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Review

ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development

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Abstract Advances in our understanding of tumour biology have encouraged reassessment of tumour classification by the site of origin in favour of molecular characteristics and/or oncogenic drivers amenable to treatment**.** The identification of *EML4*-anaplastic lymphoma kinase (*ALK*) as an oncogenic driver in non-small cell lung cancer (NSCLC) early in the clinical development of crizotinib and the observation of promising clinical responses in patients with NSCLC harbouring *ALK* translocations accelerated its clinical development in *ALK*-positive NSCLC. Phase I and II trials of crizotinib in patients with *ALK*-positive advanced NSCLC reported notably high response rates that tended to be rapid and of prolonged duration. Crizotinib was well tolerated; treatment-related adverse events were typically gastrointestinal (grade 1/2) and visual disorders (almost exclusively grade 1). Crizotinib provided NSCLC symptom relief and maintained quality of life. Based on the phase I and II trial data, the US Food and Drug Administration granted approval of crizotinib in August 2011. The consistency of the crizotinib data to date suggests accurate selection of the target population for crizotinib treatment. The ability to molecularly select patients likely to respond to an investigational agent argues that future clinical development of targeted agents should be re-evaluated. Updated trial designs incorporating molecular testing, early use of enrichment biomarkers and intermediary endpoints may accelerate and optimise clinical evaluation of targeted agents. Such trial designs should allow rapid clinical evaluation, minimise exposure of patients to therapies unlikely to be of benefit and, potentially, allow accelerated drug approval in molecularly specified populations.

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1. Introduction

1.1. Personalised medicine: from organ-driven to molecular-driven pharmacologic intervention

Crizotinib clinical development has focused primarily on molecularly selected patients with anaplastic lymphoma kinase (ALK) translocations. Following the identification of *EML4-ALK* as an oncogenic driver in non-small cell lung cancer (NSCLC) early in the clinical development of crizotinib and the observation of promising clinical responses in patients with NSCLC harbouring *ALK* translocations, *ALK*-positive NSCLC became a focus for the clinical development of crizotinib.[1,2] Trials with crizotinib have consistently reported notably high response rates, with responses of prolonged duration, often rapidly achieved.[1–5] In addition, crizotinib was well tolerated and provided symptomatic relief whilst maintaining quality of life. Accelerated Food and Drug Administration (FDA) approval of crizotinib has been granted based on the phase I and II trial data.[4–7] Advances in our understanding of tumour biology are overturning the classification of tumours by site of origin in favour of grouping by molecular characteristics and key oncogenic drivers amenable to pharmacologic modulation.[8,9] This progress, together with the realistic expectation of achieving impressive tumour responses, argues that the current approach of evaluating drugs via large empirical trials in unselected patient populations should be re-evaluated for targeted drugs. Updated trial designs incorporating customised testing, use of enrichment biomarkers as early as possible and intermediary endpoints will accelerate and optimise clinical evaluation of targeted agents.[10]

Matching patients with tumours harbouring 'drugable' genetic abnormalities with appropriate molecularly targeted agents can have dramatic results. High response rates were reported with imatinib in interferon-resistant chronic myeloid leukaemia (CML) (target: BCR-ABL; cytogenetic response rate: 54%) and gastrointestinal stromal tumour (GIST) (target: KIT; objective response rate [ORR] 54%), and with dasatinib in imatinib-resistant Philadelphia chromosome-positive leukaemias (target: BCR-ABL; haematological response rate: 92% for patients with chronic-phase CML and 70% for patients with accelerated-phase CML, CML with blast crisis or Philadelphia chromosome-positive acute lymphoblastic leukaemia).[11–13] Treatment of women with breast cancer overexpressing human epidermal growth factor receptor 2 (HER2) with trastuzumab resulted in an obvious improvement in survival and dramatic responses to endothelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were observed in patients with NSCLC harbouring *EGFR* sensitising mutations (approximately 10% of the unselected Caucasian patients enroled in early trials).[14–16] The IPASS trial, which compared gefitinib with combination chemotherapy in the first-line treatment of NSCLC, was a landmark study that not only redefined standard therapy for patients with *EGFR* sensitising mutations, but also clearly demonstrated that patient selection for targeted agents must be made on the basis of molecular characteristics.[15,17]

The relevance and ethical acceptability of randomised studies for clinical development are therefore highly questionable in poor-prognosis disease where the investigational arm is likely to be markedly more effective than the control arm. Recently, this issue came to the attention of the media when two young male cousins with melanoma enroled in a randomised trial of the investigational agent vemurafenib (PLX4032) versus a marginally active standard chemotherapy. The cousin diagnosed and randomised first received vemurafenib and responded within 2 months, whilst the cousin diagnosed second was randomised to the control arm and progressed quickly. With crossover disallowed, this was obviously very distressing for the patients, their families and the attending physician.[18] Conversely, imatinib entered phase II study in GIST on the basis of compelling preclinical data and a single highly encouraging case study.[12] Responses in the initial phase II trial were considered 'remarkable' and led to FDA approval in 2002.[12,19] The subsequent phase III study tested different doses of imatinib rather than including a control arm.[20] For GIST, it was recognised that there simply was no effective treatment option for comparison.[12] Timelines for the development of such agents are shortening as our understanding of tumour biology and our ability to select the true patient population increase; whilst 41 years elapsed between the discovery of BCR-ABL and initial trials with imatinib, it was less than 10 years for agents modulating more recently identified targets (KIT: 1998; BRAF: 2002).[21]

1.2. An evolving understanding of molecular drivers in NSCLC

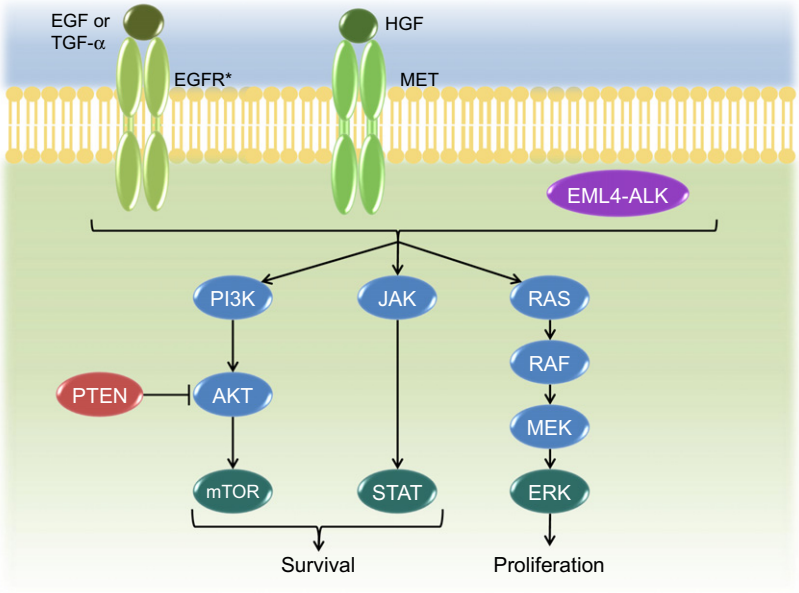
Several potential oncogenic drivers have been identified in NSCLC, including *EGFR*, *BRAF*, *KRAS*, *MET*, *HER2* and *ALK*.[22–24] The investigation of driver mutations has led to the development of specific molecularly targeted therapies, most notably gefitinib and erlotinib (both EGFR inhibitors, now known to be effective first-line therapy for tumours with *EGFR* mutations).[15,25–27] The early development of gefitinib and erlotinib was hampered by the lack of detailed molecular knowledge of lung cancer and its molecular subtypes, and clinical progress was slow as a result. Continued research into *EGFR* mutations and diagnosis developed our understanding of the molecular basis of NSCLC, and made molecular testing a familiar concept in this disease.

2. Anaplastic lymphoma kinase (ALK): a specific oncogenic driver

The nucleophosmin (NPM)–anaplastic lymphoma kinase (ALK) fusion protein was originally identified as an oncogenic driver in patients with anaplastic large-cell lymphoma (ALCL) in the early-to-mid 1990s and it quickly became apparent that *ALK*-positive and *ALK*-negative ALCLs represent distinct clinical entities.[28–31] Chromosomal translocations fusing *ALK* with a number of binding partners and resulting in ALK activation have since been described in other human cancers, including inflammatory myofibroblastic tumours, diffuse large B-cell lymphoma, breast cancer, colorectal cancer, squamous cell carcinoma of the oesophagus, and NSCLC.[32–34] In addition, a variety of ALK gain-of-function point mutations have been reported in neuroblastoma.[35,36] ALK-mediated signalling may therefore play a fundamental role in tumour development and progression irrespective of the originating organ.[32–34] Activated ALK initiates signalling via a number of interconnected pathways frequently associated with oncogenesis, the most relevant and best characterised being Ras–ERK and PI3K–Akt (Fig. 1).[37]

Identification of the ALK fusion protein as a potent oncogenic driver in NSCLC in 2007 resulted in the rapid development of the ALK inhibitor crizotinib (PF-02341066).[2,21,38,39] As for ALCL, clinical and pathological differences indicate that *ALK*-positive NSCLC is a distinct clinical entity.[1,40–47] Available methods for detecting *ALK*-positivity include fluorescence *in situ* hybridisation (FISH), immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT PCR), all of which are associated with strengths and weaknesses.[48] To date, FISH has been the test most commonly used in clinical trials and is the test approved by the FDA, but it is labour intensive and may be associated with false negatives.[49,50] IHC is widely used for surgical pathology specimens and the detection of *ALK*-positivity is improving as methods of signal enhancement and more sensitive antibodies are developed.[48] Typically, an IHC score of $\geqslant 3$ has shown 100% concordance with FISH positivity and a score of 0 has demonstrated 100% concordance with FISH negativity. A two-tier screening system for *ALK* has been proposed, comprising an initial IHC screening step followed by FISH evaluation of IHC cases scoring 1, or both 1 and 2.[51–55] Although sensitive in itself, RT PCR detection of *ALK* is limited by primer coverage due to incomplete knowledge of ALK variants/fusion partners. This method has the advantage of identifying the specific fusion present, but requires high-quality samples and several sets of PCR primer sets to cover all known *ALK* rearrangements.[48]

Reported prevalence of *ALK*-positivity in unselected NSCLC patient populations ranges from 1.6% to 8.6%,[43,44,46,53,56–61] although analyses have generally been in adenocarcinomas conducted in Asian populations using techniques with low sensitivity (e.g. PCR). Available data indicate that the prevalence of *ALK*-positivity is highest in NSCLC of adenocarcinoma histology, typically ranging from 2.4% to 5.6%, and is rarely found in squamous cell carcinoma.[41–46,46,57–59,62,63] *ALK*-positive NSCLC has been associated with younger age (median 50 years) and non- or light-smoking history.[40,42,43,45]



*EGFR homo- or heterodimer

Fig. 1. EML4-ALK signalling pathways and cellular context.

2.1. Natural history of ALK-positive NSCLC

Retrospective analyses of clinical outcomes according to *ALK*-positivity have been largely uncontrolled for potentially prognostic clinical characteristics such as age, sex, smoking status, stage, performance status and adenocarcinoma histology. As a result, the natural history of *ALK*-positive NSCLC is currently unclear.[64] Two studies in the advanced disease setting have employed case matching/adjustment controls to allow appropriate comparison, and suggest that *ALK*-positive patients may have similar-to-worse clinical prognoses compared with *ALK*-negative patients.[65,66] Similar findings were reported from an analysis of clinically comparable subsets of *ALK*-positive and *ALK*-negative patients by Shaw et al.[67] What is critical, however, is whether the natural course of *ALK*-positive disease can be altered by therapy. It should also be noted that, whilst *ALK*-positive NSCLC tends to be exclusive of other mutations, the *ALK*-negative population potentially includes any number or combination of other known abnormalities. The presence of key mutations in an *ALK*-negative comparator group (*KRAS* or *EGFR*, for example) may have a considerable effect on any comparisons with other populations. Small case cohort studies have suggested that *ALK*-positive and *ALK*-negative NSCLC do not differ significantly in their objective response rates to chemotherapy, although in numerical terms ORR was lower in *ALK*-positive patients.[40,64] Likewise, case-matching resulted in similar ORRs to first-line chemotherapy between *ALK*-positive and *ALK*-negative patients.[64] Notably, reports concur that patients with *ALK*-positive NSCLC do not respond to EGFR TKIs.[40,64]

3. Crizotinib in the treatment of *ALK*-positive NSCLC

3.1. Efficacy

Crizotinib, a potent and selective ATP-competitive inhibitor of c-Met and ALK receptor tyrosine kinases and oncogenic variants, was first studied clinically in the phase I trial.[1,68–70] In contrast with EGFR TKIs, where identification of the receptor to treatment of patients with a pharmacologic modulator took 26 years, crizotinib entered clinical testing in patients with *ALK*-translocated NSCLC early, approximately 4 months after *ALK*-fusion was first identified in that disease. Dramatic responses in the phase I study led to the initiation of a phase III study only 3 years after target identification.[21]

Data summarising patients' responses to crizotinib in the phase I and II trials are presented in Fig. 2 and Table 1. Initial results from the phase I study clearly showed significant and clinically relevant tumour shrinkage in the majority of treated patients. Notably, the shape of the waterfall plot has been largely unchanged from the earliest analysis of 19 patients through later analyses of 82 and, most recently, 119 patients (Fig. 2A).[1,3,4] ORRs at these analyses were 53%, 57% and 61%, respectively. Furthermore, consistency of results has been maintained between crizotinib trials; the shape of the waterfall from the first analysis of data from the phase II study, ORR 51%, is very similar to the plots from the various data cuts of the phase I study (Fig. 2B).[5]

In both the phase I and phase II trials, the majority of responses was achieved during the first 8 weeks of treatment and duration of response was 48.1 and 41.9 weeks, respectively (Table 1). Objective response in the phase I trial was apparently independent of line of therapy.[4,71] At the most recent analysis, median progression-free survival (PFS) in the phase I trial was 10.0 months; survival probabilities at 6 months and 12 months were 90% and 81% respectively.[4] The benefit derived from crizotinib was therefore both rapid and prolonged.

Clearly, crizotinib is an effective treatment for *ALK*-positive advanced NSCLC, but is it more effective than existing therapy? Available data are from single-arm studies and although randomised trials comparing crizotinib with standard chemotherapy in the first- and second-line settings are underway, prospective comparative data are currently lacking. Comparison of the duration of crizotinib therapy with previous lines of therapy allows patients to act as their own controls. Data from the phase I and phase II crizotinib studies show that patients remained on crizotinib longer than they remained on their preceding therapy (Table 2). For the phase I study, the median duration of the preceding therapy was 14.0 weeks and the median duration of crizotinib was 31.1 weeks for patients receiving crizotinib $\geqslant$ second-line (Pfizer Inc. Data on file; Table 2). Durations of therapy for individual patients on the phase I study are presented in Fig. 3. For the phase II study, the median duration of the preceding therapy was 12.1 weeks and the median duration of crizotinib was 22.3 weeks with 93 patients remaining on therapy (Pfizer Inc. Data on file; Table 2). Retrospective matched analyses with 'historical' *ALK*-positive, crizotinib-naïve controls also address this question. One such analysis by Shaw et al. showed that *ALK*-positive patients treated with crizotinib achieved higher ORRs, longer PFS and significantly longer overall survival (OS) than historical *ALK*-positive, crizotinib-naïve controls or *ALK*-negative/EGFR WT controls receiving standard chemotherapy (hazard ratio [HR] = 0.49, $p = 0.02$; Table 2, Fig. 4).[67] A separate retrospective analysis also indicated that crizotinib was associated with a higher ORR (61%) than chemotherapy regimens (10–24%) and model-estimated ORRs from simulated trials for the crizotinib-treated patients who had received chemotherapy (15–21%), although *ALK* status

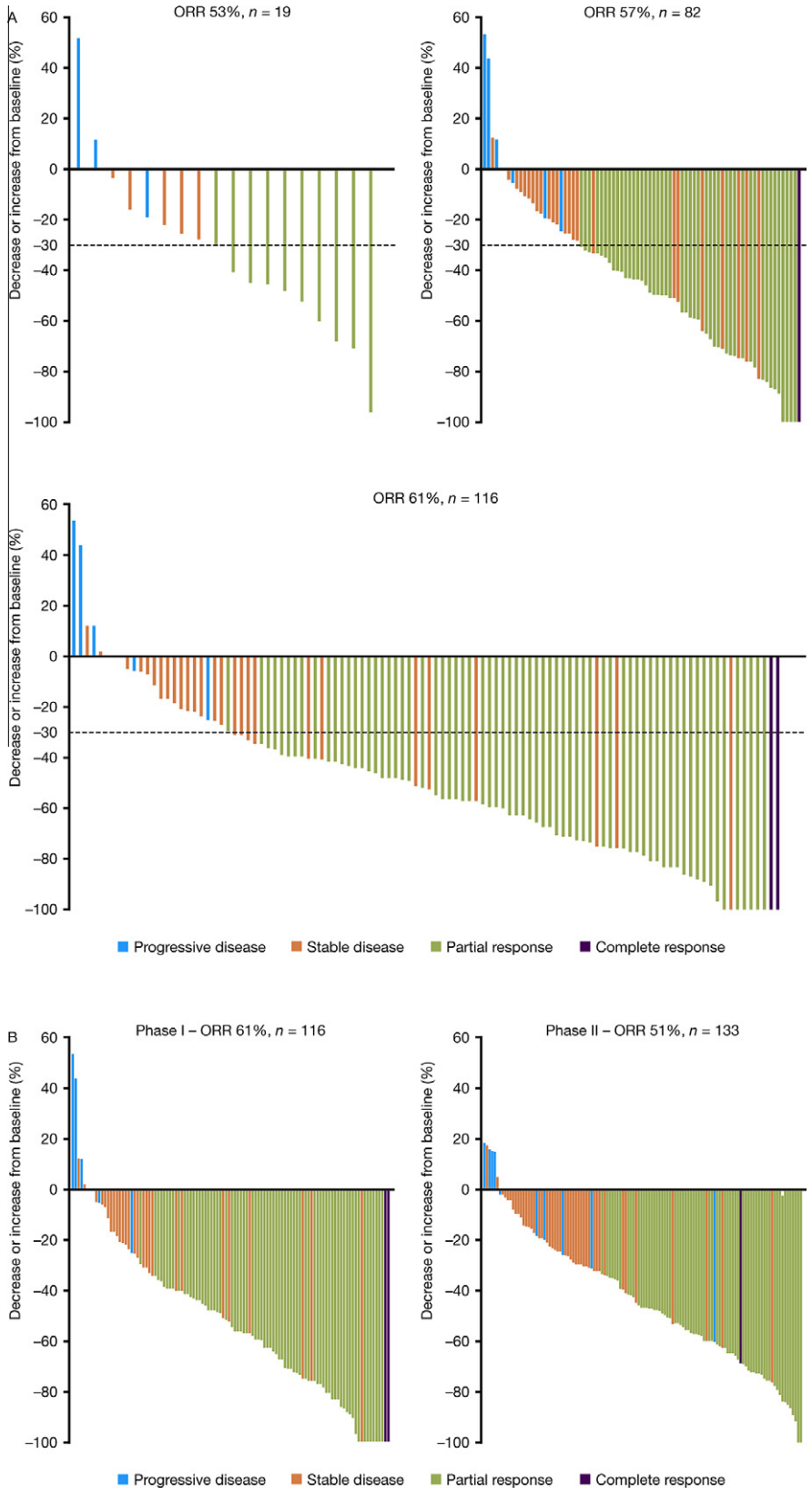


Fig. 2. Crizotinib shows consistent patterns of response throughout clinical development both (A) within Study 1001 at different timepoints ($N = 19$, $N = 82$, $N = 116$) and (B) between Studies 1001 and 1005.

was not known for the comparator population comprising case-matched patients who had not received crizotinib (Table 2).[72] Preliminary median PFS from the phase I study was longer for crizotinib versus any of the

Table 1
Crizotinib activity in the phase I and phase II trials.[4,6]

	Phase I (A8081001) $N = 119$[a]	Phase II (A8081005) $N = 136$[b]
ORR, %	61	50
Number of responders	71	68
Median (range) duration of response, weeks	48.1 (4.1+, 76.6+)	41.9 (6.1+, 42.1+)
Responses achieved during the first 8 weeks of treatment, %	55	79
Median duration of treatment, weeks	32	22
Median PFS, months[c]	10.0 (95% CI 8.2, 14.7)	NR
Survival probability		
6 months	90% (95% CI 82.7, 94.4)	NR
12 months	81% (95% CI 70.9, 87.2)	NR

CI: confidence interval; NR: not reached; ORR: objective response rate; PFS: progression-free survival.
[a] Three patients not evaluable for response.
[b] One patient not evaluable for response.
[c] After 50 events (42%; 40 disease progression events), with 69 patients (58%) censored and 59/69 (86%) patients in follow-up for PFS.

standard therapy comparison regimens (HR of 0.28–0.38; Table 2). In addition, although OS data for crizotinib are immature, the HR for OS with crizotinib versus any of the standard therapy comparison regimens was 0.27–0.47.[72]

Prospective comparison of pemetrexed or docetaxel versus crizotinib in the second-line treatment of patients with *ALK*-positive NSCLC is underway in a phase III trial (A8081007). Another phase III trial (A8081014) is comparing crizotinib with cisplatin or carboplatin, plus pemetrexed, in untreated *ALK*-positive NSCLC. Whilst data from first- and second-line phase III clinical trials are awaited, retrospective assessment of time to progression (TTP) in patients enroled in the phase II trial has been conducted to better understand the role of pemetrexed treatment in the treatment of patients with *ALK*-positive NSCLC given three recent reports suggesting that pemetrexed is effective in this patient population.[73–75] These studies, which analysed populations of patients who received pemetrexed in different lines of therapy, as a single agent or in combination, reported that *ALK*-positivity was predictive of overall response and was associated with a median PFS/TTP of approximately 9 months (higher than for other groups of patients with NSCLC of known status for specified genetic loci). Thus, preliminary observations suggest that patients with *ALK*-positive NSCLC may have better outcomes in response to pemetrexed than patients with *ALK*-negative disease. However, these were small retrospective studies that did not implement case matching or adjustment for other potential variables, and any conclusions drawn must be considered hypothesis-generating.

The retrospective assessment from the phase II study suggests that median TTP on pemetrexed for patients enroled in this study was 6.5 months for first-line combination therapy ($n = 62$), 7.1 months for second-line combination therapy ($n = 43$) and 5.5 months for second-line monotherapy (Pfizer Inc. Data on file; Table 2). These estimates of TTP (which are usually longer than PFS estimates) are of interest since they are lower than the median PFS estimate of 9 months (95% confidence interval [CI] 3–12) and median TTP $\geqslant$ second-line of 9.2 months (95% CI 4.65–13.74) documented in published studies (Table 2).[73,74] However, the phase I study reported a median PFS of 10.0 months (95% CI 8.2, 14.7) with an ORR of 61% and the phase II study reported an ORR of 50%. As noted, retrospective studies reported a median PFS of 9 months and an ORR of 17–47% for pemetrexed monotherapy (any line). Therefore, available data consistently support the hypothesis that crizotinib is more effective than pemetrexed in the treatment of *ALK*-positive NSCLC.[4,6,73,74]

3.2. Safety

The safety profile of crizotinib is tolerable and, as with efficacy findings, is consistent both within and between studies. Common treatment-related adverse events (AEs) were gastrointestinal and visual events; the majority was of grade 1 or 2 severity (Table 3).[4,5]

Visual events were distinctive and included transient problems with light/dark adjustment; shimmering, flashing lights and/or trailing lights; strings, streaks and/or floaters; overlapping shadows or after images.[4] These events occurred in approximately 60% of patients, were almost exclusively grade 1 and did not lead to permanent discontinuation.[4,5] For most patients, individual visual disturbances were of a transient nature, lasting up to 60 s, and have had little to no impact on daily life.[76] Gastrointestinal events such as diarrhoea, nausea and vomiting tended to occur early with a median time to onset of 2 days, whereas visual effects and oedema tended to occur later with a median time to onset of 13 and 74 days, respectively.[4] Grade $\geqslant$3 AEs occurred in 16% and 26% of patients in the phase I and II studies, respectively, but few were treatment-related (phase I: 0.8% grade 3 constipation; phase II: 1.5% grade 3 fatigue, 6.6% grade 3 increased alanine transaminase [ALT].[4,5] Discontinuations due to treatment-related AEs were rare: 2 patients due to pneumonitis and 1 patient due to increased ALT on the phase I study, and 2 patients due to pneumonitis and 3 patients due to increased ALT on the phase II study.[4,5] Only two treatment-related deaths have occurred, both on the phase II study; one due to causes unknown and one due to pneumonitis confounded by prior radiation therapy and history of pulmonary embolism, pleural effusion and pleural catheter treatment.[5]

Table 2
Retrospective analyses comparing crizotinib with standard therapy.

Crizotinib studies					
Phase I crizotinib study	Parameter	Immediately prior treatment	Crizotinib $N = 119$ (116 evaluable) $\geqslant$2nd-line $n = 103$		Citation
	Median duration treatment ($\geqslant$2nd-line for crizotinib), weeks	14.0	31.1		Pfizer Inc. Data on file
	ORR	NA	61%		Camidge 2011[4]
	Median PFS (5% CI), months	NA	10 (8.2, 14.7)		Camidge 2011[4]
Phase II crizotinib study	Parameter	Immediately prior treatment	Crizotinib $N = 136$ (135 evaluable)		Citation
	Median duration of treatment, weeks	12.1	22.3[a]		Pfizer Inc. Data on file
	ORR	NA	50%		Prescribing information[6]
Retrospective matched/adjusted analyses of chemotherapy					
Historical OS analysis	Parameter	*ALK*-positive patients Crizotinib $N = 30$	*ALK*-positive patients Standard therapy $N = 23$	*ALK*-negative/ EGFR wild type Standard therapy $N = 125$	Shaw 2011[67]
	Median survival, months	Not reached	6	11	
	1-year survival, %	70	44	47	
	2-year survival, %	55	12	32	
Case-matched analyses and trial simulations chemotherapy	Parameter	*ALK*-positive patients Crizotinib $N = 116$	Advanced NSCLC patients[e] Standard therapy Paclitaxel/carboplatin $N = 244$ Gemcitabine/cisplatin $N = 204$ Erlotinib $N = 259$	*ALK*-positive crizotinib-treated patients had they received standard therapy $N = 119$ (116 evaluable)	Tang 2011[72]
	ORR	61%	10–24%	15–21%	
	Median PFS, months	10[b]	4.6–5.9[c] 1.9–3.1[d]		
Retrospective non-matched/non-adjusted analyses of pemetrexed efficacy					
Mainly first-line pemetrexed (monotherapy or platinum combination), 48% of patients	Parameter	Crizotinib-naïve *ALK*-positive $N = 19$ (pemetrexed monotherapy: $n = 6$)	*EGFR* mutant ($N = 12$) *KRAS* mutant ($N = 21$) Triple-negative ($N = 37$)		Camidge 2011[73]
Second-line pemetrexed, 41% of patients	Median PFS on pemetrexed, months (95% CI)	9 (3–12)	*EGFR*: 5.5 (1–9) *KRAS*: 7 (1.5–10) Triple-negative: 4 (3–5)		
	ORR% overall (any line pemetrexed monotherapy or combination)	42	14–32		
	ORR% (any line pemetrexed monotherapy)	17	0–12		
$\geqslant$2nd-line pemetrexed monotherapy	Parameter	Crizotinib naïve *ALK*-positive ($N = 15$)	EGFR mutant ($N = 43$)	Wild-type ($N = 37$)	Lee 2011[74]
	ORR% (pemetrexed single agent, $\geqslant$2nd-line)	47	5	16	
	TTP, months (pemetrexed single agent, any line)	9.2	1.4	2.9	

(*Continued on next page*)

Table 2 (*continued*)

	TTP, months (pemetrexed single agent, ⩾2nd-line)	9.2	1.3	2.7	
	TTP, months (pemetrexed single agent, ⩾3rd-line)	6.4	1.4	4.0	
Pemetrexed history of patients in the phase II crizotinib trial					
⩾2nd-line	Parameter	Pemetrexed, 1st-line combination ($N = 60$)	Pemetrexed, 2nd-line combination ($N = 42$)	Pemetrexed, 2nd-line monotherapy ($N = 56$)	Pfizer Inc. Data on file
	Median TTP, months (95% CI)	6.5 (5.0–7.4)	7.1 (5.4–8.9)	5.5 (2.9–8.1)	

CI: confidence interval; NA, not available; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TTP: time to progression.

[a] 93 patients remain on therapy.

[b] Camidge ASCO 2011.[4]

[c] First-line paclitaxel/carboplatin, gemcitabine/cisplatin.

[d] Second-/third-line erlotinib.

[e] Patients were selected by case matching for prognostic factors and clinical characteristics as likely to be *ALK*-positive but *ALK* status was not known.

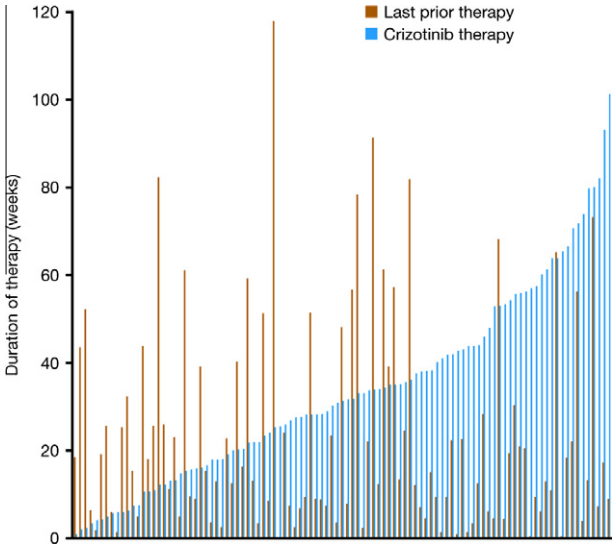


Fig. 3. Duration of crizotinib therapy and duration of last prior therapy for individual patients on the phase I study.

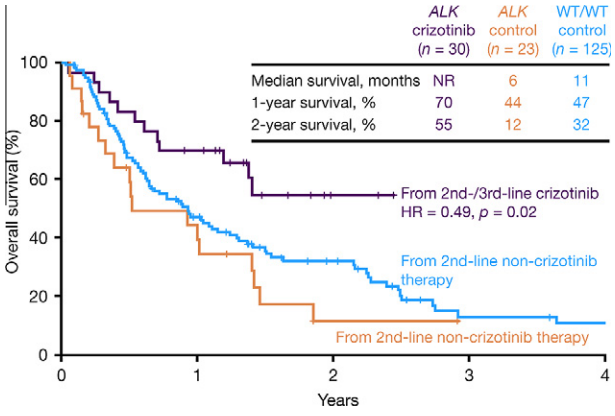


Fig. 4. Historical case-match analysis of OS in *ALK*-positive patients receiving crizotinib or standard therapy and *ALK*-negative, *EGFR* WT patients receiving standard therapy. Reprinted from Shaw AT, Yeap BY, Solomon BJ, et al. Lancet Oncol 2011;12 (11):1004–12. © 2011 with permission from Elsevier.

Given the reasonable safety profile of crizotinib, the toxicities associated with crizotinib compare favourably with those of platinum doublet and taxane chemotherapies, which are commonly associated with grade 3/4 toxicities such as cytopenia (10–40%, including febrile and non-febrile neutropenia), nausea (2–7%), vomiting (3–6%), fatigue (5–7%) and grade 1/2 alopecia (10–58%).[15,77–80] Indeed, the toxicity of chemotherapy regimens approved for the first-line treatment of advanced NSCLC is such that two-drug combinations should be administered for no more than six cycles.[81] Crizotinib has been well tolerated over extended administration periods, with many patients remaining on therapy for ⩾6 months in the phase I study and nearly 6 months in the ongoing phase II study. In addition, crizotinib offers the convenience of oral administration as opposed to the inconvenience and additional costs of inpatient care and potential complications associated with intravenous dosing.

3.3. Impact on patient-reported outcomes

Patients' quality of life is an important part of high-quality cancer care.[82] Patient-reported disease-specific quality of life was assessed in the crizotinib phase II study using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire core module (EORTC-QLQ-C30) and its lung cancer module (LC-13), which includes domains measuring symptoms and functioning. The baseline scores for patients in the phase II study were very close to those reported from other studies, indicating that the patients treated with crizotinib were very similar to reference data for the EORTC-QLQ-C30 questionnaire.[83] Preliminary data indicate that crizotinib is associated with clinical meaningful benefits (⩾10-point change from baseline) in the key symptoms of fatigue, pain, dyspnoea, cough, insomnia and appetite loss at certain time points in the follow-up period.[5,7] In addition, global quality of life was maintained over the course of therapy.[7]

Table 3
Adverse events (any causality) in ⩾10% of patients with locally advanced or metastatic *ALK*-positive NSCLC on the phase I and phase II studies.[6]

Adverse event[a]	Treatment-emergent $N = 255$		Treatment-related $N = 255$	
	All grades *n* (%)	Grade 3/4 *n* (%)	All grades *n* (%)	Grade 3/4 *n* (%)
Eye disorders				
Vision disorder[b]	163 (64)	0	159 (62)	0
Gastrointestinal disorders				
Nausea	145 (57)	2 (<1)	136 (53)	0
Diarrhoea	124 (49)	1 (<1)	109 (43)	0
Vomiting	116 (45)	3 (1)	101 (40)	0
Constipation	98 (38)	2 (<1)	69 (27)	1 (<1)
Oesophageal disorder[c]	51 (20)	3 (1)	29 (11)	0
Abdominal pain[d]	40 (16)	1 (<1)	20 (8)	0
Stomatitis[e]	27 (11)	1 (<1)	15 (6)	1 (<1)
General disorders				
Oedema[f]	97 (38)	2 (<1)	72 (28)	0
Fatigue	80 (31)	6 (2)	51 (20)	4 (2)
Chest pain/discomfort[g]	30 (12)	1 (<1)	3 (1)	0
Fever	30 (12)	1 (<1)	2 (<1)	0
Infections and infestations				
Upper respiratory infection[h]	50 (20)	1 (<1)	4 (2)	0
Investigations				
Alanine aminotransferase increased	38 (15)	17 (7)	34 (13)	14 (5)
Aspartate aminotransferase increased	29 (11)	7 (3)	24 (9)	5 (2)
Metabolism and nutrition				
Decreased appetite	69 (27)	3 (1)	49 (19)	0
Musculoskeletal				
Arthralgia	29 (11)	3 (1)	4 (2)	0
Back pain	28 (11)	0	2 (<1)	0
Nervous system disorders				
Dizziness[i]	60 (24)	0	42 (16)	0
Neuropathy[j]	58 (23)	1 (<1)	34 (13)	1 (<1)
Headache	34 (13)	1 (<1)	10 (4)	0
Dysgeusia	33 (13)	0	30 (12)	0
Psychiatric disorders				
Insomnia	30 (12)	0	8 (3)	0
Respiratory disorders				
Dyspnoea	57 (22)	16 (6)	5 (2)	3 (1)
Cough	54 (21)	3 (1)	9 (4)	0
Skin disorders				
Rash	41 (16)	0	25 (10)	0

NSCLC: non-small cell lung cancer.
[a] The phase II study used Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and the phase I study used CTCAE v3.0.
[b] Includes diplopia, photopsia, photophobia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual brightness, and visual acuity reduced.
[c] Includes dyspepsia, dysphagia, epigastric discomfort/pain/burning, oesophagitis, oesophageal obstruction/pain/spasm/ulcer, gastroesophageal reflux, odynophagia and reflux oesophagitis.
[d] Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal tenderness.
[e] Includes mouth ulceration, glossodynia, glossitis, cheilitis, mucosal inflammation, oropharyngeal pain/discomfort, oral pain, and stomatitis.
[f] Includes oedema, oedema localised and peripheral oedema.
[g] Includes chest pain, chest discomfort and musculoskeletal chest pain.
[h] Includes nasopharyngitis, rhinitis, pharyngitis and upper respiratory tract infection.
[i] Includes balance disorder, dizziness and presyncope.
[j] Includes burning sensation, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, paraesthesia, peripheral neuropathy, peripheral motor neuropathy and peripheral sensory neuropathy.

4. Crizotinib and the future clinical study of targeted agents

ALK-positive NSCLC is a discrete, molecularly defined clinical entity with distinct clinical characteristics. Appropriately case-matched/adjusted retrospective analyses suggest that *ALK*-positive patients may have a similar-to-worse clinical prognosis compared with *ALK*-negative patients.[65–67] Clinical data for crizotinib, in the context of historical data for *ALK*-positive

patients who did not receive crizotinib, suggest that the natural history of *ALK*-positive NSCLC can be fundamentally altered. This assertion is evidenced by impressive response rates in heavily pre-treated patients, the high percentage of patients with any tumour shrinkage, and the prolonged duration of response noted in and between the phase I and phase II crizotinib trials.[1,3–5]

Key to the outstanding results reported for crizotinib was the molecular identification of patients with disease suitable for treatment, allowing the true target population to be recruited. Consequently, the effect of treatment was not diluted out by the inclusion of patients who were unlikely to respond, as happens in large empirical trials in unselected populations. The phase I and II crizotinib trials only recruited patients who proved to be the target group for therapy. As a result, clinical development of crizotinib has been rapid, with phase III trials already underway.

The remarkable consistency of the crizotinib data suggests that further trials conducted in the molecularly selected populations will quite likely lead to similar results. Based on the learning curve from other malignant diseases, it is reasonably unlikely that a phase III trial of a targeted agent will fail in a population molecularly selected for the target compared with a non-selected population, as was the case for erlotinib and gefitinib.[84–87] Furthermore, the pattern of efficacy signals for crizotinib is not without precedent. The shape of the waterfall plot, which suggests that crizotinib is an effective therapy in *ALK*-positive NSCLC, is strikingly similar to that resulting from a phase III trial of vemurafenib in patients with BRAF V600E-mutated melanoma. Just as for crizotinib, the shape of the vemurafenib waterfall plot was initially documented in a small patient population in a phase I study (the phase I expansion cohort comprised only 32 patients, all prospectively enroled for V600E mutation; the ORR was 81%).[88,89] In both cases, it would appear that the drug target was a key oncogenic driver in the selected population, particularly as the waterfall for the standard chemotherapy comparator in the vemurafenib phase III trial showed that the majority of patients on this arm experienced tumour growth.

These data bring the challenges of developing effective targeted agents into sharp focus. The crizotinib studies support the accelerated development of targeted agents demonstrating strong efficacy signals early in the development in molecularly selected patient populations, and indicate that such signals can be trusted. The remarkable efficacy of targeted agents such as crizotinib urges us to facilitate available access to these agents as quickly as possible, as many patients realistically have no other effective option. With current access to crizotinib only via clinical trial in Europe, we have found ourselves in the position of requiring *ALK*-positive patients to progress on standard therapy before becoming eligible for treatment with crizotinib. This situation is illustrated by the case of 1 treatment-naïve patient known to be *ALK*-positive who had to receive first-line treatment with cisplatin, pemetrexed and bevacizumab before going onto receive crizotinib (and achieving a complete response within 5 weeks of initiating treatment).[90] In addition, patients are increasingly acutely aware of the significance of an agent such as crizotinib and want access ahead of the usual timeframe for drug development. This phenomenon is not new; patients' advocacy groups were highly visible in campaigning for access to investigational HIV therapy and, similarly, patients campaigned for access to trastuzumab.[91]

The comparator arm for the vemurafenib phase III trial in melanoma was dacarbazine, an agent known to have low activity and, as noted previously, the majority of patients experienced tumour growth whilst on chemotherapy. Controversy over ethical aspects of employing a comparator arm, widely acknowledged as suboptimal, was at the forefront of discussion with vemurafenib. Designing clinical trials to allow cross-over to investigational therapy following disease progression on the control arm, as is the case for the ongoing crizotinib phase III trials, goes some way to addressing potential ethical dilemmas, but impacts on the assessments of overall survival – potentially confounding a key study endpoint. Realistically, given the evidence of a better outcome for several targeted agents in their true target population versus standard therapies, review of traditional clinical development approaches is needed. Although randomised, comparative trials are the gold standard for determining clinical benefit between treatments, are there instances where clinical study designs may be optimised to effectively and robustly assess strong signals of clinical activity in defined populations in earlier-phase trials?

Now that we understand both tumour biology and the new generation of targeted drugs so much better than was the case when empirical randomised trials represented a real step forward, it is the time to revisit anticancer drug development practices for targeted agents and individual patients. For this, we must look at the broader picture. Whilst NSCLC is common, *ALK*-positive NSCLC is not, and is one of the several abnormalities which should shape treatment selection given current knowledge. It is essential to utilise molecular testing to identify those patients who may benefit from targeted therapy, but sequential testing for single oncogenic drivers may incur a delay in treatment selection which might not be in the patient's best interest. Therefore, we should consider comprehensive screening for multiple abnormalities at diagnosis to allow patients to enrol into an appropriate biologically driven trial in a timely manner, rather than lengthening the odds for suitable treatment by screening for just one trial.[92]

Based on worldwide experience to date, it is evident that crizotinib has a positive benefit/risk ratio; it is a highly effective therapy for *ALK*-positive advanced NSCLC and is well tolerated from both the clinical and patients' perspective. In addition, crizotinib provides further benefits of symptom relief and maintained quality of life. Crizotinib has recently been granted accelerated FDA approval and, as such, represents a truly effective treatment option for the patients with *ALK*-positive advanced NSCLC.[6]

Clinical experience with crizotinib argues that the future clinical development of targeted agents should be re-evaluated. Clinical evaluation of targeted agents could be via small early phase trials employing adaptive hypothesis testing conducted in molecularly defined populations enriched for the drug target. Such trial design should allow rapid clinical evaluation, minimise the exposure of patients to therapies unlikely to be of benefit and, potentially, allow accelerated drug approval in molecularly specified patient populations.

Conflict of interest statement

Giorgio Scagliotti has received honoraria from Eli Lilly, AstraZeneca, ARIAD, and Roche. Rolf A. Stahel has served Astellas, AstraZeneca, Bayer, Boeringer Ingelheim, Eli Lilly, Genentech, GSK, Merck Serono, Novartis, Pfizer Oncology, and Roche in a consultant/advisory role, and has received honoraria from AstraZeneca, Eli Lilly, Merck Serono, Novartis, and Roche. Nick Thatcher has served Pfizer Oncology in a consultant/advisory role and has received honoraria and other remuneration from Pfizer Oncology. Jean-Charles Soria has served Pfizer Oncology in a consultant/advisory role and has received honoraria from Pfizer Oncology. Rafael Rosell has nothing to disclose.

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