Editorial Commentary

Will INSPIRE crown iruplinalkib as a new standard choice in first-line advanced *ALK*-positive non-small cell lung cancer?

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Non-small cell lung cancer (NSCLC) represents 80–85% of lung cancers and is the leading cause of cancer-related deaths worldwide (1).

Anaplastic lymphoma kinase (*ALK*) gene rearrangements designate a class of molecular subtypes of NSCLC which accounts for 4–5% of all non-squamous NSCLC (2). The most common *ALK* fusion partner is *EML4*. Other fusion partners discovered include *KIF5B*, *KLC1*, and *TPR* (3).

EML4-ALK fusion variants (V) result from different breakpoints with the most common V1 (54.5%), followed by 3a/V3b (34%), V2 (10%), and V5a (1.5%) that have shown different treatment responses (2,4).

Typically, at baseline diagnosis patients are young (median age 55 years), female, never or light smokers and histologically adenocarcinoma, positive for thyroid transcription factor 1 (TTF-1) with a tendence of metastases to the central nervous system, pleura, and pericardium (5).

The development of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment and outcomes of oncogenic addicted NSCLC patients (6).

Crizotinib was the first ALK TKI that was granted approval in 2011 based on the results of phase I/II clinical trials showing an objective response rate (ORR) of 60–74% and median progression-free survival (PFS) of 8–11 months (7,8). Despite the results of crizotinib over chemotherapy, resistance can occur. To date, various next-generation TKIs have been developed and approved in first- and higher-lines settings such as ceritinib, alectinib, brigatinib, and lorlatinib (*Table 1*) (9-12). Additionally, ensartinib is approved in China for first-line ALK-positive NSCLC (9-11,13).

Lorlatinib is a third-generation TKI developed to overcome resistance mechanisms following second-generation TKIs. Recently, lorlatinib was also approved for first-line treatment based on results from the CROWN trial. After 5 years of follow-up, the trial demonstrated a median PFS not reached {NR [95% confidence interval (CI): 64.3–NR]} for lorlatinib, compared with 9.1 months 9.1 months (95% CI: 7.4–10.9) for crizotinib [hazard ratio (HR), 0.19 (95% CI: 0.13–0.27)].

Lorlatinib demonstrated the best PFS rate ever observed in treatment-naïve advanced NSCLC: 60% (95% CI: 51–68) versus 8% (95% CI: 3–14) for crizotinib (12). Lorlatinib also show excellent intracranial activity in patients with and without brain metastases. The median time to intracranial progression was not reached (95% CI: NR to NR) with lorlatinib versus 16.4 months (95% CI: 12.7–21.9) with crizotinib [HR, 0.06 (95% CI: 0.03–0.12)] (12). The long-term efficacy showed by lorlatinib surpassed all the other ALK TKIs. However, clinicians should keep in mind that lorlatinib has a different safety profile compared with other ALK TKIs, including hyperlipidemia and central nervous system effects (neurocognitive impairment and psychiatric

Table 1 Characteristics of oral ALK TKIs for NSCLC patients in the clinical practice

Characteristics	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Generation	I	II	II	II	III
EMA	2L: 10/2012	2L: 05/2015	2L: 02/2017	2L: 11/2018	2L: 11/2018
	1L: 11/2015	1L: 12/2017	1L: 12/2017	1L: 04/2020	1L: 01/2022
1L mPFS (HR)	10.9 months (0.45) *vs.* chemo	16.6 months (0.55) *vs.* chemo	34.8 months (0.43) *vs.* crizotinib	24 months (0.48) *vs.* crizotinib	NR (0.19) *vs.* crizotinib
1L OS HR	0.76 *vs.* chemo	0.73 *vs.* chemo	0.67 *vs.* crizotinib	0.81 *vs.* crizotinib	NA
1L RR (%)	74	72.5	75.5	74	81
TR-AEs discontinuation (%)	12	5	14.5	12	5

1L, first line; 2L, second line; AEs, adverse events; ALK, anaplastic lymphoma kinase; EMA, European Medicines Agency; HR, hazard ratio; mPFS, median progression-free survival; NA, not available; NR, not reached; NSCLC, non-small-cell lung cancer; OS, overall survival; RR, relative risk; TKIs, tyrosine kinase inhibitors; TR, treatment related.

symptoms). A pragmatic approach in order to manage the adverse events related to lorlatinib is required.

The treatment landscape for patients with *ALK*-positive NSCLC is continuously evolving and to date we have several efficient ALK-TKI that result in long-term PFS with lorlatinib actually being the "Crown" in the treatment landscape of advanced *ALK*-positive NSCLC, especially patients with brain metastases at diagnosis.

However, lung cancer specialists are always seeking new-generation ALK-TKI in order to overcome resistance and obtain better treatment sequencing, outcomes and have a favorable safety profile.

In the Iruplinaklib in Non-Small Cell Lung Cancer as a Primary Inhibitor of ALK Rearrangement Effectiveness (INSPIRE) study, a multicenter, randomized, open-label, phase III study conducted in China, Shi *et al.* aimed to confront the efficacy and safety of iruplinalkib versus crizotinib in advanced, TKI-naïve *ALK*-positive NSCLC patients (13). This multicenter investigation led by Dr. Shi and co-authors enrolled 292 patients from 40 centers in China.

After approximately 26 months of follow-up, iruplinalkib demonstrated a median PFS of 27.7 months (95% CI: 26.3–not estimable) versus 14.6 months (95% CI: 11.1–16.5) in the crizotinib group, with HR of 0.34 (98.02% CI: 0.23–0.52, P<0.0001). Higher ORR was observed in the iruplinalkib group [93.0% (95% CI: 87.5–96.6] compared with the crizotinib group [89.3% (95% CI: 83.1–93.7)], with statistically significant improvement in duration of response (median: 26.8 *vs.* 12.9 months; HR, 0.31; 95% CI: 0.22–0.45, P<0.0001) (13). Furthermore, iruplinalkib demonstrated a higher intracranial ORR [90.9% (95% CI: 58.7–99.8] *vs.* crizotinib [60.0% (95% CI: 32.3–83.7)]. Grade 3–4 treatment-related adverse occurred in 51.7% of patients in the iruplinalkib group and 49.7% in the crizotinib group. The median PFS by Independent Review Committee (IRC) for the overall population is 36.8 months, and the median PFS by IRC for the central lab-confirmed ALK-positive patients is 45.9 months (14).

The authors compared iruplinaklib with crizotinib in the *ALK*-positive Chinese population and demonstrated that iruplinaklib exhibited superior efficacy, surpassing crizotinib in key clinical outcomes. Two key messages could be drawn from the INSPIRE study based on the results of the study: first, the improved PFS, ORR and importantly the intracranial activity define iruplinalkib as a novel finding in the therapeutic armamentarium for the treatment of patients with *ALK*-positive NSCLC. Second, it demonstrated a manageable safety profile and no deaths related to iruplinalkib (13).

However, it should be noted that beyond the data of the efficacy in PFS, the INSPIRE trial has some limitations. The data of the OS are lacking, and the study is limited only to the Chinese population. Furthermore, the comparison was conducted against a first-generation TKI (crizotinib) rather than a second- or third-generation ALK inhibitor, highlighting the need for further evaluations against more advanced TKIs.

With this in mind, we believe that iruplinalkib may be a valid alternative to other ALK TKIs approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

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Footnote

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