Clinical Epidemiology

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REVIEW

Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors

This article was published in the following Dove Press journal:
Clinical Epidemiology
20 November 2014
Number of times this article has been viewed

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Abstract: Improved understanding of molecular drivers of carcinogenesis has led to significant progress in the management of lung cancer. Patients with non-small-cell lung cancer (NSCLC) with *anaplastic lymphoma kinase* (*ALK*) gene rearrangements constitute about 4%–5% of all NSCLC patients. *ALK+* NSCLC cells respond well to small molecule *ALK* inhibitors such as crizotinib; however, resistance invariably develops after several months of treatment. There are now several newer *ALK* inhibitors, with the next generation of agents targeting resistance mutations. In this review, we will discuss the prevalence and clinical characteristics of *ALK+* lung cancer, current treatment options, and future directions in the management of this subset of NSCLC patients.

Keywords: *anaplastic lymphoma kinase* (*ALK*), gene rearrangements, lung cancer, kinase inhibitors, lung adenocarcinoma

Introduction to the gene mutations in patients with non-small-cell lung cancer

Lung cancer is not only the most common cancer worldwide with 1.8 million people diagnosed per year, but is also the deadliest with 1.6 million annual deaths.[1,2] Although the majority of cases are detected in current or ex-smokers, increasingly patients with minimal or no smoking history are being diagnosed.[3] Recent efforts to improve earlier detection of non-small-cell lung cancer (NSCLC) through screening[4,5] may improve the stage of diagnosis and cure rates; however, currently most patients are diagnosed with locally advanced or metastatic disease.

The management of cancer has undergone significant evolution over the last decade due to improvement in the understanding of molecular drivers of carcinogenesis. The discovery of oncogenes, such as the *epidermal growth factor receptor* (*EGFR*), *Kirsten rat sarcoma viral oncogene* (*KRAS*), and *V-raf murine sarcoma viral oncogene homolog B1* (*BRAF*), and the development of medications that specifically target these mutations or the wild-type receptor have led to the ability to personalize therapy (Figure 1).[6–9] In a recent study, an actionable driver mutation was detected in 64% of tumors from patients with lung adenocarcinoma and oncologists can now employ specific therapies based on molecular profiling.[10]

Although the importance of *anaplastic lymphoma kinase* (*ALK*) as an oncogene in lymphoma has been recognized for many years, it has only recently become targetable using small molecule inhibitors. The success of these therapies has resulted in dramatic improvements in survival without significant toxicities.

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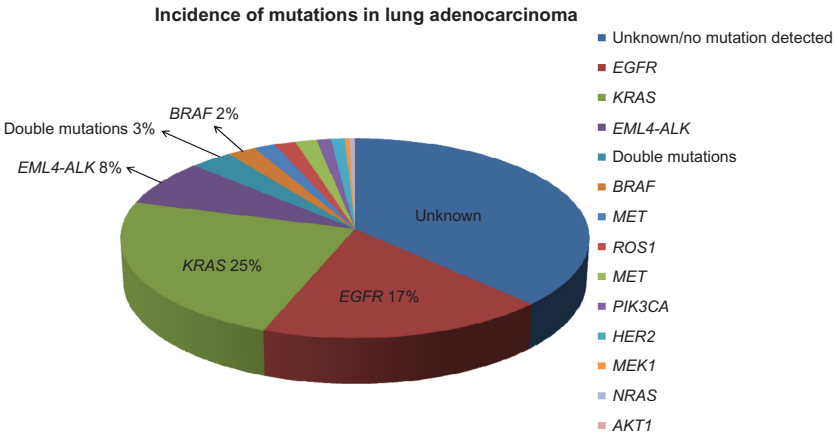

Figure 1 Incidence and variety of oncogenic drivers in lung adenocarcinoma.
Note: Data from Kris et al.[10]
Abbreviations: *ALK, anaplastic lymphoma kinase; BRAF, V-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; EML, echinoderm microtubule-associated protein-like 4; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene; MET, mesenchyme to epithelial transition.*

Here, we summarize the current literature and future directions in targeting tumors harboring *ALK* gene rearrangements (*ALK+*). We will detail the types of rearrangements present, correlation with clinicopathological features, therapeutic strategies to abrogate these pathways in addition to resistance mechanisms, and the novel agents being trialed at present.

Identification and prevalence of ALK rearrangements

ALK+ NSCLC represents approximately 4%–5% of all NSCLC patients in both Caucasian and Asian populations.[11–13] Although this population is a small fraction of the overall NSCLC population, given the worldwide prevalence of NSCLC, this still represents potentially 40,000 new cases worldwide each year.[14,15]

The *ALK* gene was initially discovered in 1994 via the cloning of the t (2; 5) (p23; q35) translocation found in a subset of anaplastic large-cell lymphomas.[16] Although the *ALK* gene is known to be an important determinant of prognosis in lymphoma, its association with NSCLC was only reported in 2007 when a small inversion within chromosome 2p that juxtaposes the 5′ end of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene with the 3′ end of the *ALK* gene, resulting in the novel fusion oncogene *EML4-ALK* in NSCLC cells, was reported (Figure 2).[6,17] Multiple *EML4-ALK* variants have been identified with variations in truncations of *EML4* on

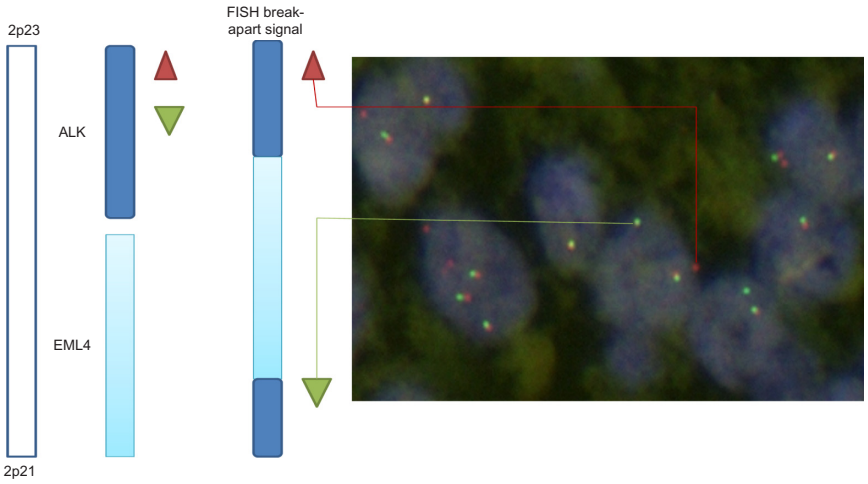

Figure 2 Illustration of *EML4-ALK* fusion oncogene in non-small-cell lung cancer and the detection by FISH.
Notes: The red and green signals are usually next to each other on chromosome 2; however, when the *ALK* translocation is present, the red and green probes separate and are seen as the classic FISH break-apart signal. *ALK* FISH image courtesy of Dr Adrienne Morey, St Vincent's Hospital, Sydney.
Abbreviations: ALK, anaplastic lymphoma kinase; EML, echinoderm microtubule-associated protein-like 4; FISH, fluorescence in situ hybridization.

different exons, but the *ALK* gene in all of them includes the exon 20 kinase domain.[6,18]

Confirmation of *EML4-ALK* as an oncogenic driver in NSCLC was demonstrated by the insertion of the fusion protein into NIH 3T3 fibroblasts that were then implanted subcutaneously into nude mice. All (eight out of eight) of the implanted mice developed lung adenocarcinomas,[19] whereas those injected without the translocation did not form tumors.

There are now over 20 *ALK* fusion partners identified in NSCLC. *EML4* represents the commonest fusion partner with 29%–33% of gene fusions identified to date.[20] After *EML4*, the commonest are *TFG* and *KIF5B*, although other partners include *NPM*, *TPM3*, *TPM4*, *ATIC*, *CLTC*, *MSN*, *MYH9*, *ALO17*, *IMT*, *SEC31A*, and *SQSTM1*.[16,21–34] This has led to some researchers developing panels of single and multiplex reverse transcription polymerase chain reaction (RT-PCR) assays suitable for rapid and accurate detection of the more common *ALK+* variants, which are a useful adjunct to fluorescence in situ hybridization (FISH) assay of tumor specimens.[35]

Detection of *ALK* gene rearrangements

Several diagnostic platforms have been developed to detect *ALK+* cells. Due to its ability to visualize rearrangements using dual color, FISH with break-apart probes has become accepted as a reference standard in the assessment of *ALK+* NSCLC.[36]

Immunohistochemistry (IHC) for *ALK* can also detect *ALK* fusion proteins; however, it is reliant on increased cellular protein levels that may not always accompany the *ALK* fusion. Several different antibodies have been developed, including the murine monoclonal *ALK*1 clones, SP8, 5A4, ZAL4, P80, 5A4, or the rabbit D5F3.[37] Although some groups have found IHC to be specific but relatively poor in sensitivity to detect *ALK* rearrangements,[38] a recent report by Wynes et al found the *ALK* IHC assay was highly sensitive (90%), specific (95%), and accurate relative (93%) to the *ALK* FISH results.[39] A recent analysis by Cabillic et al reviewed 3,244 consecutive NSCLC cases with parallel FISH and IHC *ALK* testing via the primary *ALK* monoclonal antibody clone 5A4 (Abcam, Cambridge, UK). A significant level of discrepancy was found with 70/150 (47%) found to be discordant. This study supports the need to combine testing to optimize the selection of eligible patients to be treated with *ALK* inhibitors, given that some patients with discordant testing were also found to respond to crizotinib.[40] However, IHC remains a reliable screening tool for identification of *ALK* rearrangements and is certainly more cost-effective than FISH,[41] with the caveat that occasional fusions will be missed. IHC detection of the ALK protein can be affected by a number of factors including variations in antigen retrieval, tissue fixatives, and fixation methods; varying sensitivities of reagents; and intra and interobserver variations.

Recently, RT-PCR of cDNA was reported as another useful tool that is sensitive and specific in the identification of *ALK* rearrangements,[42,43] and it also allows the fusion partner of *ALK* or *EML4-ALK* variants to be identified if the partner is screened for.[44] However, this methodology runs the risk of false negative results as RT-PCR requires high-to-moderate quality RNA that can be difficult to extract from the paraffin-embedded specimens used in daily clinical practice. It is therefore less appealing as a primary screening tool for *ALK+* NSCLC but may be an adequate test for confirming results of IHC or FISH analysis.[35] Furthermore, the need for RNA may limit this platform for routine medical testing.

Clinical features, natural history, and prognosis of patients with *ALK+* NSCLC

The median age of patients with *ALK* rearrangements is 52 years, which is younger than most NSCLC patients either with an *EGFR* mutation or an unselected NSCLC population. There is a male preponderance[11] and most patients have a never or light (<10 pack years) smoking history.[45] Shaw et al reviewed 141 patients with two or more of the following characteristics: female sex, Asian ethnicity, never/light smoking history, and adenocarcinoma histology, and found the frequency of *ALK+* NSCLC to be 22%. Although the cohort of screened patients was enriched for women, a greater percentage of men were *ALK+* (23% vs 9%). Within the same group of patients who did not have an *EGFR* mutation, the frequency of *ALK+* was 33% underscoring the importance of testing patients with this phenotype.[11] Most *ALK+* patients have advanced disease at time if diagnosis, which may reflect the aggressiveness of these tumors and their predilection for cerebral and hepatic metastases in addition to pleural and pericardial effusions.[46] The anatomical location of *ALK+* lung cancers appears to be more central and subsequently bronchoscopic cytology positivity is more common in the *ALK+* group of patients.[47]

The majority of *ALK+* NSCLCs are adenocarcinomas with only a few reports of squamous cell pathology.[48] The solid growth pattern with signet ring cell component, a feature not often seen with *EGFR* mutant or wild-type NSCLC, and

mucinous cribriform pattern with extracellular mucinous materials are the major histological findings.[49,50] Although rare reports of coexistent oncogenic driver mutations exist, most patients are wild type for other common drivers such as *EGFR*, *BRAF*, and *KRAS*.[51–53]

There are varying opinions on the implications for survival with *ALK+* NSCLC with most concluding *ALK* positivity as a poor prognostic factor in NSCLC.[11,54–58] In a study by Shaw et al, the median overall survival (OS) for *ALK+*, crizotinib-naive patients compared with *ALK−*, and *EGFR* wild-type patients did not differ significantly (20 months vs 15 months; hazard ratio [HR] =0.77, 95% confidence interval [CI] =0.50–1.19; *P*=0.244). In comparison, *ALK+* patients who were given second-line or third-line crizotinib had significantly better survival than patients with *ALK−*, *EGFR* wild-type tumors (HR =0.49, 95% CI =0.27–0.91, *P*=0.020). Fallet et al reviewed 116 French patients who were prospectively screened for *ALK* rearrangements (14.6% *ALK+*) and the median OS was not reached for *ALK+* patients (94.1% of *ALK+* patients received crizotinib), which was significantly longer than *ALK−* patients (HR for death =2.98, 95% CI =1.29–6.90, *P*=0.01).[59] Therefore, in the absence of crizotinib or *ALK* inhibitor therapy, *ALK* rearrangements are not a favorable prognostic factor for survival. Kulig et al reviewed published data between July 2007 and November 2013 and also concluded *ALK+* was a negative prognostic factor in NSCLC in studies controlling for known confounding factors.[60]

Zhang et al reviewed a group of patients without *ALK* inhibitor treatment and did not detect a survival difference according to *ALK* status after adjusting for disease stage, histology, and *EGFR/KRAS* mutation status.[61] However, other groups have subsequently found *ALK+* NSCLC to be associated with improved survival outcomes. Wu et al[62] found that patients with *ALK+* NSCLC (naive to *ALK* inhibitor treatment) identified from pleural effusion cytology had a significantly improved survival outcome compared with patients without *EML4-ALK* (median 14.7 vs 10.3 months, *P*=0.009, HR =0.53, 95% CI =0.32–0.87). Takeuchi et al[63] found that the presence of a kinase fusion (*ALK*, *ROS 1*, and *RET* fusion) was an independent favorable prognostic factor after taking into consideration age, sex, stage, and smoking status, and found no significant difference in OS between kinase positive and *EGFR* mutant groups (*P*=0.32). The difference in survival outcomes and effects could be related to several factors such as small sample size of *ALK+* patients in the studies, heterogeneous patient population between different countries, particularly the background *EGFR* mutant rate that has been noted to be higher in Asian populations and the variability of treatment regimes, including the use of *ALK* inhibitors in some studies.

The role of *ALK+* as a predictive marker for response to chemotherapy has been explored in a number of studies. For patients treated with cisplatin and pemetrexed first-line, the median time to progression was 9 months for *ALK+* patients but 6.2 months among 32 *ALK−* patients.[64] This is notably similar to another study, which also reported median progression free survival (PFS) of 9 months compared to 4 months (HR =0.36, 95% CI =0.17–0.73, *P*=0.0051) in *EGFR*, *ALK*, and *KRAS* negative patient group.[65] PROFILE 1007 involved 347 *ALK+* patients who had failed one prior platinum-based chemotherapy and were randomly assigned to receive crizotinib (250 mg twice daily) or single-agent chemotherapy with either docetaxel or pemetrexed. The response rate to pemetrexed was higher than expected – 29% as compared with 12.8% in the general population of patients with lung adenocarcinoma who had previously been treated with chemotherapy. Therefore, patients with *ALK+* NSCLC may have higher response rates with pemetrexed than patients with *ALK−* NSCLC[66] and pemetrexed may be a better chemotherapeutic option for *ALK+* patients. Supporting this, *ALK+* tumors have been shown to express significantly lower thymidylate synthase levels compared to *ALK−* adenocarcinomas. Increased thymidylate synthase expression in malignant tumors is associated with reduced sensitivity to pemetrexed.[67] This may explain the observed improved responses and survival observed in *ALK+* patients who received pemetrexed chemotherapy.[68]

Emerging treatment options for NSCLC targeting ALK rearrangements

Crizotinib was designed as a multitargeted receptor tyrosine kinase inhibitor (TKI) and entered early Phase I clinical development initially as an inhibitor of the mesenchyme to epithelial transition (*MET*) pathway. Attention was focused on *ALK+* tumors once researchers discovered dramatic clinical benefit associated with crizotinib in the first two patients who were *ALK+*.

The role of crizotinib in the management of *ALK+* lung cancer was first evaluated in an international, multicenter Phase I study (PROFILE 1001),[69,70] where overall response rates of 57% (47 of 82 patients) were observed, with 27 patients (33%) achieving stable disease. Crizotinib was shown to be tolerable with a good safety profile. The main adverse effects included visual disturbances, gastrointestinal side effects (nausea,

56%; diarrhea, 50%; vomiting, 39%; and liver function abnormalities, 12%), and pneumonitis.[70] Reduced levels of testosterone and potential hypogonadism have been observed and may also be related to the potential central effects of crizotinib on the hypothalamus/pituitary axis.[71]

In 2011, crizotinib received accelerated approval from the US Food and Drugs Administration (FDA) in view of its efficacy as a therapeutic modality for *ALK+* NSCLC based on the results from the 2009 single-arm, global Phase II study of crizotinib (PROFILE 1005, NCT00932451). The study involved 136 patients with *ALK+* NSCLC (as determined by a centralized FISH test) who had progressed after initial chemotherapy for advance disease. The objective response rate (ORR) was 51% and disease control rate at 12 weeks was 74%, which was impressive in a group of pretreated patients.[72]

The subsequent Phase III trial PROFILE 1007 demonstrated that when compared with second-line chemotherapy, crizotinib prolonged PFS, increased response rates, and improved the quality of life in patients with advanced, previously treated *ALK+* NSCLC.[66] PFS, which was the primary end point, was significantly improved in the crizotinib arm (median PFS =7.7 months vs 3.0 months, HR =0.49, 95% CI =0.37–0.64, $P<0.001$), but there was no OS benefit, which was likely due to 64% of patients crossing over to the crizotinib arm on progression.

The PROFILE 1014 trial randomized untreated stage IV *ALK+* NSCLC patients to either crizotinib or a platinum/pemetrexed combination. Not surprisingly, these data showed that crizotinib was superior to standard doublet chemotherapy in prolonging PFS, the primary objective (median =10.9 months vs 7.0 months, HR =0.454, 95% CI =0.346–0.596, $P<0.0001$). The ORR was also significantly higher with crizotinib (74% vs 45%, $P<0.0001$).[73] Table 1 details the summary of the Phase I to III studies on crizotinib for NSCLC with *ALK* rearrangements.

Although it is clear that crizoinib significantly improves response rates and survival, invariably the disease progresses at some point. Interesting recent data have also shown benefit for patients with advanced *ALK+* lung cancer to continue *ALK* inhibition with crizotinib beyond progression in terms of maintaining ECOG performance status and may even prolong survival.[74]

Challenges, resistance patterns for ALK+ lung cancer to crizotinib

Targeted therapies directed at oncogene-addicted tumors often are efficacious for a limited period of time before the onset of acquired resistance. In the case of crizotinib, the median PFS in the PROFILE studies was 7.7 months. Similarly, in *EGFR*-mutated tumors, the efficacy of TKIs is limited by the development of resistance mechanisms, the commonest of which is the secondary *T790M* mutation within exon 20 of the *EGFR* gene.[75,76] The presence of *T790M* gatekeeper resistance resulting in failure of treatment accounts for about 50% of secondary resistance[77] with other mechanisms including activation of bypass mechanisms such as amplification of the *MET* proto-oncogene and transformation into small-cell lung cancer.[78]

To circumvent these mechanisms, researchers have now developed new second- and third-generation TKIs that are able to either intrinsically target the resistant mutation or bind irreversibly to the receptor tyrosine kinase.[79,80]

For fusion genes, however, it is apparent that many different mechanisms of resistance are possible given differences in the location of the fusion and the genes (Figure 3). Around one-third of secondary resistance mutations are located in the *ALK* TK domain with the most common mutation, the *L1196M* (22%–36%).[81–83] The *L1196M* amino acid substitution is believed to hinder TKI binding through steric hindrance. Other amino acid substitutions observed include G1269A, G1202R, and S1206Y substitutions, as well as a 1151 threonine insertion. Another described resistance mechanism involves amplification of the *ALK* fusion gene

Table 1 Summary of the Phase I–III studies on crizotinib for NSCLC with *ALK* rearrangements

Trials (NCT number)	Phase	Design	Primary objective
Study 1001 (NCT00585195)	I	Crizotinib to advanced cancers to test safety and MTD	Safety, pharmacokinetic, pharmacodynamic and MTD
Study 1002 (NCT00965731)	I/II	Erlotinib with or without crizotinib in patients with advanced NSCLC (adenocarcinoma)	Safety, efficacy, and pharmacokinetics
PROFILE 1005 (NCT00932451)	II	Crizotinib in patients with NSCLC harboring a translocation or inversion event involving the *ALK* gene	ORR
PROFILE 1014 (NCT01154140)	III	Crizotinib vs cisplatin/pemetrexed or carboplatin/pemetrexed	PFS

Abbreviations: ALK, anaplastic lymphoma kinase; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PFS, progression free survival.

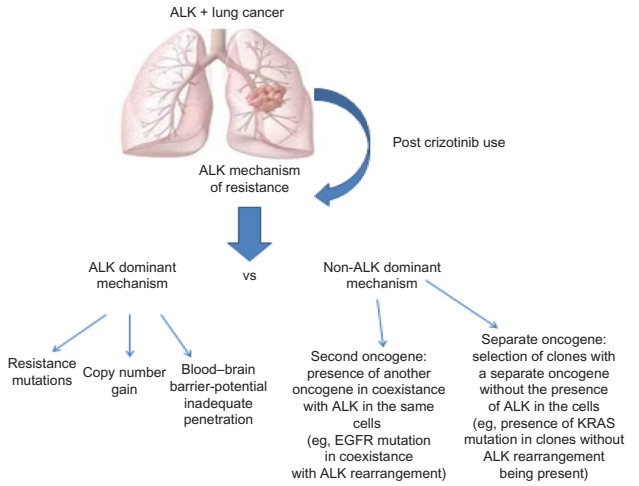

Figure 3 Potential mechanisms of resistance in *ALK+* NSCLC.
Abbreviations: NSCLC, non-small-cell lung cancer; ALK, anaplastic lymphoma kinase.

and activation of other bypass mechanisms.[84–86] *KIT* gene amplification and *EGFR* activation have also been reported as mechanisms of acquired crizotinib resistance.[82,83,86]

A number of next generation *ALK* inhibitors with the ability to bypass resistance mutations have recently been reported. Alectinib (CH5424802) is a potent, selective inhibitor of *ALK* that also potently inhibits the activity of *ALK* containing the *L1196M* gatekeeper mutation.[87,88] This compound is also known to work in patients with central nervous system metastasis as it crosses the blood–brain barrier.[89] Ceritinib (LDK378) is a second-generation *ALK* inhibitor that was granted an accelerated approval by FDA in April 2014 for treatment of patients with *ALK+* metastatic NSCLC following treatment with crizotinib. Ceritinib demonstrated efficacy in Phase I trials with a remarkable ORR of 58% (95% CI =48–67) and the median PFS was 7.0 months (95% CI =5.6–9.5).[90,91] Ceritinib was found to be efficacious in both *ALK+* patients who have previously received crizotinib and crizotinib naive patients. The side effect profile was less favorable compared to crizotinib, but was still manageable with predominantly grade 1 or 2 gastrointestinal-related adverse effects. AP26113 is a dual inhibitor for both *ALK* and *EGFR* with activating mutations. It inhibits both *L1196M* in *ALK+ NSCLC* and the *T790M* in EGFR mutants.[92] Phase I/II data for AP26113 have demonstrated efficacy in both crizotinib naive and resistant patients. It also has the ability to cross the blood–brain barrier and is active in *ALK+* brain metastasis. Table 2 details the trials that are underway to study the efficacy of ceritinib.

Preclinical studies have shown that heat shock protein 90 (HSP90) inhibitors may have activity against patients with *ALK+* lung cancer and this therapy may be useful alone or in combination with a TKI in the management of *ALK* resistance.[93–96] HSP90 is required by certain oncogenic kinases such as AKT and phosphoinositide-dependent kinase-1(PDK1)[97] for proper folding and can therefore be a useful target in cancers reliant on this mechanism. The drugs currently available and in development for *ALK* and HSP inhibitors are listed in Table 3.

Table 2 Eight available trials for ceritinib up to date from ClinicalTrials.gov

Trial identification	Phase	Study	Status
NCT01685138	II	Ceritinib in crizotinib naïve adult patients with *ALK*-activated NSCLC	Recruiting
NCT01828099	III	Ceritinib vs chemotherapy in previously untreated patients with *ALK* rearranged NSCLC	Recruiting
NCT02040870	I/II	Ceritinib in adult Chinese patients with *ALK*-rearranged (*ALK+*) advanced NSCLC previously treated with crizotinib	Not yet recruiting
NCT01772797	Ib	Phase Ib study of ceritinib and AUY922 in *ALK* rearranged NSCLC	Recruiting
NCT01685060	II	Ceritinib in adult patients with *ALK*-activated NSCLC previously treated with chemotherapy and crizotinib	Active, not recruiting
NCT01828112	III	Ceritinib vs chemotherapy in *ALK* rearranged (*ALK+*) patients previously treated with chemotherapy (platinum doublet) and crizotinib	Recruiting
NCT01964157	II	An open-label, multicenter, Phase II study of ceritinib in patients with NSCLC harboring *ROS1* rearrangement	Active, not recruiting
NCT01947608	Expanded treatment protocol	Expanded treatment protocol with ceritinib in *ALK+* NSCLC	Access available

Abbreviations: NSCLC, non-small-cell lung cancer; ALK, anaplastic lymphoma kinase.

Clinical implications for enhanced patient care

Targeting *ALK+* NSCLC has resulted in a paradigm shift in the management of advanced NSCLC. The use of crizotinib has demonstrated significant improvements in PFS and

Table 3 ALK and HSP inhibitors in development

Drugs	Company	Mechanism of action	Phase of development
Crizotinib	Pfizer, Inc., New York, NY, USA	Selective inhibitor of *ALK* and *MET*	Phase I/II/III
Ganetespib	Synta Pharmaceuticals, Lexington, MA, USA	HSP90 inhibitor	Phase I/II/III
IPI-504	Infenity	HSP90 inhibitor	Phase II
NVP-AUY922	Novartis International AG, Basel, Switzerland	HSP90 inhibitor	Phase II
AT13387	Astex Pharmaceuticals, Cambridge, UK	HSP90 inhibitor	Phase II
Debio0932	Debiopharm Group, Lausanne/Switzerland	HSP90 inhibitor	Phase I
AF802 (CH5424802)	Chugai, Japan	Selective *ALK* inhibitor	Phase I/II/III
ASP3026	Astrella, Japan	Dual *ALK*/*EGFR* inhibitor	Phase I/II
Ceritinib (LDK378)	Novartis International AG, Basel, Switzerland	Selective *ALK* inhibitor	Phase I/II/III
X-396	Xcovery, Florida, USA	Selective *ALK* inhibitor	Phase I
X-276	Xcovery, Florida, USA	Selective *ALK* inhibitor	Preclinical
NMS-E628	Nerviano Medical Science, Nerviano, Italy	Selective *ALK* inhibitor	Preclinical
NVP-TAE684	Novartis International AG, Basel, Switzerland	Selective *ALK* inhibitor	Preclinical
CEP-28122	Cephalon, Frazer, PA, USA	Selective *ALK* inhibitor	Preclinical
CEP-14083 and CEP-14513	Cephalon, Frazer, PA, USA	Selective *ALK* inhibitor	Preclinical
GSK-1838705A	GlaxoSmithKline plc, London, UK	Inhibitor of insulin-like growth factor receptor (IGF-IR), insulin receptor (IR) and *ALK*	Preclinical

Note: Reprinted from *Cancer Treat Rev*, 40(2), Gridelli C, Peters S, Sgambato A, Casaluce F, Adjei AA, Ciardiello F, ALK inhibitors in the treatment of advanced NSCLC, 300–306, © Copyright 2014, with permission from Elsevier.[102]

Abbreviations: NSCLC, non-small-cell lung cancer; ALK, anaplastic lymphoma kinase; HSP90, heat shock protein 90; IGF-IR, insulin-like growth factor receptor; IR, insulin receptor; EGFR, epidermal growth factor receptor; MET, mesenchyme to epithelial transition.

quality of life and appears to be beneficial in all lines of therapy, although resistance often develops. The development of novel inhibitors targeting these resistance mechanisms promises to expand the repertoire of therapies available, such that chemotherapy may be used as a last resort. Furthermore, combining ALK inhibitors with other pathway inhibitors promises to prolong the duration of therapy and leave cytotoxic chemotherapy as a last line of therapy.

Potential future immunotherapy management options in *ALK+* NSCLC

Immunomodulatory drugs have recently generated significant interest in the management of advanced lung cancer with checkpoint pathway antagonistic antibodies that target cytotoxic T-lymphocyte antigen 4, the Programmed Death 1 (PD-1) receptor and its ligand (PD-L1) recently demonstrating activity in various cancers including NSCLC.[98] These agents demonstrated response rates ranging from 23% to 67%[99,100] with a potential for using PD-L1 expression to select the group of patients more likely to respond.

The concept of immunotherapeutic agents with targeted therapy has not been fully investigated at this stage. D'Incecco et al tested 125 patients for the presence of mutations and their correlation with PD-L1 expression. They found 56 to harbor *EGFR* mutations, 29 *KRAS* mutations and 10 *ALK* translocations. PD-1 and PD-L1 expressions differed according to clinical and biological characteristics; PD-1 positive patients were generally male, smokers, with adenocarcinoma histology, and *KRAS* mutations; while PD-L1 positive patients were generally female, never/former smokers, with adenocarcinoma histology, *EGFR* mutated, or *ALK+*.[101] Further investigation of PD-L1 expression and *ALK* translocation will likely be undertaken and reported in future research as the number of trials using immunomodulatory agents have grown significantly.

Conclusion

The detection of *ALK* fusion genes in NSCLC has led to significant progress in the clinical care of patients with advanced lung cancer. It is important to note that while phenotypic characteristics can aid in selecting patients with *ALK+* tumors, the only way of truly determining *ALK* positivity is to perform an *ALK*-specific assay and relying on phenotype will potentially miss patients with an actionable target. While *ALK+* NSCLC is associated with a poorer clinical outcome in the absence of treatment with a targeted agent, the emergence of several different inhibitors and the development of therapeutic strategies to abrogate resistance promise to improve clinical outcome in these patients. Finally, the promise of combining targeted therapies with immunotherapies may provide a mechanism for more durable remissions, given the inevitable development of resistance to current small molecule inhibitors.

Acknowledgment

AD has received funding from Cancer Australia and the Cancer Council of Victoria. TJ is an NHMRC early career fellow and receives funding through the Victorian Cancer Agency and Cancer Council.

Disclosure

The authors report no conflicts of interest in this work.

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