Editorial

Moving molecularly directed therapies to the first-line in *ALK*-positive lung cancer: crizotinib is just the beginning

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Abstract: The increasing appreciation of oncogenic driver alterations in non-small cell lung cancer (NSCLC) has resulted in a rapid expansion of therapeutic compounds. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations are the prototypical examples and have driven the paradigm shift in NSCLC management. Early phase studies in previously treated ALK+ patients demonstrated activity and recently Solomon *et al.* confirmed the superiority of crizotinib over chemotherapy in first line treatment. The phase III PROFILE 1014 represents the culmination of the rapid development of crizotinib and provides lessons for future generation ALK inhibitors and other molecularly directed therapies in NSCLC. Important considerations for second and third generation inhibitors include the ability to overcome known resistance mechanisms, CNS activity, improvement in side effect profile, and safety in possible combination strategies.

Keywords: Crizotinib; anaplastic lymphoma kinase (ALK); lung cancer; targeted therapy; ceritinib; alectinib

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The concept of matching a drug to a specific cell surface receptor, initially referred to as "side-chain theory", dates back to Paul Ehrlich in 1901 (1). Over one hundred years later anaplastic lymphoma kinase (ALK) rearrangement was identified as a transforming oncogenic driver and potential therapeutic target in lung cancer (2). The successes of the modern versions of side-chain theory are well known, imatinib, erlotinib, ibrutinib, vemurafenib, rituximab, trastuzumab, etc., but despite the improved recognition of possible driver alterations few targeted therapies improve survival, and none are curative. Tumor heterogeneity, the ability of coexistent genomic alterations to modify response, and the invariable development of resistance have limited the therapeutic efficacy of molecularly directed therapies.

The oncogenic potential of *ALK* thus far requires chromosomal rearrangements leading to in-frame gene fusions, similar to the BCR-ABL paradigm, and single point mutations alone are not transformative. *ALK* gene fusions are translated into cytoplasmic chimeric proteins with constitutive, ligand-independent, tyrosine kinase activity. Beyond non-small cell lung cancer (NSCLC) *ALK* rearrangements have now been observed in renal cell carcinoma, inflammatory myofibroblastic tumors, thyroid, colorectal, and breast cancers, with over 20 unique fusions described, 11 in NSCLC (*Table 1*) (2-13). Early preclinical studies with ALK inhibitors conducted on cell lines derived from patients with ALK-rearranged (ALK+) NSCLC demonstrated potent growth arrest (14). Further *in-vitro* and *in-vivo* work confirmed the anti-proliferative effects of ALK inhibition in ALK+ mouse models, encouraging further clinical development (15). In 2010, the phase I clinical trial conducted by Kwak *et al.* explored the effects of the ALK inhibitor crizotinib in 82 pre-treated ALK-positive patients. This study showed an overall response rate (ORR) of 57% and stabilization of disease in an additional 33% (16). These promising results prompted a follow-up study expanding the original cohort by including 61 additional patients. The results from this study were similar with an ORR of 60.8%

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Table 1 Comprehensive list of known ALK fusion partners in NSCLC

ALK fusion partner (location)	Rearrangement type	Sensitive to crizotinib	Reference
EML4 (2p21)	Paracentric inversion	Yes	Soda *et al.* (2)
TFG (3q12.2)	Interchromosomal	Yes*	Horn *et al.* (3)
KIF5B (10p11.22)	Interchromosomal	Yes	Shaw *et al.* (4)
KLC1 (14q32.3)	Interchromosomal	Assumed	Shaw *et al.* (4)
STRN (2p22.2)	Complex rearrangement	Yes*	Majewski *et al.* (5)
HIP1 (7q11.23)	Interchromosomal	Yes*	Ou *et al.* (6)
PTPN3 (9q31)	Interchromosomal^	N/A	Jung *et al.* (7)
TPR (1q25)	Interchromosomal	Assumed	Choi *et al.* (8)
BIRC6 (2p22.3)	Paracentric inversion	Yes	Ying *et al.* (In Press)
SOCS5 (2p21)	Complex rearrangement	Yes*	Drilon *et al.* (9)
CLIP4 (2p23.2)	Cryptic inversion**	Yes*	Drilon *et al.* (9)

^, this is not a functional fusion; *, limited clinical experience, appears to be sensitive; **, due to genomic proximity (35 kb) of ALK and CLIP4, this is possible cryptic inversion. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

a median duration of response of 49.1 weeks and a median progression free survival (PFS) of 9.7 months (17). The results of these trials substantiated the FDA decision for accelerated approval of crizotinib in August 2011, followed by full approval in November 2013. A confirmatory second-line phase III study comparing crizotinib to chemotherapy, using either single agent pemetrexed or docetaxel, was conducted in 347 patients with progressive locally advanced or metastatic ALK+ lung cancer. The crizotinib treatment group showed a median PFS of 7.7 months compared to 3.0 months in the chemotherapy arm. The hazard ratio for progression or death in the crizotinib group *vs.* the chemotherapy group was 0.49 (95% CI, 0.37-0.64) with P<0.001 (18). In the recently published phase III PROFILE 1014, Solomon and colleagues demonstrated the superiority of crizotinib over modern first line platinum doublet therapy (cisplatin-pemetrexed or carboplatin-pemetrexed) in ALK+ NSCLC (19). The results themselves were not unexpected and served to confirm the previously presented crizotinib activity (16-18). The ORR of 74% *vs.* 45% and a median PFS of 10.9 *vs.* 7.0 months highlights the advantage of a molecularly directed therapy over broadly cytotoxic therapy (19).

In addition to first line justification, the PROFILE 1014 trial offers some important insights into the characteristics and natural history of ALK+ NSCLC. To our knowledge this is the largest and most well characterized cohort of treatment naïve ALK+ NSCLC. Interestingly, 26% of the population had known brain metastases at the time of presentation, a figure more than twice the rate of brain metastases in treatment naïve non ALK+ NSCLC (19,20). Prospective analysis of the intracranial efficacy from the PROFILE 1014 cohort demonstrated a trend toward improved intracranial TTP and statistically significant improvement in intracranial disease control rate (DCR) at 12 and 24 weeks (21). Whether or not ALK+ NSCLC has a particular tropism for early CNS spread cannot be concluded from PROFILE 1014, and crizotinib superiority over chemotherapy was not affected by the presence of CNS metastases (19). Importantly, later generation ALK inhibitors may offer further improvements in CNS activity.

Solomon and colleagues should be commended for the use of a modern platinum doublet (carboplatin or cisplatin plus pemetrexed) with known activity in ALK+ disease as the crizotinib comparator arm. The PFS reported for the chemotherapy arm of PROFILE 1014 (7.0 months) compares favorably with previously reported chemotherapy trials. Maintenance therapy in NSCLC has demonstrated improvements in PFS and OS, however, the median PFS from the pemetrexed maintenance arm of the phase III PARAMOUNT trial was 4.1 months, and increased to 7.4 months in the AVAPERL trial, and we would not predict maintenance therapy to significantly affect the PROFILE 1014 results (22,23).

Overall, the well-conducted PROFILE 1014 is an important and necessary addition to the management of ALK+ NSCLC, but also raises several concepts important for the future of ALK-directed therapies. First, the ORR

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of 74% is significantly greater than chemotherapy, but also suggests that 1 in 4 untreated patients with ALK+ NSCLC (by Vysis ALK Break Apart FISH) failed to achieve a RECIST response and/or have de-novo resistance. Second, while a PFS of 11 months is an improvement, why are these responses not more durable? Finally, if second and third generation inhibitors offer significant activity after crizotinib failure, then what is the optimal sequence of ALK-directed therapy in NSCLC?

Improvements in diagnostic sensitivity has led to the recognition that a subset of malignant clones in epidermal growth factor receptor (EGFR) mutant tumor carry de-novo T790M resistance mutations, and that patients with pre-existing T790M mutations derive less benefit from first line erlotinib (24). In fact, 66% of patients harbored de-novo T790M mutations and the PFS was 9.7 months for T790M+ *vs.* 15.8 months for T790M-tumors in the pivotal EURTAC trial (24). Crizotinib resistance mechanisms include the gatekeeper L1196M mutation, solvent front mutations such as G1202R and S1206Y, ALK fusion gene amplification, EGFR and c-KIT pathway activation, and likely several others yet to be identified (4). Increasingly sensitive tests may identify subsets of ALK+ patients harboring de-novo resistance mutations, perhaps underlying the variability in response duration observed clinically. The second generation ALK inhibitors ceritinib and alectinib can overcome some of the resistance mechanisms, which may partly explain the improved response rates observed in early trials (6,25-28). Comprehensive profiling assays will continue to refine the mutational landscape of ALK+ NSCLC and identify co-existent alterations that may modify response and resistance to ALK-directed therapies. Sequencing-based approaches have the additional advantage of identifying novel fusion partners, something that cannot be done with immunohistochemistry or gold standard FISH testing.

The superiority of crizotinib to first line chemotherapy is likely to be eclipsed by other ALK inhibitors but represents an important advance and proof that understanding tumor biology translates to improved outcomes. If crizotinib represents a first try at one of Ehrlich's "silver bullets", then we hope the future of ALK-therapies parallels the pace of weapons advancements since 1900.

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Footnote

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