Editorial Commentary

Optimizing long-term treatment with ALK inhibitors: balancing efficacy and safety

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Lung cancer is the primary cause of cancer-related deaths globally, and it is estimated that 2–5% of patients with advanced non-small cell lung cancer (NSCLC) harbor anaplastic lymphoma kinase (*ALK*) fusions (1,2). The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized treatment approaches, thus leading to exceptional survival rates and quality of life. Epidermal growth factor receptor (EGFR) inhibitors are typically divided into three generations: first, second, and third (3). ALK inhibitors are classified into several categories. Crizotinib is a first-generation ALK inhibitor, whereas alectinib and brigatinib are second-generation ALK inhibitors. Lorlatinib is a third-generation inhibitor that exhibits distinct features such as efficacy; resistance profiles; and characteristics including ALK inhibition, off-target effects, and intracranial penetration (4).

Figure 1 shows the secondary structures of various ALK inhibitors, including crizotinib, alectinib, ensartinib, ceritinib, brigatinib, lorlatinib, envonalkib, iruplinalkib, ficonalkib, repotrectinib, Apg-2449, and zotizalkib. These ALK inhibitors have been evaluated in clinical trials and are listed in order of their PubChem chemical identifiers (CIDs). Crizotinib has an aminopyridine backbone; alectinib has a tetracyclic ketone structure; ensartinib and iruplinalkib share a pyrrolopyridine structure; ceritinib, brigatinib, ficonalkib, and Apg-2449 share a 2,4-diaminopyridine backbone; lorlatinib has a macrocyclic 2-aminopyridine; envonalkib contains a piperazine structure; repotrectinib is characterized by a pyrrolopyrimidine structure; and zotizalkib has an isoquinolinone structure.

Iruplinalkib (also known as WX-0593) is a novel and highly selective oral TKI that specifically targets ALK and ROS proto-oncogene 1 (ROS1) (5). It is a potent inhibitor of wild-type *ALK*, the resistant mutants of wild-type *ALK*, and *EGFR* L858R/T790M mutation and is comparable to brigatinib. In preclinical studies, iruplinalkib showed strong anti-tumor activity against crizotinib-sensitive and crizotinib-resistant NSCLC tumors and the superior inhibition of *ALK* and crizotinib-resistant *ROS1* mutants (excluding ROS1-G2032R and ROS1-L1951R). These findings suggest that iruplinalkib is a promising treatment option for patients with *ALK*- or *ROS1*-rearranged NSCLC (5).

ALK-targeted TKIs, including crizotinib, ceritinib, alectinib, brigatinib, ensartinib (available only in China), and lorlatinib, have been approved as first-line treatments for patients with *ALK*-positive NSCLC (6). These agents have demonstrated significant improvements in progression-free survival (PFS) compared with crizotinib and are recommended as first-line therapies in various clinical guidelines, such as those of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). According to the ASCO and NCCN guidelines, alectinib, brigatinib, and lorlatinib are recommended as first-line therapies (7,8).

Table 1 compares the effectiveness of six ALK inhibitors, namely alectinib (9-14), brigatinib (15,16), ensartinib (17),

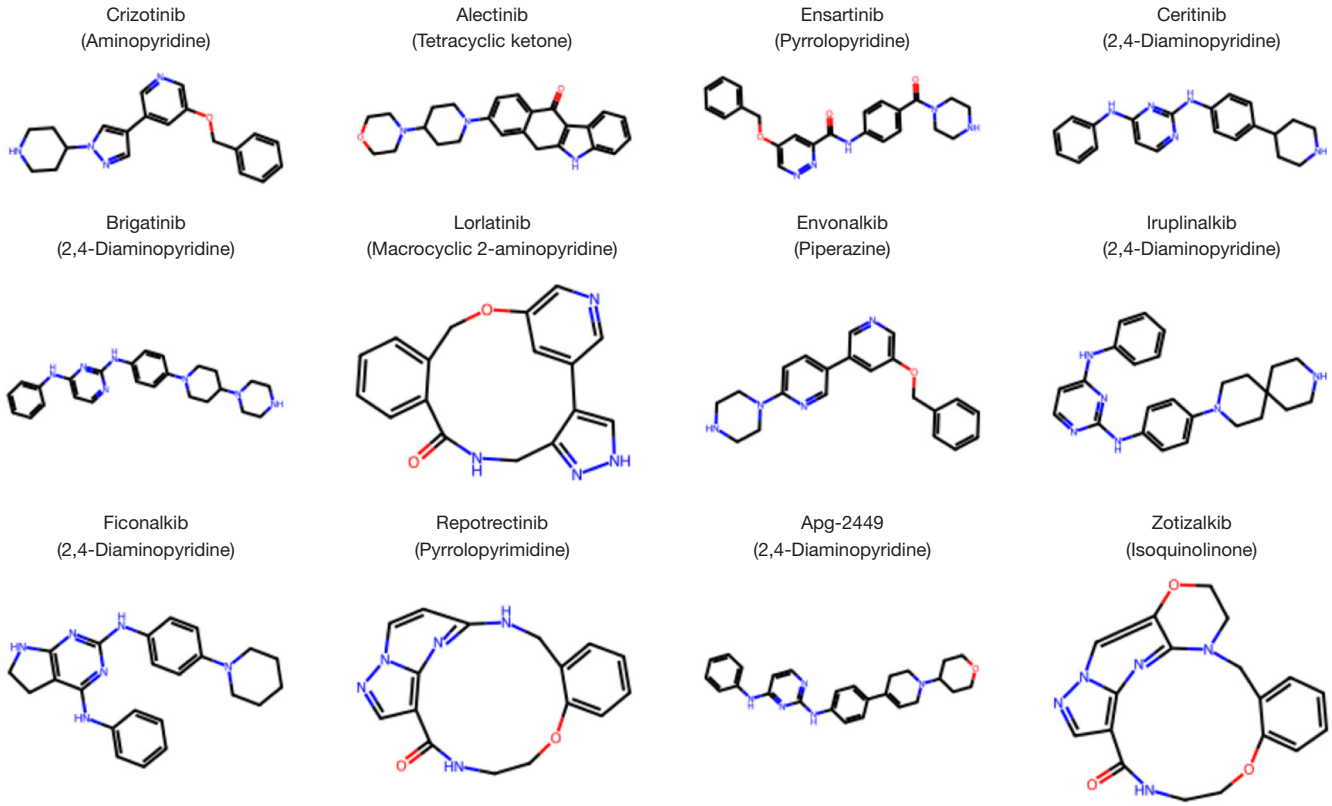

Figure 1 Structure of ALK-TKIs. This figure illustrates the secondary structures of various ALK-TKIs. The PubChem CID for each ALK-TKI is provided as follows: crizotinib (11626560), alectinib (49806720), ensartinib (56960363), ceritinib (57379345), brigatinib (68165256), lorlatinib (71731823), envonalkib (76899983), iruplinalkib (118639856), ficonalkib (135211735), repotrectinib (135565923), Apg-2449 (138678712), and zotizalkib (156024486). The SMILES strings for each compound were converted into molecular objects using RDKit. Murcko scaffolds were then extracted from these molecular objects to obtain the core structures. Finally, the SMILES scaffold was visualized to represent the secondary structure of each compound. ALK-TKI, anaplastic lymphoma kinase tyrosine kinase inhibitor; CID, chemical identifier; SMILES, Simplified Molecular Input Line Entry System.

lorlatinib (18-20), envonalkib (21), and iruplinalkib (22), against crizotinib. Notably, a recent study suggested that iruplinalkib may provide a more favorable PFS benefit than other ALK inhibitors, particularly in Asian populations. This finding highlights the potential importance of ethnicity in treatment response and warrants further investigation (23). All agents showed promising overall response rates (ORRs) and median PFS (mPFS) rates. Lorlatinib demonstrates excellent central nervous system (CNS) penetration and has shown efficacy in the treatment of patients with intracranial metastases following treatment with second-generation ALK inhibitors. The CROWN trial (Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer), which was presented at ASCO 2024 and subsequently published (18), revealed five-year follow-up data indicating a PFS of 60% at 60 months. Furthermore, lorlatinib exhibited the lowest hazard ratio (HR) at five years (0.06), with 92% of patients experiencing no intracranial progression.

In *Journal of Thoracic Oncology*, Shi *et al.* conducted an interim analysis of the efficacy of the phase III INSPIRE study [Iruplinalkib (WX-0593) Versus Crizotinib in ALK TKI-Naive Locally Advanced or Metastatic ALK-Positive NSCLC: Interim Analysis of a Randomized, Open-Label, Phase 3 Study], which randomized 292 patients with treatment-naïve *ALK*-positive NSCLC to receive iruplinalkib or crizotinib in a Chinese population (22). Patients were ineligible for the study if they had previously received an ALK-targeting TKI, although first-line chemotherapy was acceptable. Crossover was not allowed in this study. Iruplinalkib successfully met the primary endpoint of PFS, as determined by a blinded independent

Table 1 Summary of clinical trials evaluating the efficacy and safety of ALK inhibitors compared to crizotinib

ALK-TKI	Clinical study	N	ORR (%)	mPFS (months)	mOS (months)	TRAEs (G3–G5, ~5%)
Alectinib	J-ALEX (9,10)	103	92	34.1	NR	CPK increased (5%), interstitial lung disease (5%)
	ALEX (11,12)	152	82.9	34.8	NR	ALT increased (15%), AST increased (11%)
	ALESIA (13,14)	125	91	41.6	NR	Weight increased (9%)
Brigatinib	ALTA-1L (15,16)	137	74	24	NR	CPK increased (26%), lipase increased (15%), hypertension (14%), amylase increased (6%), pneumonia (5%)
Ensartinib	eXalt3 (17)	143	74	25.8	NR	Rash (11%)
Lorlatinib	CROWN (18-20)	149	76	NR*	NR	Hypertriglyceridemia (20%), weight increased (17%), hypercholesterolemia (16%), hypertension (10%)
Envonalkib	(21)	131	81.6	24.87	NR	Neutrophil count decreased (18%), WBC decreased (8%), ALT increased (7%), ECG QT prolongation (6%)
Iruplinalkib	INSPIRE (22)	143	93	27.7	NR	Hypertension (9%), sinus bradycardia (9%), ALT increased (8%), AST increased (6%)

*, the 4-year and 5-year PFS rates with lorlatinib were 63% and 60%, respectively (95% CI: 51–68%). ALESIA, Alectinib Versus Crizotinib in Untreated Asian Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer; ALEX, Alectinib Versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer; ALK-TKI, anaplastic lymphoma kinase tyrosine kinase inhibitor; ALT, alanine transaminase; ALTA-1L, Brigatinib Versus Crizotinib in ALK Inhibitor-Naive Advanced ALK-Positive NSCLC; AST, aspartate transaminase; CI, confidence interval; CPK, creatine phosphokinase; CROWN, Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer; ECG, electrocardiogram; eXalt3, Ensartinib *vs*. Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer; INSPIRE, Iruplinalkib (WX-0593) Versus Crizotinib in ALK TKI-Naive Locally Advanced or Metastatic ALK-Positive NSCLC: Interim Analysis of a Randomized, Open-Label, Phase 3 Study; J-ALEX, Alectinib Versus Crizotinib in Patients With ALK-Positive Non-Small-Cell Lung Cancer in Japan; mOS, median overall survival; mPFS, median PFS; NR, not reached; ORR, overall response rate; PFS, progression-free survival; TRAEs, treatment-related adverse events; WBC, white blood cell.

review committee (BIRC), with an mPFS of 27.7 months compared with 14.6 months for crizotinib [HR =0.34, 95% confidence interval (CI): 0.23–0.52, P<0.0001]. Additionally, the ORR by BIRC was 93% (95% CI: 87.5–96.6%) compared with 89.3% (95% CI: 83.1–93.7%) for the crizotinib group. These results are consistent with those of the ALTA-1L study (Brigatinib Versus Crizotinib in ALK Inhibitor-Naive Advanced ALK-Positive NSCLC) using brigatinib (PFS of 24 months) and the eXalt3 study (Ensartinib *vs*. Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer) using ensartinib (PFS of 25.8 months), both of which included previous chemotherapy. The INSPIRE trial demonstrated that iruplinalkib had a favorable HR for PFS in most subgroups, including those with CNS metastasis at baseline, with an impressively high intracranial ORR of 90.9% for iruplinalkib compared with 60% for crizotinib. Additionally, the cumulative incidence of brain metastasis at 18 months was significantly lower with iruplinalkib than with crizotinib (3.2% *vs*. 12.2%, HR =0.39, P=0.0081). Furthermore, updated data from the extended follow-up of the INSPIRE study, presented at European Society for Medical Oncology (ESMO) 2024 (24), have shown that iruplinalkib continues to demonstrate sustained efficacy in preventing brain metastases, reinforcing its potential advantage in CNS disease control.

ALK inhibitors exhibit distinct adverse effects. Alectinib is associated with a low incidence of severe adverse events (AEs), thus making it the most widely used drug currently. However, it can occasionally lead to severe treatment-related AEs (TRAEs) such as elevated creatine phosphokinase (CPK), alanine transaminase (ALT), aspartate transaminase, interstitial lung disease, and weight gain (10). Brigatinib is associated with a higher frequency of diarrhea and severe grade 3–5 TRAEs, including hypertension and elevated CPK and lipase levels (16). Lorlatinib is associated with significant neurological AEs, including cognitive effects in 26% of patients, mood changes in 17%, speech disturbances in 5%, psychiatric effects in 5%, and peripheral neuropathy in 34% (20). Additionally, lorlatinib is associated with grade 3–5 TRAEs such as hypertriglyceridemia and weight gain. Ensartinib is known for its high incidence of rash,

which is classified as a grade 3–5 TRAE (17). Envonalkib is associated with a high incidence of diarrhea and grade 3–5 TRAEs including decreased neutrophil and white blood cell counts (21). According to Shi *et al.*, the most common grade 3–5 TRAEs associated with iruplinalkib treatment are hypertension, hepatic dysfunction, and ALT elevation (22).

We are at a point where the overall survival results are still pending, but six drugs have demonstrated higher efficacies than crizotinib. To navigate this landscape, it is crucial to control intracranial metastases and monitor the progression of resistance to mutations. Given the extended treatment duration, we must be vigilant regarding the accumulation of AEs over time. This transition represents a significant shift from an era that prioritizes immediate treatment efficacy to one in which a holistic approach to long-term management is paramount. In this new paradigm, we must balance the benefits of advanced therapies with a comprehensive understanding of their long-term effects on the quality of life of patients.

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