum-based treatment. Treatment tolerance was good with low-grade and reversible side effects (38% grade 3+ adverse events). Only 3% of the patients discontinued the treatment due to a drug-related adverse event. Finally, BLU-667 has demonstrated central nervous system activity. In Switzerland, selpercatinib is available through a market access study (NCT03906331) currently running at Kantonsspital Luzern. The approval for selpercatinib is expected in 2021.

MET ALTERATIONS

Mesenchymal-epidermal transition (MET) is a receptor tyrosine kinase, which undergoes homodimerization by binding its ligand, hepatocyte growth factor (HGF). Homodimerization and autophosphorylation of MET lead to the activation of various intracellular signaling pathways including RAS-RAF-MAPK, and PI3K-AKT-mTOR.[130] Gain-of-function alterations of *MET* can occur by gene amplification or by MET exon 14 skipping mutations, which impairs the degradation of MET receptors.[131] In NSCLC, *MET* exon 14 skipping mutations occur in 2–4% of patients with AC, but have been described in up to 30% of pulmonary sarcomatoid carcinoma.[132,133] *MET* exon 14 skipping mutations are more frequent in former smokers and in predominantly older female patients.[131] The prevalence of MET amplification is reported to be 4–5%.[133,134] However, it is much more frequent as a resistance mechanism as for example, in *EGFR* mutated NSCLC treated with EGFR-TKI. Crizotinib, capmatinib, and tepotinib are active drugs in patients with tumors harboring *MET* alterations. Crizotinib, a non-selective MET-inhibitor, has demonstrated clinical efficacy both for *MET* amplifications and *MET* exon 14 mutations. Crizotinib has been tested in 69 patients with advanced NSCLC harboring *MET* exon 14 alterations in the phase I/II PROFILE 1001 trial.[135] Most of the included patients (62%) had more than one previous treatment line. The ORR for crizotinib was 32%, and the median PFS was 7.3 months. Responses to crizotinib have also been observed in tumor with high-level *MET* amplification.[136]

Capmatinib, a selective MET-inhibitor, has been evaluated in the multicenter, multi-cohort GEOMETRY mono-1 phase II trial.[137] This trial has included patients with advanced NSCLC with *MET* gene copy number gain and/or *MET* exon 14 mutations. In treatment-naïve patients with NSCLC bearing *MET* exon 14 mutations, capmatinib led to an ORR of 68%, median duration of response (mDOR) of 11.1 months, and a median PFS of 9.7 months, while previously treated patients had an ORR of 41%, a mDOR of 9.7 months and a mPFS of 5.4 months.[138] The intracranial activity in both cohorts was 54% with a favorable safety profile. Most common treat-

ment-related adverse events across all cohorts (n=334) were peripheral edema (41.6%), nausea (33.2%), increased blood creatinine (19.5%), and vomiting (18.9%).

Tepotinib is another small molecule MET-inhibitor. VISION, a multicenter, multi-cohort phase II trial, assessed tepotinib in patients with locally advanced or metastatic NSCLC with *MET* exon 14 skipping mutation and *MET* amplifications.[139] Among 152 patients with *MET* exon 14 skipping mutations treated with tepotinib, 99 were included in the efficacy population. The ORR in this patient group was 46%, mDOR reached 11.1 months, and median PFS 8.5 months. Activity in patients with brain metastases was observed (intracranial ORR 55%), with a comparable safety profile to capmatinib.Other MET-inhibitors that are currently tested in clinical studies include telisotumzumab vedotin (NCT03539536) and savolitinib (NCT03778229). Currently, there is no Swissmedic approved MET-inhibitor.

NTRK GENE FUSIONS

Neurotrophic tyrosine receptor kinase (*NTRK*) genes encode tropomyosin receptor kinase (TRK) fusion proteins that act as oncogenic driver in different types of tumors.[140] Numerous fusion partners have been identified. *NTRK* fusions occur very rarely in patients with NSCLC (0.2%) and do generally not overlap with other oncogenic drivers.[141] Different multikinase agents display some activity against TRK (e.g., cabozantinib, crizotinib, nintedanib), but the most potent inhibitors of TRK fusion proteins are the first-generation TRK tyrosine kinase inhibitors, larotrectinib, and entrectinib. Larotrectinib (LOXO-101) and entrectinib (RXDX-101) have both been tested in a tumor-agnostic setting. Larotrectinib in an adult phase I trial, a pediatric phase I/II trial (SCOUT), and an adult/adolescent phase II basket trial (NAVIGATE).[142] The first publication reported on 55 patients with *NTRK* gene fusion-positive disease across a range of tumors with an ORR of 75%. Of note, this study included patients with 17 different malignancies and only 4 patients with NSCLC. In a recent update, results from 159 patients (including 12 patients with lung cancer) were presented.[143] ORR was 79% in the whole population and 73% in adult patients. Tumor response was seen irrespective of tumor type. Based on RECIST criteria, 9 out of 12 lung cancer patients (75%) did show a response. Larotrectinib showed good tolerability, with only very few serious adverse events (anemia, liver enzyme elevation, fatigue) and a low rate of patients who discontinued (2%) or reduced the dose (8%) of the drug due to treatment-related adverse events.

Entrectinib was tested in an adult phase I trial (ALKA-372-001), an adult phase I trial (STARTRK-1), a phase II basket trial (STARTRK-2), and a phase I/II pediatric trial (STARTRK-NG).[63,144,145] So far, entrectinib showed an ORR of 57%.[146] Again, response occurred regardless of tumor type. The mDOR was 10 months. Similar to larotrectinib, entrectinib showed a favorable safety profile. Currently, 2nd-generation NTRK-inhibitors, for example, repotrectinib (NCT04094610, NCT03093116) and selitrectinib (NCT03215511), are investigated in clinical studies. In May 2020, larotrectinib was approved by the Swissmedic for *NTRK* fusion-positive tumors, while entrectinib was approved in August 2020 by the EMA.[147,148]

CONCLUSIONS

Recent developments in the subgroup of NSCLC with oncogenic driver alterations, highlighted in the present review, have brought a significant clinical patient benefit and established an individualized treatment approach. The treatment landscape of oncogenic-addicted NSCLC is becoming increasingly complex. The choice of the optimal treatment strategy and management of TKI-therapy, including adverse events, requires expertise and a multidisciplinary approach. While further progress is expected, the prerequisite for this is an ongoing effort to include patients in clinical trials.

TAKE-HOME MESSAGES

- Non-small cell lung cancer (NSCLC) is a heterogeneous disease entity.
- Molecular characterization of NSCLC patients, in particular patients with adenocarcinoma, is a standard diagnostic procedure.
- Targeted therapies lead to high response rates and, in many subgroups to a significant and clinically relevant extension of progression-free time and overall survival compared to conventional chemotherapy.
- Current research in the field of targeted therapies in NSCLC focuses on the establishment of even more selective therapies and the understanding of resistance mechanisms, which in turn are accessible to a specific therapy.
- In order to make progress, especially in rare molecular subgroups and in the field of resistance mechanisms, it is essential to include patients in clinical studies.

CONFLICT OF INTEREST

David König (D.K.) received travel grants from Bristol-Myers Squibb (BMS) and Takeda.

Sacha Rothchild (S.R.) received honoraria (paid to institution) from AstraZeneca, BMS, Boehringer-Ingelheim, MSD, Novartis, and Roche; and received consultancy/advisory fees (paid to institution) from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Eli Lilly, Merck, MSD, Novartis, Pfizer, Roche, and Takeda. He received research funding from AbbVie, AstraZeneca, BMS, Boehringer-Ingelheim, and Merck. He received remuneration for travel and accommodation expenses from Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, MSD, and Takeda. S.R. serves as a member of the Federal Drug Commission of the Federal Office of Public Health (FOPH) and as a member of the board of the Swiss Group for Clinical Cancer Research (SAKK).

Author Contributions

D.K. and S.R. have written the manuscript.

Both authors have approved the final version for publication.

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