Review Article

Strategies to overcome resistance to ALK inhibitors in non-small cell lung cancer: a narrative review

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Background and Objective: Anaplastic lymphoma kinase (ALK) rearrangements are detected in 3–7% of advanced non-small cell lung cancer (NSCLC). There are currently 5 U.S Food and Drug Administration (FDA)-approved ALK tyrosine kinase inhibitors (TKIs) for the treatment of patients with ALK-positive lung cancer in the advanced/metastatic disease setting. Despite these advances, most patients with ALK-positive lung cancer who are treated with ALK TKI therapy ultimately experience disease progression due to various mechanisms of drug resistance. In this review, we discuss strategies to address acquired therapeutic resistance to ALK inhibition, novel agents and combinatorial strategies in development for both on and off-target resistance, and some emerging approaches to prolong response to ALK inhibitors.

Methods: We performed a search of peer-reviewed literature in the English language, conference abstracts, and trial registrations from the MEDLINE (Ovid), Embase (Elsevier), and CENTRAL (Cochrane Library) databases and major international oncology meetings up to August 2022. We then screened for studies describing interventions to overcome ALK resistance based on review of each title and abstract.

Key Content and Findings: For patients with oligo-progression, treatment may include maintaining the same systemic treatment beyond progression while adding local therapies to progressing lesions. Strategies to combat ALK TKI resistance mediated by on-target resistance mechanisms include 4th generation TKIs (TPX-0131, NVL-655) and proteolysis-targeting chimeras (PROTACs) currently in development. While for those patients who develop tumor progression due to off-target (ALK independent) resistance, options may include combination therapies targeting ALK and other downstream or parallel pathways, novel antibody drug conjugates, or combinations of ALK inhibitors with chemotherapy and immunotherapy. Lastly, other potential strategies being explored in the clinic include circulating tumor DNA (ctDNA) surveillance to monitor for molecular mediators of drug resistance prior to frank progression on imaging studies and utilization of ALK TKIs in the adjuvant and neoadjuvant settings.

Conclusions: Strategies to overcome resistance to currently available ALK inhibitors are urgently needed. Given the variety of resistance mechanisms, tailormade approaches are required for disease control.

Keywords: Anaplastic lymphoma kinase (ALK); acquired resistance; lung cancer; clinical trial

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Introduction

Background

Anaplastic lymphoma kinase (ALK), a member of insulin receptor protein tyrosine kinase superfamily, has been shown to play a role in development of central and peripheral nervous systems (1). Rearrangements involving the *ALK* gene on chromosome 2p have been reported in a variety of human tumors, both solid organ tumors as well as hematologic malignancies (1,2). These rearrangements result in hybrid mutant oncoproteins which contain the amino-terminal portion of a fusion partner in frame with the entire tyrosine kinase domain of ALK. Multiple ALK fusions have been described, with *EML4–ALK* being the most prevalent in non-small cell lung cancer (NSCLC). The resultant oncoprotein drives activation of the ALK signaling pathways, promoting cell proliferation, survival, and evasion of programmed cell death. ALK fusions are validated therapeutic targets across multiple types of tumors (3-5).

ALK rearrangements are detected in 3–7% of advanced NSCLC and are typically—albeit not exclusively—associated with young age, non-smoking and adenocarcinoma histology (6). The treatment landscape for and prognosis of patients whose tumors harbor ALK rearrangements (hereafter called ALK-positive lung cancer) has significantly improved with the advent of small molecule tyrosine kinase inhibitors (TKIs) targeting ALK (7).

Rationale and knowledge gap

Since the approval of the first ALK TKI, crizotinib, in 2011, a plethora of basic science and clinical studies have rapidly advanced the field through the development of "next-generation" ALK TKIs, which have increased on-target potency and improved central nervous system (CNS) efficacy. As of the timing of the writing of this narrative, there are currently 5 TKIs approved by the U.S Food and Drug Administration (FDA) and European Medicines Agency for the treatment of patients with ALK-positive lung cancer in the advanced/metastatic disease setting, including crizotinib (8) [1st generation]; ceritinib (9), alectinib (10), brigatinib (11) [all 2nd generation]; and lorlatinib [3rd generation] (12) (*described in detail by Drs. Meador and Piotrowska in this issue*). Ensartinib [a 2nd generation ALK TKI] is also currently approved in China (13).

Despite these advances, most patients with ALK-positive lung cancer who are treated with ALK TKI therapy ultimately experience disease progression due to various mechanisms of drug resistance (*described in detail by Drs. Meador and Piotrowska in this issue*).

Objective

In this review, we first discuss strategies to address acquired therapeutic resistance to ALK inhibition, broken down by the type of progression observed (oligoprogression *vs.* systemic progression). We then describe the novel agents and combinatorial strategies in development for both on and off-target resistance. Lastly, we summarize some potential approaches to prolong response to ALK inhibitors. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-708/rc).

Methods

We performed a search of peer-reviewed literature in the English language, conference abstracts, and trial registrations from the MEDLINE (Ovid), Embase (Elsevier), and CENTRAL (Cochrane Library) databases and major international oncology meetings up to August 2022. We prespecified the searches to studies written in or translated into English and discussing keywords "Anaplastic Lymphoma Kinase", "non-small cell lung cancer", "NSCLC", "ALK positive", and "ALK resistance". We then screened for studies describing interventions to overcome ALK resistance based on review of each title and abstract (*Table 1*).

Management of oligoprogression

The term "oligoprogression" is used to describe the clinical scenario in which tumor growth/progression occurs at a limited number of disease sites in patients with otherwise controlled widespread/systemic disease (14). Tumor intrinsic factors, such as intra- and inter-tumoral heterogeneity, as well as patient specific factors, such as differences in drug exposure at different disease sites, may lead to and manifest as oligoprogression (15,16).

Oligoprogression can be managed by maintaining the same systemic treatment beyond progression while adding metastasis-directed therapy (*Figure 1*). This enables extension in duration of targeted treatment while delaying switch to next systemic treatment, prolonging the benefit of TKIs and improving survival (17). Stereotactic Radiotherapy

Table 1 The search strategy summary

Items	Specification
Date of search	August 28, 2022
Databases and other sources searched	MEDLINE (Ovid), Embase (Elsevier), and CENTRAL (Cochrane Library) databases and major international oncology meetings
Search terms used	"Anaplastic Lymphoma Kinase", "non-small cell lung cancer", "NSCLC", "ALK positive", and "ALK resistance"
Timeframe	2010–2022
Inclusion and exclusion criteria	Inclusion criteria: Human, English only studies, focusing on interventions to overcome ALK resistance
Selection process	AD conducted selection, CML reviewed and provided inputs

ALK, anaplastic lymphoma kinase.

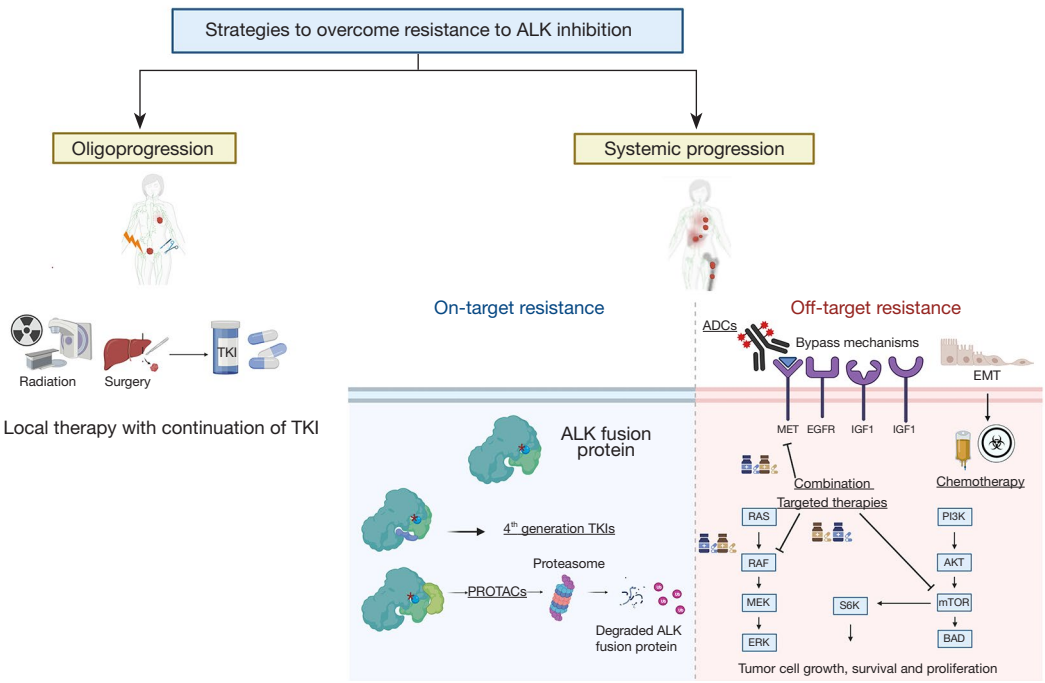

Figure 1 Strategies to overcome resistance to ALK inhibition. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; ADC, antibody drug conjugate; EMT, epithelial to mesenchymal transition; PROTACs, proteolysis-targeting chimeras.

[which includes stereotactic radiosurgery (SRS) for brain lesions and stereotactic body radiation (SBRT) for lesions elsewhere] is most commonly used for oligoprogressive disease in lung cancer patients. Continuation of ALK TKIs while addition of SBRT may increase radiosensitivity of tumor cells providing rationale for combinatorial strategies (18,19).

Multiple retrospective studies have established safety and efficacy of combining stereotactic radiation with ALK inhibitors. Gan *et al.* described 14 patients with extra-cranial oligoprogression treated with radiation therapy and showed that local therapy in patients taking crizotinib allowed an extended duration of exposure to crizotinib (28 *vs.* 10.1 months), which was subsequently associated with longer overall survival (OS) (72% *vs.* 12%, P=0.0001) (20). Similarly, another study demonstrated that the median

progression-free survival (PFS) 2 (PFS2, defined as time from radiologic progression to crizotinib discontinuation) was numerically longer among patients who received local therapy compared to those who did not receive local therapy (9.9 *vs.* 4.2 months, P=0.094) (21).

With demonstrated neurotropism for ALK-positive NSCLC (22), CNS relapse or progression with controlled extracranial disease was a common event with first-generation TKI (crizotinib) treatment due to reduced blood-brain barrier penetration (23). However, retrospective evaluation did show benefit for continuation of crizotinib treatment after radiotherapy for isolated CNS progression (24). With the advent of next generation TKIs which have improved intracranial activity (25), rates of isolated CNS progression have decreased. For example, data from the CROWN study demonstrated a lower 12-month cumulative incidence of CNS progression for lorlatinib *vs.* crizotinib in patients with (7% *vs.* 72%) and without (1% *vs.* 18%) brain metastases at baseline (26). Similar results were seen with alectinib in the ALEX trial where the time to CNS progression was significantly longer with alectinib *vs.* crizotinib and comparable between patients with and without baseline CNS metastases (P<0.0001) (27).

Recently reported data from the Consolidative Use of Radiotherapy to Block (CURB) trial showed that disease control can be improved with local therapy to progressive lesions alone in oligoprogressive disease (28). CURB, a randomized phase II trial, enrolled patients with oligoprogressive lesions (≤5) amenable to SBRT in patients with metastatic cancers of the lung and breast. Among patients with NSCLC, median PFS was improved with SBRT compared to standard of care (44 *vs.* 9 weeks, P=0.004). However, the majority (86%) of patients in this study did not have tumors that harbor an actionable mutation. Regardless, this study demonstrated the importance of local therapy in oligoprogressive disease. To that end, other ongoing studies including the phase II trial SUPPRESS-NSCLC (NCT04405401), phase II HALT trial (NCT03256981) and phase II STOP trial (NCT02756793) will provide further evidence of the role of SBRT in oligoprogressive disease (*Table 2*). The HALT trial planned to enroll patients with actionable mutation positive advanced NSCLC with oligoprogressive disease following initial response to a TKI, with the aim to study whether the use of SBRT to ≤3 sites of oligoprogressive disease with continuation of TKI improves PFS compared with continuation of TKI alone.

Management of systemic progression

Unfortunately, despite initial response, most patients ultimately experience progression of disease due to acquired therapeutic resistance. Molecular mechanisms leading to acquired resistance can be broadly classified as "on-target" or "ALK dependent" (i.e., acquired mutations in the ALK tyrosine kinase domain which alter drug sensitivity) or off-target mechanisms or "ALK independent" (such as upregulation of bypass signaling pathways and epithelial mesenchymal transition) (29,30).

Strategies to combat ALK TKI resistance mediated by on-target resistance mechanisms

On-target resistance mechanisms can vary between the different generations of ALK TKIs. For example, L1195M and G1269A are common resistance mutations detected in crizotinib-resistant tumors compared to G1202R and F1174C/L, which occur more commonly in tumors that develop resistance to 2^{n}d generation ALK TKIs (31). Interestingly, sequential ALK inhibitor therapy may lead to emergence of compound mutations, i.e., ≥2 resistance mutations in the ALK tyrosine kinase domain, which can be challenging to target with the currently FDA-approved ALK TKIs (32). Shiba-Ishii *et al.* recently described that for patients whose disease is progressing on lorlatinib, about 29% of samples evaluated had compound mutations, with the most common being either G1202R (57%) or I1171N (21%) (33). Thus, development of effective therapies which can overcome such compound mutations represents an area of major unmet need for patients whose disease progresses on lorlatinib. Novel strategies including development of 4th generation macrocyclic TKIs and proteolysis targeting chimeras (PROTACs) are currently under development and described below.

Novel 4th generation TKIs

There are currently two 4th generation TKIs that are being developed which can inhibit the acquired compound ALK mutations along with a wide spectrum of single mutations:

TPX-0131: TPX-0131 is a macrocyclic molecule designed to fit into the ATP pocket and inhibit ALK resistance mutations, including solvent front mutations, gatekeeper mutations, and compound mutations (34). *In vitro* data suggests that TPX-0131 is potent against mutation in the ALK solvent front mutations (e.g., G1202R

Table 2 Ongoing clinical trials for ALK + non-small cell lung cancer

NCT identifier (trial name)	Phase	Line of therapy	Mechanism of investigational agent	Treatment arm(s)	Current status (as of 9/25/2022)
NCT04405401 (SUPRESS-NSCLC)	2	First-Line	Radiation (for oligoprogression)	SABR *vs*. standard of care	Recruiting
NCT03256981 (HALT)	2	Second-Line	Radiation (for oligoprogression)	SBRT and continued TKI therapy *vs*. continued TKI therapy alone	Recruiting
NCT02756793 (STOP)	2	Second-Line	Radiation (for oligoprogression)	SABR *vs*. standard of care	Active, not recruiting
NCT04849273 (FORGE-1)	1–2	Second line or later	4th Gen TKI	TPX-0131	Recruiting
NCT05384626 (ALKOVE-1)	1–2	Second line or later	4th Gen TKI	NVL-655	Recruiting
NCT0429119	1–2	Second line or later	ALK inhibitor + ALK inhibitor	Lorlatinib + crizotinib	Recruiting
			ALK inhibitor + MEK inhibitor	Lorlatinib + binimetinib	
			ALK inhibitor + SHP2 inhibitor	Lorlatinib + TNO155	
NCT04005144	1	Second line or later	ALK inhibitor + MEK inhibitor	Brigatinib with binimetinib	Recruiting
NCT03202940	1–2	Second line	ALK inhibitor + MEK inhibitor	Alectinib and cobimetinib	Recruiting
NCT04800822	1	Second line or later	ALK inhibitor + SHP2 inhibitor	Lorlatinib + PF-07284892	Recruiting
NCT02321501	1	Second line or later	ALK inhibitor + mTOR inhibitor	Ceritinib + Everolimus	Active, not recruiting
NCT04227028	1	Second line or later	ALK inhibitor + VEGF inhibitor	Brigatinib + bevacizumab	Recruiting
NCT04484142 (Tropion Lung-05)	2	Third line or later	Trop-2 ADC	Datopotamab deruxtecan	Active, not recruiting
NCT04644237 (Destiny Lung-02)	2	Second line or later	HER-2 ADC	Trastuzumab deruxtecan	Active, not recruiting
NCT04495153	2	Second line or later	Oncolytic viral therapy	Gene Mediated Cytotoxic Immunotherapy (GMCI™)	Recruiting
NCT03645928	2	Second line or later	Tumor infiltrating lymphocytes	Autologous tumor infiltrating lymphocytes	Recruiting
NCT03313778	1	Second line or later	mRNA-based vaccine	mRNA-4157 + pembrolizumab	Recruiting
NCT04302025 (NAUTIKA1)	2	Neoadjuvant and Adjuvant	2nd generation TKI	Neoadjuvant and adjuvant alectinib *vs*. standard of care	Recruiting
NCT03456076 (ALINA)	3	Adjuvant	2nd generation TKI	Chemotherapy followed by alectinib *vs*. chemotherapy alone	Active, not recruiting

Current status of clinical trial enrollment is obtained from clinicaltrials.gov with status updated as found on 25th September 2022. ALK, anaplastic lymphoma kinase; NCT, National Clinical Trial; TKI, tyrosine kinase inhibitor; ADC, antibody drug conjugate; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiation.

with IC_{50} of 0.9 nmol/L) and hinge region (e.g., L1198F with IC_{50} of 1 nmol/L). TPX-0131 also has a wide range of activity across various compound ALK mutations (with IC_{50} ranging from <0.2–14.9 nmol/L). This compound demonstrated dose-dependent *in vivo* anti-tumor activity against xenografted tumors harboring EML4-ALK variant 1 fusion protein with G1202R/L1198F and EML4-ALK G1202R/L1196M. In terms of CNS penetrance, TPX-0131 was found to have brain penetration at approximately 66% of the plasma concentration, while its concentration

in CSF was about 3.6% of that in observed in plasma in preclinical animal studies (34). Despite its encouraging activity across a wide mutational spectrum, TPX-0131 seems to have a reduced potency against I1171N (IC_{50}: 2.3 nmol/L) and G1269S (IC_{50}: 6.6 nmol/L) mutations. Based on this encouraging preclinical activity, TPX-0131 is currently being studied in the phase I/II study FORGE-1 (NCT04849273) trial. The phase I portion of the study will aim to determine the safety, tolerability, PK, and RP2D of TPX-0131, while the phase II portion will include patients with advanced ALK-positive NSCLC who have received <3 prior lines of ALK TKI therapy, including >1 prior 2nd or 3rd generation ALK TKI. The primary outcome will be objective response rate (ORR).

NVL-655: NVL-655 is a novel ALK inhibitor designed to have activity against single and compound ALK mutations, while sparing TRKB (35). Across a panel of 335 wild-type kinases, 5 kinases are inhibited by NVL-655 with IC_{50} ≤10-fold of ALK, which include ROS1, LTK, PYK2, TRKB, and FAK. *In vitro* data, NVL-655 shows single digit nanomolar efficacy against G1202R (IC_{50}: <0.73 nmol/L), G1202R/L1196M (IC_{50}: 7 nmol/L), G1202R/G1269A (IC_{50}: 3 nmol/L), and G1202R/L1198F (IC_{50}: 3 nmol/L). NVL-655 is also efficacious in a Ba/F3 xenograft model harboring EML4-ALK variant 1 containing the compound G1202R/L1196M mutation, with greater *in vivo* tumor activity compared to lorlatinib. Recently, NVL-655 has also demonstrated activity in the MR448re (EML4-ALK v3 G1202R/T1151M) model with compound ALK mutation (36). In terms of CNS penetration, NVL-655 demonstrated a high unbound brain-to-plasma partition coefficient (Kp_{uu}=0.16 at 1 h) and a high cerebrospinal fluid (CSF)-to-unbound plasma partition coefficient (1.2 at 1 h) after a single oral dose of 10 mg/kg in Wistar Han rats. Given its increased selectively for ALK while sparing TRKB, this drug has the potential to minimize TRK-related CNS adverse events (35). Given encouraging preclinical evidence of efficacy across various ALK fusion partners, EML4 breakpoint variants, and tumor contexts, NVL-655 is currently being studied in the phase I/II ALKOVE-1 trial (NCT05384626). The phase I portion of the study will aim to determine the RP2D and MTD of NVL-655, while the phase II portion will evaluate efficacy of NVL-655 in lung cancer and other solid tumors that harbor *ALK* genomic alterations. Four cohorts are included in this trial: cohort a: for lung cancer patients who have received one prior 2nd generation ALK TKI; cohort b: for lung cancer patients who have received two to three prior 1st/2nd generation ALK TKIs; cohort c: for lung cancer patients who have received two to three prior ALK TKIs, with lorlatinib second to third line; cohort d: for lung cancer patients not eligible for cohorts a-c or for any patient with ALK-positive solid tumor who has received >1 prior systemic therapy.

PROTACs

PROTACs are hetero-functional molecules which utilize the endogenous cell proteasome degradation system to degrade protein of interest. PROTACS are typically composed of 3 parts: (I) ligand for target protein, (II) ligand to bind E3 ubiquitin ligase and (III) linker connecting the two ligands. PROTACs recruit the target protein to proximity of the E3 ubiquitin ligase which subsequently leads to ubiquitination and degradation of the target protein by the proteasome machinery (37). PROTAC mediated targeting of ALK fusion proteins may provide a complementary treatment strategy for patients with ALK-positive lung cancer.

Currently, there are 6 different ALK based PROTACs designed based on the second generation TKIs ceritinib and brigatinib (38-41). Ceritinib based ALK PROTACs exhibited moderate protein degradation ability, with PROTACs using pomalidomide as CRBN E3 ligase ligand (TL13-112) exhibiting stronger degradation compared to those using VHL ligand (TD-004) (42). Zhang *et al.* demonstrated that a CBRN ligand based ALK PROTAC could degrade NPM-ALK and EML4-ALK variant 3 in lung cancer cell lines at concentrations of 3–60 nM (41). Unfortunately, there was no improvement with ceritinib based ALK degraders over ceritinib in terms of anti-proliferative effect against ALK-positive lung cancer cells. Furthermore, non-specific degradation of Aurora A was observed, which could contribute to a different selectivity profile for these molecules (39). In addition, the brigatinib-based ALK PROTAC (SIAIS117), which utilizes VHL as the E3 ubiquitinase ligand, demonstrated degradation of NPM-ALK, EML4-ALK, as well as ALK fusion proteins with the G1202R resistance mutation (40).

Although PROTAC technology is still in development, there is encouraging data of tumor regression in patients with prostate cancer with other PROTAC degraders (43). The promising *in vitro* activity of ALK targeting PROTACs and the success of PROTAC technology in clinic provides another possible opportunity to overcome resistance to current ALK TKIs.

Ultimately, the challenge with TKIs is the seemingly inevitable emergence of on-target resistance mutations, even with 4th generation TKIs. Thus, therapeutic strategies

combining agents that inhibit the driver oncogene (in this case, ALK) together with additional drugs that target parallel signaling pathways and bypass nodes will ultimately be required to overcome resistance. We discuss such combination strategies in the next section.

Strategies to combat ALK TKI resistance mediated by off-target resistance mechanisms

Resistance to ALK TKI therapy may also be driven through ALK-independent mechanisms, including activation of downstream pathways (e.g., MAPK pathway) and parallel pathways (e.g., MET, EGFR, HER2/HER3, IGF-1R) as well as through histological transformation (44). Strategies to overcome off-target resistance may include combination therapies targeting ALK and other downstream or parallel pathways, novel antibody drug conjugates (ADCs), or combinations of ALK inhibitors with chemotherapy and immunotherapy.

Combination targeted therapies

Activation of downstream signaling pathways

Mutations in multiple members of the MAP kinase signaling pathway have been identified in tumors with acquired resistance to lorlatinib, including NRAS, KRAS, MEK, and MAP3K (16,29,32,45). These findings form the basis of combinatorial strategies utilizing an ALK inhibitor with a MEK inhibitor (binimetinib, cobimetinib, trametinib). At the time of this writing, there are three ongoing trials combining lorlatinib with binimetinib (NCT0429119), brigatinib with binimetinib (NCT04005144), alectinib and cobimetinib (NCT03202940).

Activation of parallel pathways

MET: *MET* amplification (*MET*amp) has been shown to mediate acquired resistance to next generation ALK inhibitors alectinib (46). Crizotinib, the 1st generation ALK TKI, was actually initially developed as a MET inhibitor, and crizotinib treatment has been shown to result in an anti-tumor response in a patient who developed alectinib-resistance due to *MET*amp (47). Thus, combination of lorlatinib with crizotinib is currently being tested in patients with ALK-positive NSCLC with *MET*amp (NCT04292119).

Similar to ALK-positive NSCLC, *MET*amp is a defined acquired resistance mechanism in EGFR-mutant NSCLC. In this context, various approaches have emerged where additional agents are being tested in combination with the 3rd generation EGFR TKI, osimertinib. The INSIGHT2 trial tested the combination of tepotinib (MET TKI) plus osimertinib for patients with *EGFR*-mutant NSCLC whose tumors acquired *MET*amp after progression on first-line osimertinib. This study showed an ORR of 45–56% based on *MET*amp detection from tissue or liquid biopsy (48). Similarly, preliminary results from the SAVANNAH phase II trial revealed that osimertinib plus savolitinib (MET TKI) demonstrated an ORR 49% in patients with *EGFR*-mutant NSCLC with high levels of MET overexpression and/or amplification (49).

SHP2: SHP2 is a protein tyrosine phosphatase that activates multiple downstream tyrosine kinases as a way to bypass ALK signaling, therefore mediate resistance to ALK TKI therapy (50). Inhibition of SHP2 with SHP099 has been previously shown to halt the growth of resistance cell lines when combined with ceritinib (50). Based on this observation, there is a growing interest to combine SHP2 inhibitors such as PF-07284892 and TNO155 with lorlatinib to overcome acquired resistance to TKI therapy (NCT04800822, NCT04292119).

mTOR: Alterations in mTOR as well as NF2, an important tumor suppressor involved in regulation of PI3K-AKT-mTOR pathway, have suggested potential role for mTOR inhibitors in overcoming resistance to lorlatinib (51,52). NCT02321501 is a phase I study evaluating ceritinib and everolimus in patients with solid tumors with an expansion cohort of patients with ALK-positive NSCLC.

VEGF: Finally, ALK TKI combinations are being studied with VEGF inhibitors such as bevacizumab. A phase I study of brigatinib with bevacizumab is currently ongoing in patients with ALK-positive NSCLC (NCT04227028).

ADCs

ADCs are composed of monoclonal antibodies linked to cytotoxic drugs (the "payload"). There are several ADCs currently in clinical trials for NSCLC and SCLC (53). Some of the ADCs in development target pathways which are implicated in off-target resistance to ALK TKI therapy and therefore have garnered interest as potential combination therapies to combat disease progression.

Telisotuzumab Vedotin (ABBV-399, Teliso-V) is a first-in-class ADC composed of ABT-700, an anti-c-Met antibody, conjugated to monomethyl auristatin E (a

microtubule inhibitor) (54). With *MET*amp being one of the more common mechanisms of resistance to ALK TKI therapy (55), telisotuzumab may have activity in this setting given the correlation between *MET*amp and overexpression (56). In fact, recent data from a phase I study of telisotuzumab with the EGFR TKI, osimertinib, after failure of prior osimertinib in patients with advanced, c-MET overexpressing *EGFR*-mutant NSCLC showed impressive responses with ORR 58%, providing a proof-of-concept for utilizing this ADC in combination with TKIs targeting other oncogenes (such as ALK) as a strategy to potentially overcome MET driven resistance (57).

Datopotamab deruxtecan is an ADC with targeting Trop-2 with a humanized directed IgG1 monoclonal antibody linked to a topoisomerase 1 inhibitor payload. With preliminary efficacy ranging from 21% to 23% across doses in patients with relapsed advanced NSCLC, this compound has demonstrated encouraging activity in this setting (58). Specifically, in the heavily pretreated population with actionable genomic alterations (*EGFR* mutations, *ALK/ROS1/RET* fusions), the ORR was 35% with median duration of response (mDOR) of 9.5 months. A phase II study is currently evaluating the efficacy and safety of datopotamab deruxtecan in patients with advanced or metastatic NSCLC with known genomic alterations (including ALK) who had previously received treatment with 1 or more kinase inhibitors and platinum-based chemotherapy (TROPION-Lung05, NCT04484142).

Trastuzumab deruxtecan (T-DXd) is a humanized anti-HER2 IgG1 monoclonal antibody with a tetrapeptide based cleavable linker and a topoisomerase I inhibitor payload (deruxtecan). It is currently approved by the FDA in breast cancer and gastric cancer (59,60). Given the observed clinical outcomes (ORR: 55%, mDOR: 9.3 months) with T-DXd in the *HER2*-mutant cohort of the phase II DESTINY-Lung01, this drug may be an attractive option to overcome resistance mediated by *HER2* alterations such as mutations (61). DESTINY-Lung 02, a randomized phase 2 study to evaluate T-DXd (5.4 or 6.4 mg/kg) in patients with *HER2*-mutant NSCLC who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy including a platinum-based chemotherapy drug is currently underway (NCT04644237).

Chemotherapy

Traditional platinum based cytotoxic chemotherapy may play a role in the treatment of ALK TKI resistant disease. Lin *et al.* demonstrated in a retrospective study that platinum/pemetrexed-based chemotherapy shows modest efficacy (ORR: 29.7%, mDOR: 6.4 months) in ALK-positive NSCLC after failure of second-generation ALK TKIs (62). Interestingly, in this cohort patients who received combination of ALK TKI with chemotherapy had a longer PFS compared to those who received chemotherapy alone [6.8 *vs.* 3.2 months, hazard ratio (HR): 0.33, P=0.025]. Notably, this study did not identify the molecular mechanism of disease progression. Regardless, these data are hypothesis generating and could pave the way for future combination of targeted therapy with chemotherapy as a strategy to curb resistance.

In rare cases, histologic transformation from ALK-positive NSCLC to ALK-positive small cell lung cancer (SCLC) may be identified on post-progression biopsies (63,64). The molecular mechanisms leading to lineage plasticity/histological transformation remain poorly understood at the current time. Similar to *de novo* SCLC (63,65), most cases of transformed SCLC harbor mutations in *TP53* and *RB1*. *Lineage plasticity is described in more detail by Drs. Meador and Piotrowska in this issue*. Platinum-based chemotherapy regimens remain the backbone of therapy when SCLC transformation is identified. Further studies are needed to determine the role of immunotherapy and of continuing the oncogene directed TKIs in the context of transformed SCLC.

Immunotherapy

Immunotherapy has changed the landscape of treatment for advanced and early-stage NSCLC (66). Despite this, its role in the subset of genomically driven advanced NSCLC is not clearly elucidated.

Efficacy of single-agent immune checkpoint inhibitors is limited in patients with *EGFR/ALK*-altered NSCLC (67). A phase 2 trial with pembrolizumab in combination with chemotherapy in recurrent *EGFR/ALK*-altered NSCLC demonstrated ORR of 29% within the ALK-positive subset (n=7) (68). The most robust evidence on incorporation of immunotherapy in the treatment of ALK-positive NSCLC comes from the IMPower 150 study (69). The IMPower150 study demonstrated superiority of atezolizumab with bevacizumab plus chemotherapy among patients with metastatic nonsquamous NSCLC, regardless of programmed death-ligand 1 (PD-L1) expression and EGFR or ALK genetic alteration status. In the subset of patients with *EGFR* or *ALK* alterations (n=108), atezolizumab with

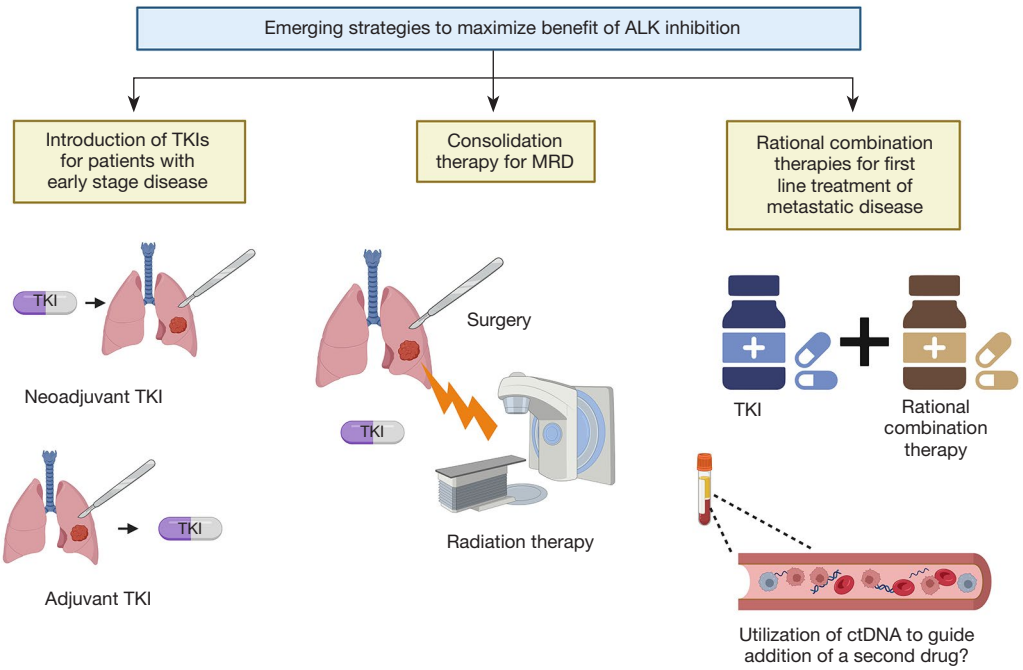

Figure 2 Emerging strategies to maximize benefit of ALK inhibition. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; MRD, minimal residual disease; ctDNA, circulating tumor DNA.

bevacizumab plus chemotherapy improved median PFS (9.7 *vs.* 6.1 months, HR: 0.59, range, 0.37–0.94). Thus, IMPower150 regimen provides another potential strategy for overcoming resistance by incorporating immunotherapy in the treatment algorithm for ALK-positive NSCLC.

Lastly, many novel immunotherapy-based approaches are currently underway including oncolytic viral immunotherapy (NCT04495153), autologous tumor infiltrating lymphocytes (TILs) (NCT03645928) and combination of existing immunotherapies with mRNA-based vaccines (NCT03313778) which may play a key role in the future treatment of ALK-positive NSCLC.

Other potential strategies to maximize response to ALK TKI therapy

Early introduction of targeted therapy

The improvement in disease-free survival observed with introduction of adjuvant osimertinib in patients with early stage *EGFR*-mutant lung cancer has opened new avenues for targeted therapies in early stages of NSCLC (70). Furthermore, the lack of improvement in outcomes in patients with *EGFR*-mutant NSCLC with consolidation durvalumab in PACIFIC trial raises the question whether a consolidation strategy with a targeted therapy may be more effective in this setting (71,72). Extrapolating this data to the ALK-positive NSCLC setting, there may be benefit from ALK inhibitors in the adjuvant setting for early stage NSCLC and in the consolidation setting for stage III unresectable NSCLC (*Figure 2*). There is also potential to improve outcomes further by incorporating targeted therapy in the neoadjuvant setting. To this end, the LCMC4 Lung Cancer Mutation Consortium trial will screen for 11 actionable driver mutations, including ALK to identify patients who are candidates for neoadjuvant therapy (NCT04712877). NAUTIKA1 (NCT04302025) also aims to study neoadjuvant and adjuvant therapies in biomarker-selected populations with resectable NSCLC. The ALK cohort within NAUTIKA1 will receive up to 8 weeks of neoadjuvant alectinib treatment followed by surgical resection and subsequent adjuvant chemotherapy and alectinib (for up to 2 years), with the primary endpoint of assessing major pathologic response. Finally, ALINA (NCT03456076) is a phase III study of alectinib *vs.* chemotherapy as adjuvant therapy in patients with stage IB–IIIA ALK-positive NSCLC. The primary endpoint in this trial is disease-free survival per investigator, with OS, safety, and pharmacokinetics as secondary endpoints.

Circulating tumor DNA (ctDNA) monitoring and TKI switch strategy

Standard approaches to biomarker testing in NSCLC use tissue biopsy samples to identify patients who may benefit from targeted therapy, with consideration of blood-based testing if insufficient tissue is present (73). Multiplex next generation sequencing (NGS)-based ctDNA assays are currently commercially available, for detecting *ALK* rearrangements in metastatic NSCLC (74). Recently, the results of ALK-positive cohort from the Blood First Assay Screening Trial (BFAST) (75) showed that administration of alectinib based on *ALK* alterations using only NGS of ctDNA showed ORR of 92% with mDOR at 12 months in 75% of patients, consistent with results from the pivotal ALEX trial (10). This provides a proof-of-concept that ctDNA screening is beneficial and comparable to tissue-based screening of biomarkers for treatment selection.

There is an evolving application of ctDNA especially in identification of resistance mechanisms post progression, when obtaining tissue biopsy may not be possible. For example, in the FLAURA trial, patients were evaluated with liquid biopsy to identify resistance mechanisms to first-line osimertinib (76). Similarly, utility of ctDNA in ALK-positive NSCLC has been demonstrated for identifying genomic alterations that may mediate TKI resistance and for longitudinal monitoring to predict disease progression prior to radiographic evidence of disease progression (77,78).

Thus, there is potential to utilize ctDNA as a monitoring tool to identify evolving clones of resistance to ongoing treatment and perhaps offering an opportunity to switch TKI therapy early before florid disease progression. This concept, while not standard of care in lung cancer, is currently applied clinically in chronic myeloid leukemia (CML) where early switch is recommended if specific response criteria are not met (79).

Targeting drug tolerant persister (DTP) cells

Some cancer cells may evade cell death by entering a DTP state (80). This DTP state may provide cancer cells with a survival advantage to then enable them to acquire additional mechanisms of resistance to drug therapy (81). These so called "persister" cells may undergo epigenomic, transcriptomic, and metabolomic changes which allow them to escape the effects of the oncogene directed therapy (82). Thus, targeting persister cells represents a possible additional node of intervention to thwart drug resistance. Various strategies touted to date include: sustaining tumor cells in persister state through CDK4/6 inhibitor mediated cell cycle arrest), targeting factors that maintain a persister state (via histone deacetylase inhibitors, IGF-1R inhibition), and inhibiting pathways that regulate transcription (such as YAP-TEAD) (82). One practical yet significant limitation to the rigorous analysis of the DTP state is that sampling of persister tumor cells requires on-treatment biopsies, which are not considered standard of clinical care. Such on-treatment biopsies may be done as part of a clinical trial (with informed consent from the patient), and rigorous mutiomic analyses of these on-treatment samples is expected to further our understanding of drug tolerance, with the ultimate goal of driving higher response rates and greater depth of response.

Conclusions

In conclusion, strategies to overcome resistance to currently available ALK inhibitors are urgently needed. Given the variety of resistance mechanisms, tailormade approaches are required for disease control. It is time we apply the core principles of precision oncology, not just with biomarker driven first-line treatments, but also in later line therapies to improve outcomes and quality of life for our patients with ALK-positive NSCLC.

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