Mini Review
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ALK inhibitors in NSCLC- crizotinib and beyond

Abbreviations: EGFR, epidermal growth factor receptor; ALK-EML4, anaplastic lymphoma kinase echinoderm microtubule-associated protein-like 4; NSCLC, non-small cell lung cancer; PFS, progression free survival; RR, response rate; CNS, central nervous system; HR, hazard ratio; FDA, food and drug administration; mg, milligram

Volume 8 Issue 3 - 2017

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Received: May 19, 2017 | **Published:** August 02, 2017

Introduction

Lung cancer is the most common cancer diagnosed in developed countries, and it is the leading cause of cancer related death worldwide.[1]. Over 70% of lung cancer patients are diagnosed with advanced disease at presentation, and receive palliative treatment only. Until a decade ago, the treatment included chemotherapy alone, with a limited survival benefit.[2]

The identification of molecular subtypes of NSCLC revolutionized the treatment for patients diagnosed with NSCLC harboring molecular alterations. The most common are the *EGFR* mutation; which is found at 10-15% of patient, and the *ALK-EML4* rearrangement.[3], which is found at 4-7% of patients. Several ALK tyrosine kinase inhibitors were developed in the last decade, and we hereby review the current and future ALK inhibitors and the up to date treatment of ALK-rearranged NSCLC.

Currently approved ALK inhibitors

The detection of ALK rearrangement has changed the treatment and prognosis in this subgroup of patients. Crizotinib, which was originally developed for treatment of anaplastic large-cell lymphoma.[4] Table 1 was the first ALK inhibitor to be approved by the FDA in November 2014 for treatment of ALK rearranged NSCLC in the second line setting. The approval was based on the results of the PROFILE 1007, with PFS of 7.7 months, compare to 3months in the chemotherapy arm, and the RR was 65%.[5] Crizotinib waslater on approved for the 1st line treatment based on the results of the PROFILE 1014 phase III trial, showing PFS of 10.9 months vs. 7 months, and RR of 74% vs. 45% in the Crizotinib and chemotherapy arm, respectively.[6] The toxicity profile of crizotinib is different from chemotherapy, and includes vision disorders, diarrhea, nausea, vomiting, constipation, elevated liver aminotransferase levels and edema (Table 1). Currently, crizotinib is the standard 1st line treatment for NSCLC harboring ALK rearrangement, although most of the patients will develop resistance to treatment after a median of 10 months. Resistance to treatment is uasually related to the emergence of new resistant clones.[7] About a quarter of patients with ALK-rearranged NSCLC will have CNS involvement at time of diagnosis, and that site is the most frequent site of disease progression.[8] The inevitable resistance to treatment raised the need for new ALK inhibitors, with high penetrance of the blood-brain barrier and activity against the resistant clones in the second line setting and beyond.

Ceritinib was the next agent to demonstrate high anti-tumor activity for patients who progressed on crizotinib, as well as higher rate of CNS penetration. The drug was approved by the FDA in the second line setting in April 2014 in accelerated process after a phase I trial-the ASCEND 1 trial, which showed high RR among both crizotinib naïve and pretreated patients, of 58% and 56%, respectively.[9] Ceritinib has also showed prolonged duration of response, more than 8 months in the pretreated patientsIn the first line setting, ceritinib demonstrated superiority over chemotherapy, with PFS of 16.6 months vs. 8.1 months on the chemotherapy arm (HR=0.55). The toxicity profile of ceritinib included mostly GI toxicity, with diarrhea, nausea and vomiting (Table 1).[10]

The third ALK inhibitor approved in December 2015 was Alectinib, after 2 phase II clinical trials.[11] demonstrating PFS of 8.1 to 8.9 months and RR around 50% in pretreated patients. The toxicity profile of alectinib is considered favorable, and includes headache, neutropenia, fatigue, myalgia, peripheral edema, liver enzyme abnormality and hypophosphatemia. Alectinib also has improved CNS activity (Table 1).

Future ALK inhibitors

Additional ALK inhibitor approved in April 2017 was Brigatinib.[12] (Table 1), which demonstrated PFS of 8.8 months with the daily dose 90 mg, and 11.1 months with the 180 mg dose, although the starting dose will be 90 mg. The overall RR was 46% and 54% in each arm, respectively. Several other ALK inhibitors are currently under investigation (Table 1), such as Lorlatinib,[13] which similarly to Crizotinib, also acts as a ROS-1 inhibitor, and results from phase II and phase III clinical trials are pending.

Sequence of treatment

The best sequence of treatment for ALK-rearranged NSCLC patients is not clear yet, and several trials are comparing the different ALK inhibitors in first line setting to establish the preferred order of agents. The multinational phase III ALEX trial is comparing alectinib to crizotinib in the first line setting, and data from the Japanese subgroup has showen significant improvement in the PFS in the alectinib group, with HR=0.34 and a PFS of 10.2 months in the crizotinib arm vs. PFS not reached in the alectinib arm.[14] The final data from this trial demonstrated favorable PFS of alectinib (not reached vs. 11.1months with crizotinib), and hazard ratio of 0.47.[15]

Table 1 Characteristics of different ALK inhibitors in NSCLC

Agent	Standard dose	Additional targets	Mechanism of resistance	PFS in months	Side effects
Crizotinib (Xalkori)16-20	250mg twice daily	C-MET ROS1	Mutations in L1196M (Gatekeeper), L1152R, C1156Y, 1151Tins, G1202R, S1206Y, and G1269A, F1174L ALK/ EGFR/KIT amplification, KRAS mutation	2nd line 7.7m 1st line 10.9m	Visual disturbance, nausea, diarrhea, elevated liver enzymes, lymphopenia, pneumonitis, hypophosphatemia, pulmonary embolism
Ceritinib (Zykadia)26-28, 74	750mg once daily	IGF-1R STK22D PLT3 Alectinib resistant mutation I1171T/N/S		7m	diarrhea, vomiting, nausea, dehydration, elevated liver enzymes, hypophosphatemia
Alectinib (Alecensa) 34-37	600mg twice daily	RET Crizotinib resistant mutation L1196M	I1171T/N/S mutations	8.1-8.9m	Headache, neutropenia, fatigue, myalgia, peripheral edema, liver enzyme abnormality, hypophosphatemia.
Brigatinib (Alunbrig)	Arm A:90 Arm B:180 mg once daily	ROS1 EGFR STK22D PLT3		A: 8.8 m B: 11.1 m	Nausea, diarrhea, fatigue, dyspnea, increased lipase, hypoxia, elevated liver enzymes and amylase. pneumonia, pyrexia, pulmonary embolism
Lorlatinib	100mg	ROS1 Crizotinib resistant mutation L1196M LTK (TYK1)	L1198F	-	Hypercholesterole, peripheral edema

NSCLC, non- small cell lung cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KIT, tyrosine-protein kinase Kit; C-MET, tyrosine-protein kinase MET; ROS1, proto-oncogene tyrosine-protein kinase ROS; IGF-1R, insulin-like growth factor 1 receptor; STK22D, serine/threonine kinase; RET, RET proto-oncogene; PFS, progression free survival.

Conclusion

ALK TKIs have demonstrated favorable outcomes on ALK rearranged advanced NSCLC compare to standard chemotherapy, and became the standard of care for this subgroup of patients. Crizotinib is the current standard of care for 1st line treatment, and the new ALK TKIs, including ceritinib and alectinib, are used in advanced lines of treatment. Trials evaluating the sequence of ALK inhibitors are ongoing. There are several new ALK inhibitors currently assessed in clinical trials, and patients harboring the ALK rearrangement can benefit multiple lines of treatment with ALK TKI, which prolong their life.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Funding

None.

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Citation: Hamzeh A, Mor M. ALK inhibitors in NSCLC- crizotinib and beyond. *J Cancer Prev Curr Res.* 2017;8(3):249–251.
DOI: 10.15406/jcpcr.2017.08.00275

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Citation: Hamzeh A, Mor M. ALK inhibitors in NSCLC- crizotinib and beyond. *J Cancer Prev Curr Res.* 2017;8(3):249–251.
DOI: 10.15406/jcpcr.2017.08.00275