Anaplastic lymphoma kinase inhibitors in brain metastases from ALK+ non-small cell lung cancer: hitting the target even in the CNS

Samuel J. Klempner, Sai-Hong Ignatius Ou

Department of Medicine, Division of Hematology-Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA 92868, USA

Correspondence to: Samuel J. Klempner. Department of Medicine, Division of Hematology-Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA 92868, USA. Email: sklempne@uci.edu.

Abstract: The paradigm shift occurring in non-small cell lung cancer (NSCLC) is encapsulated by the management of patients harboring oncogenic anaplastic lymphoma kinase (ALK) rearrangements. The unprecedented improvements in patient outcomes resulting from ALK-directed therapy have led to the appreciation of patterns of disease progression. Early studies have suggested that some tyrosine kinase inhibitors (TKIs), including ALK TKIs, inefficiently penetrated the blood brain barrier. With the increasing appreciation of the CNS as a sanctuary site in ALK TKI-treated patients, there is increasing focus and importance on the prevention and control of CNS metastases in ALK-rearranged NSCLC. The spectrum of CNS activity is variable among the currently available ALK TKI therapies and further studies are ongoing. In the following review we discuss the ability of current and future ALK inhibitors (ALK-i) to control and prevent CNS progression in patients with ALK-rearranged NSCLC. The potential implications for TKI sequencing and important future research directions are discussed.

Keywords: Anaplastic lymphoma kinase (ALK); CNS; brain; non-small cell lung cancer (NSCLC); alectinib; crizotinib; ceritinib

Submitted Apr 02, 2015. Accepted for publication May 14, 2015.
doi: 10.3978/j.issn.2304-3865.2015.05.03
View this article at: http://dx.doi.org/10.3978/j.issn.2304-3865.2015.05.03

Introduction

The diagnostic and therapeutic approach to patients with non-small cell lung cancer (NSCLC) has undergone a paradigm shift since 2003. Increasingly NSCLC is classified by the presence or absence of specific genomic alterations, several of which have immediate therapeutic implications. Rearrangements involving the anaplastic lymphoma kinase (ALK) gene were first appreciated as potent oncogenic drivers in 2007, spawning the development of ALK tyrosine kinase inhibitors (TKIs) (1,2). The clinicopathologic features of ALK-rearranged (ALK+) NSCLC are well described, and ALK+ disease is thought to represent 4-7% of all NSCLC (3-5). The clinical benefit and feasibility of targeting ALK was demonstrated first with the multitargeted TKI crizotinib, and subsequently confirmed in phase II and III trials (6-9). Second generation ALK inhibitors (ALK-i) may offer further improvements in overall response rate (ORR), median progression free survival (PFS), and overall survival (OS), and phase III trials are ongoing (10,11).

Increasing clinical experience and improved survival durations have led to the appreciation of failure patterns in patients treated with ALK-i. Understanding the landscape of acquired resistance to ALK-i has improved, but this has been almost exclusively studied from progression biopsies in extra-cranial disease sites. Patients with CNS disease represent a disproportionate minority in clinical trials despite the relative frequency of brain metastases in NSCLC (12,13). In unselected surgical series the frequency of ALK+ NSCLC approaches 3% in resected brain metastases, approaching the frequency across all NSCLC (14). The ability of ALK-directed therapies to control and prevent the development of CNS metastases
remains incompletely studied, with early reports suggesting inefficient cerebrospinal fluid penetration for crizotinib (15). In the following review we discuss the CNS activity of FDA-approved and investigational ALK-directed therapies. Important future directions and correlative studies needed to refine the use of ALK-i in ALK+ patient with CNS disease are highlighted.

**Crizotinib**

Crizotinib is a small molecule TKI with activity against the receptor tyrosine kinases (RTK) ALK, ROS1, and MET (16-18). In pre-clinical ALK+ NSCLC cell line models the IC_{50} for crizotinib is 60-120 nM, well below the median steady state plasma concentration of 570 nM/L (274 ng/mL) achieved with the approved 250 mg twice daily oral dosing (Table 1) (19,29). Anecdotal reports have suggested a poor CSF penetration with a CSF concentration of only 1.4 nM/L suggesting a very poor CSF-to-plasma concentration ratio (Table 1) (15). Despite the low CSF-to-plasma ratio significant CNS radiographic responses to crizotinib have been described, suggesting factors beyond pharmacokinetic resistance alone.

A recent retrospective analysis focusing on crizotinib in ALK+ patients with brain metastases who were enrolled in the PROFILE 1005 and 1007 trials highlights broader CNS TKI issues (13). Among the 888 patients in the pooled PROFILE 1005 and 1007 studies, 275 were known to have brain metastasis (BM) at study entry (109 untreated, 166 previously treated). The intracranial response rate was 18% in untreated BM and 33% in previously treated BM, significantly lower than the over 50% systemic ORR (13). Interestingly, the median intracranial time to progression (TTP) was nearly doubled in patients whose BM were treated prior to crizotinib initiation (7.0 vs. 13.2 months). Further, among the 275 patients with BM at study entry, the CNS was a site of progressive disease (PD) in 70% of cases of PD on crizotinib (13). This series confirms the clinical observation that the CNS is a common site of progression in ALK+ NSCLC, and is hypothesis generating for future studies and comparisons amongst ALK TKIs. Should all patients undergo CNS-directed therapies such as whole brain radiotherapy (WBRT) or stereotactic brain radiotherapy (SBRT) prior to or at progression on crizotinib? There is a strong suggestion of added benefit to continuing crizotinib after disease progression (30,31). However, in the phase II crizotinib trial the most common site for single organ PD was the CNS (32). While crizotinib has demonstrated CNS activity, next-generation ALK-i has demonstrated further improvements and is discussed below.

**Ceritinib**

The second generation ALK-i ceritinib (LDK378) is a potent ATP-competitive inhibitor with increased activity against common ALK point mutations including L1196M, G1269A, S1206Y, and I1171T (20,33,34). Although less active against the uncommon ALK alterations C1156Y, L1152P, G1202R, F1174C and 1151T-ins ceritinib demonstrated approximately 20-fold greater efficiency in ALK+ NSCLC cell lines and prolonged activity in xenograft models (Table 1) (20,35). Phase I testing determined a plasma C_{MAX} 800±205 ng/mL at a dose of 750 mg orally once per day (11). The activity of ceritinib in ALK+ NSCLC has been confirmed in phase I and II testing with

<table>
<thead>
<tr>
<th>Compound</th>
<th>ALK enzymatic IC_{50} (nM)</th>
<th>ALK in vitro/vivo GI_{50} (H3122, H228) (nM)</th>
<th>Trough plasma concentration (nM/L)</th>
<th>CSF concentration (nM/L)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>3.6</td>
<td>245, 107</td>
<td>570</td>
<td>1.4</td>
<td>(17,19,20)</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>0.15</td>
<td>6.3, 3.8</td>
<td>1,254</td>
<td>N/A</td>
<td>(11,20)</td>
</tr>
<tr>
<td>Alectinib</td>
<td>1.9</td>
<td>33, 53</td>
<td>951</td>
<td>2.7</td>
<td>(10,21-23)</td>
</tr>
<tr>
<td>AP26113</td>
<td>0.62</td>
<td>4, 10</td>
<td>~1,000</td>
<td>N/A</td>
<td>(24-26)</td>
</tr>
<tr>
<td>PF-06463922</td>
<td>&lt;0.07</td>
<td>1.3</td>
<td>551 (rat)</td>
<td>3,475 nM/h</td>
<td>(27,28)</td>
</tr>
</tbody>
</table>

The reported *in vitro* data represent the most commonly referenced values. The GI_{50} is highly variable across different ALK mutations, and the GI_{50} presented represents reported values using cell lines H3122 and H228 expressing the *EML4-ALK* rearrangement. Data for H3122 and H228 models are not available for PF-06463922, and are shown for 3T3 EML4-ALK engineered cell lines. Activity across differing ALK mutations is reviewed in the appropriate references. ALK, anaplastic lymphoma kinase; N/A, not available.
ORR of 58% in patients receiving at least 400 mg daily, and 56% in the 80 patients previously treated with crizotinib (11). In the 34 crizotinib-naive patients who received at least 400 mg the ORR was 62%. Among the 114 ALK+ NSCLC patients receiving at least 400 mg daily the median PFS was 7.0 months, and was similar (6.9 months) in the crizotinib resistant subgroup (n=80) (11). Based on this data ceritinib was approved in April 2014 for ALK+ NSCLC patients who progressed or were intolerant to crizotinib. Subsequently, the European Medicines Agency (EMA) has recommended ceritinib for approval in Europe in March 2015.

The CNS activity of ceritinib is less well studied, and CSF measurements are not available (Table 1). However, 64 (49%) patients in the phase I ceritinib study had BM, and in the updated presentation the ORR was 54% in 124 patients with BM at study entry (36). Further, the ORR was 69.2% in ALK-i naive BM and 50.0% in patients previously exposed to ALK-directed therapy. Overall, the median PFS for patients with BM at entry was 6.9 months, not statistically different from the overall study population (37). The improved CNS activity likely reflects the improved chemical potency and/or improved CNS penetration. Routine CSF sampling can be cumbersome to incorporate into early phase clinical trials, but provides important details needed to refine ALK-directed therapy. Further, direct comparisons across ALK-i in terms of CNS activity are confounded by a lack of CSF pharmacokinetic parameters.

### Alectinib

Alectinib (CH5424802, RO5424802) is another highly selective orally available ALK-i with favorable preclinical studies in ALK-driven cancer models. Alectinib demonstrates potent ALK inhibition with an in vitro kinase IC\textsubscript{50} of 1.9 nM, and is also active against the F1174L, R1275Q, and gatekeeper L1196M ALK mutations (21-23). The clinical activity of alectinib was demonstrated in a phase I-II studies at doses of 300 and 600 mg twice daily. In the phase I study of crizotinib naive patients receiving alectinib 300 mg twice daily the plasma trough concentration is 463±369 ng/mL with a C\textsubscript{MAX} of 575±322 ng/mL, well above the levels needed for ALK inhibition (Table 1) (10). Of the 46 patients in the phase II portion of the alectinib trial the response rate was 93.5% with treatment duration over 7 months (10). Over 30% (33%, n=15) of the 46 patients in the phase II portion had known BM. Although 26% (n=12) with BM had undergone prior radiation, disease control in the CNS was favorable, with a median of 6.5 months in the original study. Subsequently, the activity of alectinib in crizotinib resistant or intolerant patients has been confirmed in a phase 1/2 study (38). Twenty-one patients enrolled in this trial had BM at study entry, and the response rate in the CNS was 52% (n=11) across all CNS subgroups. In the four patients with no prior CNS radiation there were two complete responses, one partial response, and one patient with stable disease. Paired steady state and CSF samples from alectinib at 600 and 900 mg twice daily demonstrate a CSF trough concentration of about 2.7 nM/L for the phase II dose of 600 mg orally twice per day (38). In animal models alectinib reaches the cerebral hemispheres and cerebellum at tissue concentrations comparable to the level in plasma (39).

The study by Gadgeel and colleagues raises several important considerations for the management of ALK+ NSCLC with CNS metastases. The response assessment in the CNS used standard RECIST criteria, in which only nine patients had measurable CNS lesions at baseline, thereby limiting the conclusions due to small sample size. The problems with RECIST evaluation of CNS lesions is further highlighted by an interesting patient in the phase I alectinib study. A patient with systemic partial response developed RECIST progression in a previously SBRT-treated occipital metastasis (40% enlargement) in the context of response in the two other known CNS lesions. Due to isolated progression this patient was taken for surgical resection with pathological examination indicating the lesion was entirely necrotic, with no viable tumor (38). Thus, this case represents pseudoprogression, possibly related to the use of RECIST, rather than a CNS specific response assessment system such as the RANO criteria (40-42). Overall, alectinib demonstrates CNS activity in both crizotinib naive and crizotinib resistant ALK+ NSCLC. Numerically the CNS response rates are comparable to ceritinib and more rigorously studied in the case of alectinib. However, the small sample sizes, use of imprecise assessment tools (RECIST), and relatively short follow up duration limit direct comparisons and conclusions.

### AP26113 and PF-06463922

AP26113 is a next-generation ALK and EGFR (mutant EGFR only) inhibitor with activity across all known crizotinib resistant ALK mutations. Preclinical studies have identified potent ALK inhibition with sub-nanomolar in vitro kinase IC\textsubscript{50}, and achievable plasma concentrations well above the GI\textsubscript{50} for several cell lines models (Table 1) (24-26). Early
clinical activity is comparable to alectinib, and among 72 evaluable ALK+ NSCLC the response rate is 72% (n=52) with a median response duration of 49 weeks (43). A similar response rate of 69% and median PFS of 47.3 weeks was seen in the ALK+ NSCLC with prior crizotinib therapy (n=65). In the 14 patients with untreated or progressing BM the response rate was 71% (n=10) with four complete CNS responses (43). The CNS responses occurred almost exclusively in patients at the 180 mg daily dosing, and have not yet been confirmed at the 90 mg daily dose moving forward in phase II testing. The promising phase I-II results led the FDA to assign AP26113 breakthrough designation in October 2014. Further studies including the phase II ALTA trial in refractory ALK+ NSCLC are ongoing and will provide further data on optimal dose schedule (90 mg daily or 90 mg lead in followed by 180 mg daily) as well as clarify CNS activity.

PF-06463922 is another next-generation ALK-i structurally engineered to have improved CNS penetration. The p-glycoprotein (Pgp) mediated efflux mechanism is a known barrier to achieving optimal CNS penetration and optimal CSF to free plasma ratios (44,45). The macrocyclic chemical structure, lipophilicity, relatively lower molecular weight (406.4 g/M), and area under the curve ratio of CSF to free plasma of 0.31 demonstrated favorable CNS penetration with a PF-06463922 (27). By way of comparison, the CSF to plasma ratio is 0.0026 for crizotinib (plasma concentration, 273 ng/mL; CSF, 0.616 ng/mL) (15). Further suggestion of CNS penetration can be extrapolated from the activity of PF-06463922 in the transgenic FIG-ROS1-driven glioblastoma mouse model where significant tumor regression has been shown (28). Beyond the CNS PF-06463922, like AP26113 is a potent ALK-i with promising preclinical efficacy against the gatekeeper L1196M ALK mutation (Table 1) (28,46). Based on promising pre-clinical systemic and CNS activity PF-06463922 is currently in early phase clinical trials in ALK+ NSCLC.

Conclusions

The biologic understanding and therapeutic options in NSCLC have changed drastically in the last 10 years. The identification of a subset of NSCLC driven by ALK-rearrangements has led to the rapid development and approval of ALK-directed therapies that have already drastically improved patient outcomes compared to chemotherapy (8,9). Despite improved outcomes, therapy is not curative and resistance universally develops, with the CNS as the most common site of PD. Not surprisingly, the CNS activity of ALK-i tends to parallel the chemical potency of the compound. Although incompletely studied, the idea that in the event of equal CNS pharmacokinetic parameters, the more potent inhibitor is likely to have improved clinical activity appears to bear out in early clinical investigations. The next-generation ALK-i has improved CNS activity over crizotinib but several important issues warrant consideration moving forward.

Increasingly, whether through tissue or blood-based assays, progression biopsies are informing subsequent therapeutic choices. The current next-generation inhibitors have highly variable inhibitory activity across differing ALK mutations. With the anticipated approval of multiple next-generation ALK-i will the choice of therapy, including BM, be based on pharmacokinetic (PK) parameters in the observed resistance mutation? There is a further paucity of data studying whether the molecular determinants of ALK-i resistance are the same in CNS and extracranial disease. Increasing use of surgical resection, and possible CSF sampling, may help to answer these questions.

Similarly, the current criteria used to assess CNS response in solid tumors are imperfect. The proposed Response Assessment in Neuro-Oncology (RANO) group criteria accounts for pseudoprogression resulting from radiation necrosis within 3 months of radiotherapy completion in primary CNS malignancies such a glioblastoma multiforme (40). However, neither RECIST nor the RANO criteria outline pseudoprogression determination in non-primary CNS solid tumors such as NSCLC. We expect that with the CNS activity of next-generation ALK-i the incidence of pseudoproggression will increase, and further diagnostic modalities (steroid challenge, short interval repeat MRI, MR spectroscopy, and surgical biopsy/resection) will need to be explored prior to removing a potentially active ALK-i from a given patients’ therapy (47).

Finally, the optimal sequence of ALK-i remains to be determined. Next-generation agents such as alectinib can salvage CNS disease in patients treated with both crizotinib and ceritinib (48). Larger head to head trials such as the phase III ALEX trial (alectinib vs. crizotinib) will directly investigate PFS in the CNS and may provide further information to inform treatment decisions for ALK+ patients with BM. Overall, the outcomes for ALK+ with CNS disease are expected to continue to improve with the introduction of increasingly effective therapies. Here we have reviewed the current data in ALK+ NSCLC with CNS
disease and suggested several CNS-specific considerations that are important to determine the optimal management of BM moving forward.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Klempner SJ, Ou SH. Anaplastic lymphoma kinase inhibitors in brain metastases from ALK+ non-small cell lung cancer: hitting the target even in the CNS. Chin Clin Oncol 2015;4(2):20. doi: 10.3978/j.issn.2304-3865.2015.05.03