Oncogene addiction in non-small-cell lung cancer (NSCLC) has profound diagnostic and therapeutic implications. ALK, ROS1 and NTRK rearrangements are found in about 2–7%, 1–2% and 0.2% of unselected NSCLC samples, respectively; however, their frequency is markedly higher in younger and never-smoker patients with adenocarcinoma histology. Moreover, ALK, ROS1 and NTRK rearrangements are often mutually exclusive with other known driver alterations in NSCLC. Due to such a low frequency, diagnostic screening with accurate and inexpensive techniques such as immunohistochemistry is useful to identify positive cases; however, confirmation with fluorescent in situ hybridization or next-generation sequencing is often required due to higher specificity. In ALK-rearranged NSCLC, sequential treatment with second-generation and third-generation tyrosine kinase inhibitors leads to long-lasting disease control with most patients surviving beyond 5 years with metastatic disease. In ROS1-rearranged NSCLC, first-line treatment with crizotinib or entrectinib and subsequent treatment with lorlatinib at disease progression leads to similar results in patients with metastatic disease. NTRK1–3 fusions are extremely rare in unselected NSCLC. However, treatment with TRK inhibitors yields high response rates and durable disease control in most patients; diagnostic screening through multigene DNA/RNA-based next-generation sequencing testing is therefore crucial to identify positive cases.

This article is part of the Treatment of advanced non-small-cell lung cancer: one size does not fit all Special Issue: https://www.drugsincontext.com/special_issues/treatment-of-advanced-non-small-cell-lung-cancer-one-size-does-not-fit-all/

Keywords: ALK, lung adenocarcinoma, NSCLC, NTRK, ROS1, TKI.

Citation
Marinelli D, Siringo M, Metro G, Ricciuti B, Gelibter AJ. Non-small-cell lung cancer: how to manage ALK-, ROS1- and NTRK-rearranged disease. Drugs Context. 2022;11:2022-3-1. https://doi.org/10.7573/dic.2022-3-1

Introduction
Paper is divided into three sections for ALK, ROS1 and NTRK-rearranged disease. All the available treatments are evaluated with particular attention to the specific target.

ALK-rearranged NSCLC
Clinical and biological characteristics of ALK-rearranged NSCLC
Anaplastic lymphoma-kinase (ALK) rearrangements are detectable in approximately 2–7% of patients with non-small-cell lung cancer (NSCLC) with an estimated 40,000 cases annually worldwide. Patient characteristics are quite dissimilar from the overall patient population with NSCLC. They are generally younger (median age 52 years old), are never-to-light smokers and exclusively have adenocarcinoma histology, often with signet ring or acinar histopathological features. Ethnic differences amongst patients with lung cancer represent a critical issue in many aspects, including genetic characteristics, treatment response, drug toxicity and prognosis. ALK is a transmembrane receptor tyrosine kinase that belongs to the superfamily of insulin receptors. It activates multiple downstream pathways and may trigger neoplastic transformation. It catalyses the phosphorylation reaction of a tyrosine residue on a substrate protein that transmits ALK-mediated signals to downstream signalling pathways, even if the activation mechanism is not completely understood. ALK rearrangements, which cause overexpression of a constitutively active kinase, are amongst the most common targetable alterations in NSCLC.
The most common gene alteration is an intrachromosomal inversion within the short arm of chromosome 2, joining exons 1–13 of the EML4 gene to exons 20–29 of the ALK gene; the resulting EML4–ALK fusion protein contains an N-terminal portion encoded by EML4 and a C-terminal portion (intracellular signalling portion of the receptor tyrosine kinase) encoded by ALK. At least 15 EML4–ALK variants have been described in lung cancer with variants 1, 2 and 3a/b accounting for approximately 90% of them. The consequent chimeric protein activates multiple downstream known cancer signalling pathways such as PI3K–AKT, JAK–STAT and RAS–RAF–MEK–ERK. In addition, at least 20 different fusion partners have been reported, including TGF–ALK, KIF5B–ALK and STRN–ALK. Along with other kinase fusion-positive NSCLC tumours, ALK-rearranged tumours harbour a lower tumour mutational burden than kinase fusion-negative NSCLC.

Molecular diagnostics of ALK-rearranged NSCLC

Tumour tissue sampling has traditionally been the most widely used approach to detect ALK translocation. Diagnosis is made using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) or next-generation sequencing (NGS) of the tumour tissue. FISH is the diagnostic gold standard to detect rearrangements in the ALK locus. EML4 and ALK are only separated by 12.5 megabases on chromosome 2p; therefore, FISH can be prone to false negatives when used to detect this rearrangement. Moreover, FISH is useful to determine whether there is a break in the ALK locus but does not distinguish between different ALK fusion partners.

IHC is based on highly sensitive ALK antibodies to detect ALK-positive tumours. It is an inexpensive diagnostic technique that requires less expertise and is widely available in most hospital settings, giving results faster than FISH; however, as a diagnostic tool to measure ALK protein expression on tumour cells, IHC does not identify ALK fusion partners.

Molecular approaches for the detection of ALK fusions, such as quantitative reverse transcription PCR (qRT-PCR), can facilitate diagnosis by resolving discordant or borderline cases; however, qRT-PCR is unable to detect unknown variants and fusion partners. Amplicon-based NGS is able to detect fusions with known and unknown partners or an unknown breakpoint. NGS is also able to detect alterations in multiple driver genes at diagnosis and discriminates FISH-negative and IHC-positive cases. Moreover, tissue-based or plasma-based NGS is critical in the identification of on-target and off-target resistance mechanisms to ALK inhibitors.

Clinical activity of ALK-targeted therapies in NSCLC

Approximately 70% of patients with ALK-rearranged lung cancer develop intracranial metastases, with up to 30% with intracranial disease at the time of diagnosis with significant morbidity during their disease course (Table 1). The presence of rearrangements in the ALK locus renders the cancer sensitive to tyrosine kinase inhibitors (TKIs), which bind to receptor tyrosine kinases and inhibit the activation of downstream signalling pathways. The treatment landscape for ALK-rearranged lung cancer has evolved rapidly over the last years (Figure 1).

First-generation ALK TKIs

Crizotinib

The first-in-class TKI crizotinib showed significant efficacy in the PROFILE 1001 and PROFILE 1005 (phase I and II) trials, which reported median progression-free survival (PFS) of 8–10 months amongst participants with previously treated, ALK-rearranged NSCLC. The first phase III trial was PROFILE 1007, which compared crizotinib with chemotherapy (pemetrexed or docetaxel) in the second-line setting in patients with locally advanced or metastatic ALK-rearranged NSCLC after progressing on one prior platinum-based regimen. Median PFS was longer in the crizotinib arm (7.7 versus 3 months, HR 0.49), and the overall response rate (ORR) was 65% versus 20%; overall survival (OS) was not different between treatment arms likely due to the high rates of crossover to crizotinib in patients progressing on chemotherapy.

The phase III PROFILE 1014 trial compared crizotinib with standard platinum-based chemotherapy as first-line treatment for advanced ALK-rearranged NSCLC. Crizotinib showed longer PFS (median 10.9 versus 7 months in the chemotherapy arm) and higher ORR (74% versus 45%, respectively). Chemotherapy-related adverse events (AEs), such as fatigue, neutropenia and stomatitis, had a lower incidence in the crizotinib arm whilst low-grade vision disorders, diarrhoea and oedema were more frequent with crizotinib; however, hypertransaminasaemia was more common with crizotinib than with chemotherapy, with 14% of patients experiencing grade 3–4 AEs. A greater improvement in global quality of life (QoL) from baseline was seen amongst patients who received crizotinib than amongst those who received chemotherapy.

Although most patients with ALK-rearranged NSCLC respond to crizotinib, tumours inevitably relapse, often after only 1 or 2 years of treatment because of acquired resistance. About 70% of patients with central nervous system (CNS) metastases at baseline have brain progression, whilst about 20% of patients without CNS metastases at baseline develop them. Drug failure in the CNS is linked to a pharmacokinetic issue because crizotinib is a substrate for P-glycoprotein and showed significantly lower concentrations in cerebrospinal fluid (CSF) than in plasma.

Second-generation ALK TKIs

The second-generation ALK TKIs ceritinib, alectinib, brigatinib and ensartinib were developed to overcome acquired resistance to crizotinib and more efficiently penetrate the blood–brain barrier.
Ceritinib
Ceritinib is an ATP-competitive, highly selective ALK inhibitor and a potent inhibitor of IGFR1, ROS1 and insulin receptor but is not an efficient inhibitor of c-MET. It is 20 times more potent than crizotinib against ALK and is effective against the L1196M, G1269A, C1156Y, I1171T and S1206Y ALK-resistance mutations.

In the ASCEND-4 trial, ceritinib was compared to chemotherapy in patients with untreated, advanced ALK-rearranged NSCLC showing 72.5% ORR compared to 26.7% with chemotherapy, a median PFS of 16 months compared to 8 months with chemotherapy, and 73% intracranial response rate in patients with brain metastases at baseline. However, due to an unfavourable toxicity profile because of gastrointestinal side-effects and liver toxicity, ceritinib is not listed as a preferred option in the first-line setting.
**Alectinib**

Differently from crizotinib, alectinib does not inhibit MET and ROS1 but inhibits RET with a similar potency to ALK, which is five times higher than crizotinib.\(^9\) It targets several ALK mutations that confer resistance to crizotinib (L1196, the most common mutation in crizotinib-resistant specimens, C1156Y, F1174L, R1275Q and G1269A) and has improved penetration in the CNS because it is not a substrate of P-glycoprotein. Alectinib is a preferred choice in the first-line setting in ALK-rearranged NSCLC, but it is active both in crizotinib-naive and crizotinib-resistant ALK-rearranged tumours.

Alectinib was compared to crizotinib in Japanese patients in the ALEX trial (J-ALEX) showing a 92% ORR versus 79% with crizotinib and improved PFS (not reached versus 10.2 months).\(^30\) These results were confirmed in the Asian ALESIA trial and the global phase III ALEX trial, which compared alectinib with crizotinib, confirming a median PFS of 34.8 versus 10.9 months and an ORR of 83% versus 75%, respectively; the intracranial response rate was 81% with alectinib, with 38% of patients showing intracranial complete responses, and 50% with crizotinib.\(^31,32\) In the final results of the ALEX trial, the OS benefit of alectinib was evident across all patient subgroups with a 5-year OS rate of 62.5% versus 45.5%.\(^33\) Patients treated with alectinib had a lower incidence of CNS progression both in patients with and without baseline brain metastases; moreover, the intracranial response rate in patients with prior radiotherapy was 85.7% with alectinib and 71.4% with crizotinib, whilst it was 78.6% and 40% in patients without prior radiotherapy, respectively.\(^34\) Patients treated with alectinib had low rates of grade 3–4 hypertransaminasemia and an overall lower incidence of nausea, vomiting and diarrhoea when compared to patients treated with crizotinib.\(^35\) Furthermore, patients treated with alectinib showed improvements in lung cancer symptoms for longer than patients treated with crizotinib, with longer duration of clinically meaningful improvements in health-related QoL and better patient-reported tolerability.\(^35\)

**Brigatinib**

Brigatinib is a TKI with activity against ALK, ROS1, IGF1R and FLT3 as well as EGFR deletions and point mutations; it showed activity against multiple ALK-resistance mutations and a 12-fold higher potency than crizotinib against ALK.\(^36\) Brigatinib showed efficacy both in treatment-naive and in crizotinib-resistant ALK-rearranged tumours.\(^37\)

In patients with crizotinib-resistant, ALK-rearranged NSCLC, ORR was 62%, median PFS was 14.5 months and duration of response was 11.2 months.\(^38\) First-line brigatinib was compared with crizotinib in untreated, ALK-rearranged NSCLC in the phase III ALTA-1L trial; grade 3–4 increased blood creatine kinase levels, hypertension and increased lipase levels were more common with brigatinib than with crizotinib.\(^39\) In the final results of ALTA-1L, brigatinib showed median PFS of 24 versus 11 months for crizotinib, median intracranial duration of response in patients with measurable brain metastases at baseline of 27.9 versus 9.2 months with crizotinib, and the 3-year intracranial PFS rate was 31% with brigatinib and 9% with crizotinib (HR 0.29).\(^40\) Health-related QoL and multiple functional and symptom scales were improved in patients treated with brigatinib in the ALTA-1L trial when compared to patients treated with crizotinib.\(^41\)

**Ensartinib**

Ensartinib is a second-generation small-molecule TKI that selectively inhibits ALK with a potency more than 10 times greater than crizotinib. It also potently inhibits most common crizotinib-resistance mutations, including F1174, C1156Y, G1269A, L1196M, S1206R and T1151.\(^42\) Objective response with ensartinib was achieved in 52% of patients and median PFS was 9.6 months in patients with crizotinib-resistant, ALK-rearranged NSCLC.\(^43\)

The eXalt3 randomized phase III trial compared ensartinib with crizotinib amongst patients with previously untreated ALK-rearranged NSCLC. In the intention to treat population, the median PFS was significantly longer with ensartinib than with crizotinib (25.8 versus 12.7 months respectively, HR 0.51) and the intracranial response rate was 63.6% versus 21.1%, respectively, for patients with brain metastases at baseline. About 11% of patients treated with ensartinib had grade 3 rash, which was managed by drug withholding and dose reductions.\(^44\)

**Third-generation ALK TKIs**

**Lorlatinib**

Lorlatinib is a third-generation ALK inhibitor with activity against ALK and ROS1 as well as against TYK1, FER, FPS, TRK A/B/C, FAK, FAK2 and ACK; it was developed specifically to penetrate the blood–brain barrier and to overcome secondary resistance mechanisms emerging after treatment with first-generation and second-generation ALK inhibitors, including the G1202R mutation.

Lorlatinib has significantly improved (>50-fold) inhibitory potency and was initially tested in ALK-rearranged NSCLC population either with progression on crizotinib and at least one more ALK inhibitor or in patients with progression on either alectinib or ceritinib as first-line therapy.

Amongst 198 patients previously treated with one or more ALK inhibitors, ORR with lorlatinib was 47%; amongst patients who had failed two or more ALK TKIs, ORR was 39% and median PFS was 6.9 months. Furthermore, lorlatinib showed improved efficacy in patients with ALK-resistance mutations, with the most common being the ALK G1202R mutation; those findings suggested higher lorlatinib activity in ALK-rearranged tumours that have acquired on-target resistance mechanisms.\(^45\)

Recently, the phase III randomized CROWN trial compared lorlatinib with crizotinib in 296 patients with untreated, advanced and ALK-rearranged NSCLC. The results showed that median PFS was not reached with lorlatinib versus
Mechanisms of resistance to ALK inhibitors

As with most targeted therapies, resistance mechanisms to ALK inhibitors are broadly divided into on-target and off-target mechanisms.

As already discussed, whilst CNS progression on crizotinib may often be due to its lower concentrations in the CSF, on-target resistance mutations or ALK gene amplification typically arise in about one-third of crizotinib-resistant samples and in about half of alectinib/ceritinib-resistant specimens.47 On-target mutations highlight persistent ALK oncogenic activation evolving through different resistance mutations in time and space under selective pressure imposed by different ALK TKIs.48 Accordingly, lorlatinib efficacy is improved in patients with on-target mutations arising after treatment with first-generation or second-generation ALK TKIs; in more detail, lorlatinib retains activity against the G1202R mutation—the most common resistance mutations arising after treatment with second-generation ALK TKIs.49 However, sequential treatment with ALK inhibitors fosters the development of ALK compound mutations, leading to resistance to all available inhibitors.50 Compound mutations have the utmost frequency in extensively pre-treated, lorlatinib-resistant tumour specimens; nonetheless, off-target oncogenic drift due to the acquisition of bypass mechanisms of resistance can, at any time, override ALK-centred oncogene addiction, leading to multiple hard-to-treat resistance patterns.51 Fourth-generation ALK inhibitors are being developed to retain activity against compound ALK resistance mutations.52 Different fusion variants may also shape sensitivity to ALK TKIs and the emergence of ALK-resistance mutations.53–56

Suggested approach in ALK-rearranged NSCLC

First-line treatment with second-generation ALK TKIs is critical due to the highly relevant impact on survival and patient-related outcomes shown in multiple comparisons with crizotinib in phase III clinical trials. In case of asymptomatic CNS metastases, local therapy can often be deferred due to high intracranial response rates. However, local ablative therapies are a major treatment option both in cases of oligoprogressive disease in the brain and in cases of non-CNS oligoprogression, with the aim of maintaining the benefit from each ALK-directed line of treatment and to prolong time to chemotherapy.

Whilst lorlatinib showed major efficacy in the first-line setting, in the absence of head-to-head comparisons with second-generation ALK TKIs and whilst waiting for mature survival data, its most appropriate use may be after resistance to second-generation TKIs. However, results from the phase III CROWN study showed the highest efficacy amongst all ALK-directed TKIs; therefore, the optimal choice for first-line therapy in ALK-rearranged lung cancer remains unclear. As of May 2022, the NCCN NSCLC Panel lists alectinib, brigatinib and lorlatinib as preferred options for patients with ALK-rearranged metastatic NSCLC.57 Drug availability and drug pricing are an issue both in western and developing countries and can influence the choice of treatment, whilst long-term management of AEs is critical.

ALK tumours displayed poor sensitivity to single-agent immune-checkpoint inhibitors likely due to an unfavourable microenvironment.58 However, sensitivity to platinum/pemetrexed combination chemotherapy is retained both in tumours that are TKI naive and in those pre-treated with TKIs, and chemotherapy is a viable alternative at progression from all available ALK TKIs.59,60 Because ALK-rearranged tumours were excluded from most chemoimmunotherapy trials, chemotherapy/immunotherapy combinations are not indicated at the progression from ALK-directed therapies.61

Liquid biopsy was shown to be able to track the evolution of resistance to TKIs during therapy; blood-based monitoring of resistance mechanisms can provide critical information on treatment sequencing. However, broad standardization of techniques to monitor resistance is lacking, and such efforts should be limited to centres with significant expertise.

ROS1-rearranged NSCLC

The proto-oncogene ROS1 encodes a receptor tyrosine kinase with an unclear role in human physiology whose kinase domain is highly homologous with ALK; approximately 1–2% of NSCLC harbour ROS1 rearrangements.62,63 In the last 10 years, multiple TKIs have shown efficacy in ROS1-rearranged NSCLC, significantly reshaping the therapeutic landscape for patients harbouring this aberration.
Clinical and biological characteristics of ROS1-rearranged NSCLC

**ROS1** rearrangements in NSCLC occur predominantly in younger patients with adenocarcinoma histology and light or no smoking history; large cell and squamous histology are uncommon, and median age at diagnosis is 50 years.64 The spectrum of incidence is highly overlapping with **ALK**-rearranged NSCLC; in particular, **ROS1** fusions were described in 2.2% of never smokers, whilst **ALK** rearrangements were described in 5.6% of patients in the same cohort.65 About a third of treatment-naive patients with metastatic disease have brain metastases, and progressive disease in the CNS is found in up to 50% of patients pre-treated with TKIs.66 **CD74**–**ROS1** fusions displayed a higher frequency of CNS metastases when compared to non-**CD74** fusion partners; however, it is unclear whether fusion type affects CNS spread.67 Moreover, venous thromboembolic events are described in about 40% of patients with **ROS1**-rearranged NSCLC and are more frequent than in unselected patients with NSCLC.68,69 thus, specific attention to signs and symptoms of deep vein thrombosis and pulmonary embolism is needed in this subpopulation.

Heterogeneity in partner genes is described in solid tumours harbouring **ROS1** rearrangements; however, the most common fusions in NSCLC are **CD74**–**ROS1** (found in about 44% of patients), **EZR**–**ROS1** (16%), **SDC4**–**ROS1** (14%) and **SLC34A2**–**ROS1** (10%). The pattern of structural rearrangement involves loss of the extracellular **ROS1** domain and fusion of the kinase domain with the N-terminal portion of a partner gene.70 **ROS1**-rearranged tumours harbour a low tumour mutational burden;71 the co-occurrence of **ROS1** rearrangements with **EGFR** or **KRAS** mutations and **ALK** rearrangements in the same tumour is rare.72 Whilst **ROS1**-rearranged tumours may seldom show high PD-L1 expression, the efficacy of immune-checkpoint inhibitor monotherapy is likely to be modest.73

**Molecular diagnostics of **ROS1**-rearranged NSCLC**

Due to the rarity of **ROS1** rearrangements and the limitations associated with any diagnostic test, false-positive and false-negative results may occur.74 Break-apart FISH is regarded as a diagnostic gold standard: split probes binding to the 5’ and 3’ ends of **ROS1** or isolated 3’ signals in more than 15% of tumour cells on a minimum of 50 cells identify positive cases.74 RT-PCR detects known fusion patterns through specific primers;75 both FISH and RT-PCR were used to identify eligible patients in seminal trials.70 IHC is a useful screening tool for **ROS1** rearrangements due to its high sensitivity and specificity; however, confirmation by FISH or RT-PCR/NGS is required after IHC positivity, whilst IHC-negative cases can be interpreted as negative for **ROS1** rearrangements.76–83 DNA-based NGS is able to identify cases with negative results on non-NGS testing.84 RNA-based tests may further increase sensitivity due to the lack of coverage of introns inferred to be the site of the genomic breakpoints by DNA-based NGS and because high expression of the fusion mRNA can mitigate false-negative results of DNA-based NGS due to low tumour purity.85

Clinical activity of **ROS1**-targeted therapies in NSCLC

Crizotinib, a first-generation **ALK** TKI, showed efficacy against **ROS1**-rearranged NSCLC in the phase I PROFILE 1001 trial amongst 53 pre-treated patients, showing 72% ORR, median PFS of 19 months and a median OS of 51.4 months; median time to response was 7.9 weeks (Table 2).76,86 Similar results were confirmed in a single-arm, phase II trial amongst 127 East Asian pre-treated patients, with an ORR of 71.7% and median PFS of 15.9 months87 (Figure 2). Moreover, further phase II European trials (EUCROSS,88 Acé,89 METROS90) confirmed an ORR of 65–70%. Median PFS was 20 and 22.8 months for EUCROSS and METROS; however, despite a similar ORR, the Acé trial reported a median PFS of only 5.5 months in a more heavily pre-treated population with 25% of patients with ECOG PS2 amongst the **ROS1**-positive cohort. The intracranial efficacy of crizotinib is not well characterized in patients with **ROS1**-rearranged disease; intracranial ORR in the METROS trial was 33% (2 out of 6 patients). However, crizotinib CSF concentrations are low, and intracranial efficacy is inferior to second-generation and third-generation TKIs.23 Accordingly, **CNS** is a critical and frequent site of progression in patients positive for **ALK** and **ROS1** treated with crizotinib, even if **ROS1**-rearranged tumours seem to have decreased tropism for the brain when compared to **ALK**-rearranged tumours.91

Entrectinib is a TRK A/B/C, **ALK** and **ROS1** TKI with a 40-times greater potency than crizotinib in vitro in **ROS1**-rearranged cancer models.92 Moreover, it was developed to efficiently cross the blood–brain barrier.93 Results from two phase I trials (ALKA-372-001, STARTRK-1)94 and one phase II trial (STARTRK-2)95 are available. In a **ROS1** TKI-naïve population, entrectinib showed a 77% ORR amongst 53 evaluable patients; amongst 17 patients with CNS metastases at baseline, intracranial ORR was 55%, median PFS was 19 months in the overall population and 13.6 months in patients with baseline CNS metastases, and in patients without baseline CNS metastases, median PFS was 26.3 months.95 Thus, entrectinib compares favourably with crizotinib in a **TKI**-naïve population due to a greater efficacy shown in patients with CNS disease; however, due to its activity against tropomyosin receptor kinase (TRK), entrectinib showed a peculiar toxicity profile causing dizziness, weight gain, paraesthesias and cognitive changes.

The second-generation **ALK** and **ROS1** inhibitor ceritinib also showed efficacy in a **ROS1**-rearranged **TKI**-naïve population in a Korean phase II study on 32 patients;96 however, due to an unfavourable toxicity profile, crizotinib and entrectinib remain the preferred options in the **TKI**-naïve setting.
Lorlatinib is a third-generation ALK and ROS1 TKI with improved CNS activity due to high CSF fluid concentrations through the reduction of P-glycoprotein-mediated efflux. In a phase I/II study, lorlatinib showed a 62% ORR amongst 21 patients with ROS1-rearranged disease who were TKI naive and a 35% ORR amongst 40 patients pre-treated with crizotinib. Amongst patients with brain metastases, lorlatinib showed intracranial ORR in 64% of 11 TKI-naive patients and in 50% of 24 patients pre-treated with crizotinib. Median PFS was 21 months in TKI-naive patients and 8.5 months in patients pre-treated with crizotinib.

Repotrectinib is a next-generation TKI with efficient blood–brain barrier penetration, developed to inhibit both wild-type and TKI-resistant mutations. It showed a 66% ORR in TKI-naive patients and a 63% ORR in TKI-pre-treated patients.

Table 2. Clinical activity of ROS1 TKIs.

| ROS1 TKI   | Clinical trial                  | Setting                          | Outcomes                                      |
|-----------|---------------------------------|----------------------------------|-----------------------------------------------|
| Crizotinib| PROFILE 1001                    | Advanced ROS1+ NSCLC             | mPFS 19 months; mOS 51.4 months 72% ORR       |
| Crizotinib| NCT01945021                     | Advanced ROS1+ NSCLC             | mPFS 15.9 months; 71% ORR                     |
| Crizotinib| EUCROSS                         | Advanced ROS1+ NSCLC             | mPFS 16.8 months; 83.3% ORR                   |
| Crizotinib| Acse                            | Advanced ROS1+ NSCLC             | mPFS 5.5 months; mOS 17.2 months 69.4% ORR    |
| Crizotinib| METROS                          | Advanced ROS1+ NSCLC             | mPFS 22.8 months; mOS not reached; 65% ORR    |
| Entrectinib| ALKA-372-001, STARTRK-1, STARTRK-2 | Advanced ROS1+ NSCLC             | mPFS 19 months; mOS not reached 77% ORR; 55% intracranial ORR |
| Ceritinib | NCT01964157                     | Advanced ROS1+ NSCLC             | mPFS 9.3 months; mOS 24 months; ORR 62%       |
| Lorlatinib| NCT01970865                     | TKI-pre-treated ROS1+ NSCLC      | mPFS 21 months (TKI naive); mPFS 8.5 months (TKI pre-treated); 62% ORR (TKI naive); 35% ORR (TKI pre-treated) |
| Repotrectinib| TRIDENT-1                     | TKI-pre-treated ROS1+ NSCLC      | 86% ORR (TKI naive); 40–67% ORR (TKI pre-treated) |
| Taletrectinib| NCT02279433, NCT02675491       | TKI-pre-treated ROS1+ NSCLC      | 66% ORR (TKI naive); 33% ORR (TKI pre-treated) |

mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.
and solvent-front mutations involving ROS1, TRK A/B/C and ALK. In the phase I/II TRIDENT-1 trial, repotrectinib showed an ORR of 86% amongst 7 patients with ROS1-rearranged disease who were TKI naive and of 40–67% amongst patients pre-treated with TKIs. Taletrectinib is a pan-TRK and ROS1-selective inhibitor active against the ROS1 solvent-front mutation G2032R, which showed a 33% ORR and 88% disease control rate amongst six patients pre-treated with crizotinib and a 66% ORR in patients with ROS1-rearranged disease who were TKI naive.

**Mechanisms of resistance to ROS1 inhibitors**

An on-target G2032R resistance mutation shared amongst multiple metastatic sites was first described after treatment with crizotinib in a patient with ROS1-CD74 rearranged disease in 2013. On-target resistance mutations are the most common resistance mechanism to crizotinib, found in over 50% of patients, with ROS1 G2032R being the most frequent, causing steric interference with crizotinib and preventing effective binding. Amongst patients with CNS progression on crizotinib, it is likely that pharmacokinetic mechanisms leading to low CSF concentration may lead to resistance in the CNS rather than to on-target resistance mutations. There were no responses to lorlatinib amongst six patients pre-treated with crizotinib with on-target resistance mutations; ROS1 resistance mutations were also described in circulating tumour DNA samples after treatment with entrectinib. On-target resistance mutations were also observed in 46% of cases after treatment with lorlatinib, with G2032R found in 32% of the total cases and the discovery of compound resistance mutations (G2032R–L2086F, G2032R–S1986F–L2086F, S1986F–L2000V) in the same sample.

Off-target, ROS1-extrinsic resistance mechanisms were also described through downstream activating mutations on multiple kinases and epithelial-to-mesenchymal transition. Moreover, spatial and temporal heterogeneity can lead to the co-occurrence of multiple resistance mechanisms in the same patient both on-target and off-target.

**Suggested approach in ROS1-rearranged NSCLC**

In the first-line setting, both crizotinib and entrectinib are approved by the FDA andEMA in ROS1-rearranged NSCLC, and both are preferred drugs as per NCCN guidelines. In case of metastatic CNS disease, entrectinib is preferred over crizotinib due to its higher intracranial efficacy; in case of symptomatic CNS metastases, local control with surgery or radiotherapy is needed before treatment with entrectinib. In patients with no evidence of CNS metastases, crizotinib may be preferred due to a more favourable toxicity profile; however, careful monitoring of signs and symptoms of brain metastases is needed, along with contrast-enhanced brain computed tomography or magnetic resonance imaging. Oligoprogressive disease may be treated with local therapy. In case of systemic progression from first-line entrectinib or crizotinib, if available, lorlatinib is indicated. Enrolment in clinical trial therapy is strongly recommended for patients with ROS1-rearranged tumours.

**NTRK-rearranged NSCLC**

Encoded by NTRK genes, TRKs are critical in neuronal development and functioning and act as receptors for multiple neurotrophins. Chromosomal rearrangements involving NTRK1, NTRK2 or NTRK3 lead to constitutive downstream signalling and oncogenic TRK activation in a ligand-independent fashion. Whilst oncogenic NTRK rearrangements are pathognomonic amongst specific rare cancers, such as secretory cancers of the salivary gland, their frequency amongst the most common solid tumours is extremely low.

**Clinical and biological characteristics of NTRK-rearranged NSCLC**

NTRK1–3 rearrangements arise in 0.17–0.23% of unselected NSCLC, more commonly in non-smokers with adenocarcinoma histology and young age (median age 48 years); however, NTRK rearrangements are also identified in older patients or in patients with squamous cell or neuroendocrine histology. Similarly to ALK-rearranged and ROS1-rearranged tumours, NTRK-rearranged tumours exhibit a low tumour mutational burden. NTRK1 fusions were described in 3.3% of NSCLC samples negative for oncogenic alterations. Rearrangements occur through fusion of the 3’ NTRK1, NTRK2 or NTRK3 sequence with the 5’ sequence of a partner gene; partner genes are frequently characterized by oligomerization domains, which contribute to the oncogenic potential of the chimeric protein. The first to be described and most common fusion partner in adult NTRK-fusion-positive tumours is ETV6, followed by many others (TPM3, TPR, SQSTM1, IRF2BP2).

**Molecular diagnostics of NTRK-rearranged NSCLC**

Given the rarity of NTRK1, NTRK2 and NTRK3 rearrangements in NSCLC, broad molecular profiling through DNA-based or RNA-based NGS testing for multiple alterations is critical. Known fusions can be efficiently detected through amplicon-based DNA sequencing, whilst hybrid capture library preparation is able to detect both known and novel fusion partners; however, rearrangements involving intronic regions can lower DNA-based NGS sensitivity. DNA-based sequencing can detect chromosomal rearrangements, which may or may not lead to functional fusion transcripts, whilst RNA-based NGS is a critical tool for diagnosis of de novo, transcribed gene fusions.
Anchored multiplex PCR, amplicon-based multiplex PCR and hybrid capture-based RNA NGS provide high sensitivity and concordance and can detect gene rearrangements in samples that appear negative for driver mutations after DNA-based NGS. Nevertheless, the labile nature of RNA in formalin-fixed paraffin-embedded archival samples may lead to false-negative results. A parallel or sequential DNA-based and RNA-based NGS approach maximizes diagnostic sensitivity and appropriate evaluation of driver mutations. IHC screening is an inexpensive diagnostic tool; however, IHC staining patterns are not specific for NTRK rearrangements and can detect wild-type TRK expression. In case of positive results, confirmation with FISH or NGS is required.

Clinical activity of NTRK-targeted therapies in NSCLC

Larotrectinib is a first-in-class, highly selective TRK A/B/C inhibitor showing 75% ORR in TRK-fusion-positive cancers in adults and children. Amongst 20 heavily pre-treated patients with TRK-positive NSCLC with a median age at diagnosis of 48 years, larotrectinib showed a 73% ORR amongst 15 evaluable patients and 63% intracranial ORR amongst 8 evaluable patients. Median OS was 40.7 months.

As previously discussed, entrectinib is active both against ALK/ROS1 and NTRK-rearranged tumours. Amongst 54 adults with advanced NTRK-positive solid tumours entrectinib showed 57% ORR. Amongst 13 patients with NTRK-positive NSCLC, entrectinib showed a 69% ORR with a median PFS and OS of 14 months; amongst 8 patients with baseline CNS metastases, entrectinib showed a 63% intracranial ORR.

As the TRK pathway is involved in appetite, balance and pain sensitivity, TRK inhibitors frequently lead to on-target AEs such as dizziness, weight gain, withdrawal pain and paraesthesias. Weight gain and pain upon TRK inhibitor withdrawal were associated with longer treatment exposure, whilst dizziness showed a median time to onset of 2 weeks and was frequently managed with dose reductions. Paraesthesias often had a perioral distribution and were mostly mild in grade, often requiring no therapeutic intervention.

Mechanisms of resistance to TRK inhibitors

As with most TKIs, the emergence of on-target, solvent-front or gatekeeper mutations are major mechanisms of acquired resistance to TRK inhibitors; nonetheless, off-target activation of downstream pathways was also associated with therapeutic resistance. Next-generation TRK inhibitors were developed to address on-target resistance mechanisms such as repotrectinib and selitrectinib.

Suggested approach in NTRK-rearranged NSCLC

Whilst drug availability is an issue in some countries, patients with NTRK-rearranged metastatic NSCLC should be considered for treatment with a TRK inhibitor whenever possible, unless ongoing benefit from standard treatment is evident; entrectinib and larotrectinib are both listed as preferred first-line options for NTRK-rearranged NSCLC in the NCCN guidelines. Due to the extremely low frequency of NTRK rearrangements in NSCLC, comparisons with standard treatments are difficult; however, treatment with a TRK inhibitor should be preferred due to a favourable toxicity profile, higher CNS activity and the achievement of durable responses in most patients.

Conclusions

ALK-, ROS1- and NTRK-rearranged tumours represent a distinct clinical and molecular entity amongst NSCLC and have the highest frequency amongst young, non-smoker patients. Identification and proper treatment of ALK-, ROS1- and NTRK-rearranged tumours with specific inhibitors are critical due to the clinically relevant benefits in QoL, AEs and survival outcomes when compared to standard treatment for fusion-negative, advanced NSCLC.

Contributions: AG, DM and MS: conceptualization, writing of original draft and final editing. GM and BR: writing, review and editing. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published. The authors did not receive medical writing assistance.

Disclosure and potential conflicts of interest: AJ Gelibter received honoraria for advisory board involvement from Astra Zeneca, MSD, BMS, Roche and Boheringer. The authors declare that they have no other conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2022/09/dic.2022-3-1-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

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REVIEW – Non-small-cell lung cancer: how to manage ALK-, ROS1- and NTRK-rearranged disease

Article URL: https://www.drugsincontext.com/non-small-cell-lung-cancer-how-to-manage-alk-ros1-and-ntrk-rearranged-disease

Correspondence: Alain Gelibter, Division of Medical Oncology B, Policlinico Umberto I, Sapienza – Università di Roma, Rome, Italy.
Email: alain.gelibter@uniroma1.it

Provenance: Invited; externally peer reviewed.

Submitted: 3 March 2022; Accepted: 18 August 2022; Publication date: 12 October 2022.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 1003893. VAT GB 252 7720 07.

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