



Review

Management of crizotinib therapy for *ALK*-rearranged non-small cell lung carcinoma: An expert consensus



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ABSTRACT

Within 4 years of the discovery of anaplastic lymphoma kinase (*ALK*) rearrangements in non-small cell lung cancer (NSCLC), the *ALK* inhibitor crizotinib gained US and European approval for the treatment of advanced *ALK*-positive NSCLC. This was due to the striking response data observed with crizotinib in phase I and II trials in patients with *ALK*-positive NSCLC, as well as the favorable tolerability and safety profile observed. Recently published phase III data established crizotinib as a new standard of care for this NSCLC molecular subset. A consequence of such rapid approval, however, is the limited clinical experience and relative paucity of information concerning optimal therapy management. In this review, we discuss the development of crizotinib and the clinical relevance of its safety profile, examining crizotinib-associated adverse events in detail and making specific management recommendations. Crizotinib-associated adverse events were mostly mild to moderate in severity in clinical studies, and appropriate monitoring and supportive therapies are considered effective in avoiding the need for dose interruption or reduction in most cases. Therapy management of patients following disease progression on crizotinib is also discussed. Based on available clinical data, it is evident that patients may have prolonged benefit from crizotinib after Response Evaluation Criteria in Solid Tumors-defined disease progression, and crizotinib should be continued for as long as the patient derives benefit.

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1. Introduction

Rearrangements of the gene encoding the receptor tyrosine kinase anaplastic lymphoma kinase (*ALK*) in non-small cell lung

cancer (NSCLC) were identified in 2007 and shown to contribute to carcinogenesis in a subgroup of lung cancer patients [1–3]. While only 3–5% of NSCLC tumors are *ALK*-rearrangement-positive [1,2,4], this translates into a considerable number of patients affected worldwide.

Crizotinib (XALKORI; Pfizer Inc., New York, NY, USA) is an inhibitor of *ALK*, *MET*, and *ROS1* [5–7]. Crizotinib gained approval in the US for the treatment of adults with *ALK*-positive advanced NSCLC within 4 years of the discovery of the importance of *ALK* rearrangement and has subsequently been approved

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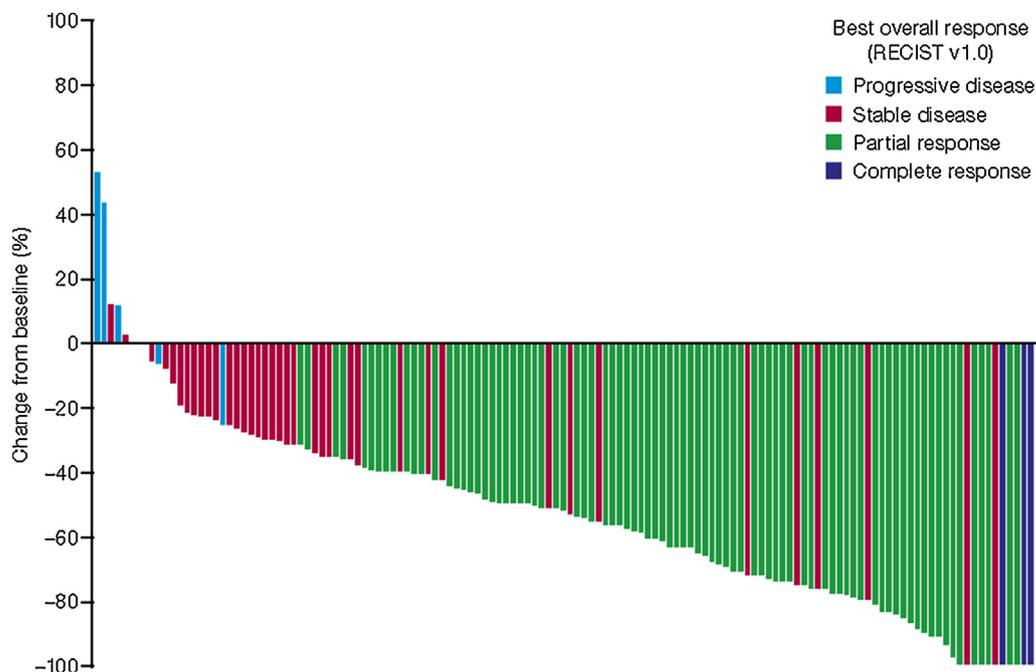


Fig. 1. Best percentage change in target lesions from baseline in 133 patients with ALK-positive NSCLC who received crizotinib in PROFILE 1001. Excludes patients with early death before re-imaging, non-measurable non-target disease, or indeterminate responses. Adapted from *The Lancet Oncology*, Vol. 13, Camidge DR, et al., Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study, p. 1013, Copyright 2012 [11] with permission from Elsevier.

multinationally [8]. Crizotinib has since become a recommended standard of care for ALK-positive lung cancer in European [9] and US NSCLC treatment guidelines [10]. The rapid approval of crizotinib was granted on the basis of consistent efficacy findings from phase I and II clinical trials, coupled with a favorable toxicity profile and concurrent development of a diagnostic test for ALK rearrangement. In the most recent update from the phase I study, PROFILE 1001, the objective response rate (ORR) was 61% with a median progression-free survival (PFS) of 9.7 months and a median duration of response of 49 weeks among 143 evaluable patients [11]. Preliminary estimates of overall survival were 88% and 75% at 6 and 12 months, respectively, and the majority of patients experienced tumor shrinkage (Fig. 1) [11]. A single-arm, multicenter phase II study in patients with advanced previously treated ALK-positive NSCLC (PROFILE 1005) reported similar findings. Crizotinib was associated with an ORR of 60%, a median duration of response of 46 weeks, and a median PFS of 8.1 months among 259 evaluable patients [12]. A reduction in key lung cancer-related symptoms including cough, pain, and dyspnea was also observed [13].

A phase III trial, PROFILE 1007 ($N=347$), compared standard chemotherapy (docetaxel or pemetrexed) with crizotinib as second-line treatment for advanced/metastatic ALK-positive NSCLC [14]. The median PFS with crizotinib was 7.7 months versus 3.0 months with chemotherapy (hazard ratio, 0.49; $p<0.0001$); the ORR with crizotinib was more than three times that observed with chemotherapy (65% vs. 20%, $p<0.0001$). In comparison with chemotherapy, crizotinib improved symptom control and quality of life [14]. For patients who received pemetrexed in the chemotherapy arm of PROFILE 1007, PFS was longer (4.2 months vs. 2.6 months) and the ORR was higher (30% vs. 9%) than for patients who received docetaxel. More recently, results from a first-line phase III trial in ALK-positive NSCLC, PROFILE 1014, revealed the superiority of crizotinib vs. pemetrexed plus cisplatin or carboplatin [15]. The median PFS was 10.9 months for crizotinib vs. 7.0 months for chemotherapy (hazard ratio, 0.45; $p<0.0001$). The treatment effect on PFS was in favor of crizotinib for all subgroups analyzed, including patients with brain metastases at baseline. In this study, the

ORR was 74% with crizotinib and 45% in the control arm ($p<0.0001$) [16].

As a consequence of the rapid approval of crizotinib for patients with ALK-positive NSCLC, there is limited clinical experience and a paucity of information concerning optimal therapy management. The aim of this publication is to provide guidance for clinicians on the appropriate use of crizotinib and management of its associated adverse events (AEs). This report reflects consensus views put forward during a European Crizotinib Therapy Management Advisory Board meeting held on March 22, 2013 in Frankfurt, Germany.

2. Management of adverse events

2.1. General safety profile

To date, the most commonly reported AEs (occurring in >25% of patients) with crizotinib across clinical trials (PROFILE 1001, PROFILE 1005, and PROFILE 1007) are visual disturbances, nausea, diarrhea, vomiting, edema, elevated transaminases, constipation, and fatigue, with most events being grade 1/2 in severity [8,14]. The most frequently reported AEs in PROFILE 1007 [14] are listed in Table 1. The incidence of treatment-related AEs leading to discontinuation with crizotinib was 2% (PROFILE 1001), 4% (PROFILE 1005), and 6% (PROFILE 1007) [8,14]. Sinus bradycardia was also very commonly observed, although it was not always reported as an AE since it was usually asymptomatic [8,17]. Other important but less common toxicities included pneumonitis [8,11,14], QTc prolongation [8,14], and severe hepatotoxicity [8,18]. In addition, in male patients hypogonadism was reported to occur as a consequence of crizotinib treatment [19]. Events with a fatal outcome attributed to crizotinib by investigators include hepatic failure, pneumonitis, and ventricular arrhythmia [14,18]. Elevated levels of alanine aminotransferase (ALT; grades 1–4, 71%) and aspartate aminotransferase (AST; grades 1–4, 61%) were commonly observed in crizotinib clinical trials [4,11,12,14].

Table 1

Adverse events of any cause in PROFILE 1007 that occurred in $\geq 15\%$ of patients in either treatment arm and differed in incidence by $\geq 5\%$.^a

Adverse event	n (%)			
	Crizotinib (N = 172)		Chemotherapy (N = 171)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Vision disorder ^{b,c}	103 (60)	0	16 (9)	0
Diarrhea ^d	103 (60)	0	33 (19)	1 (<1)
Nausea ^d	94 (55)	2 (1)	64 (37)	1 (<1)
Vomiting ^d	80 (47)	2 (1)	30 (18)	0
Constipation	73 (42)	4 (2)	39 (23)	0
Elevated aminotransferase levels ^b	66 (38)	27 (16) ^e	25 (15)	4 (2)
Edema ^b	54 (31)	0	27 (16)	0
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Upper respiratory tract infection ^b	44 (26)	0	22 (13)	1 (1)
Dysgeusia	44 (26)	0	16 (9)	0
Dizziness ^b	37 (22)	1 (1)	14 (8)	0
Dyspnea ^{b,f}	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0	29 (17)	0
Alopecia	14 (8)	0	35 (20)	0

From *The New England Journal of Medicine*, Shaw AT, et al., Crizotinib versus chemotherapy in advanced ALK-positive lung cancer, Vol. 368, p. 2391 [14]. © (2013) Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

^a Not adjusted for the longer duration of treatment of crizotinib (31.0 weeks) versus chemotherapy (12.3 weeks).

^b Item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.

^c Vision disorders included (in descending order of frequency) visual impairment, photopsia, blurred vision, vitreous floaters, halo vision or photophobia, chromatopsia or diplopia, and reduced visual acuity.

^d The use of antiemetic agents was significantly higher in the chemotherapy group than in the crizotinib group (67% vs. 20%).

^e Included one case meeting the criteria for Hy's law (serum bilirubin level $\geq 3 \times$ upper limit of normal in the absence of biliary obstruction or Gilbert's syndrome) with grade 5 hepatic failure occurring after the cut-off date.

^f One case of grade 5 dyspnea was reported in each treatment group (<1% of patients in each group).

2.2. Vision disorder

Grade 1/2 visual disturbances were the most frequently reported AEs across crizotinib clinical trials (59–62%) [4,11,12,14]. These included visual impairment, photopsia, blurred vision, vitreous floaters, photophobia, and diplopia. In practice, patients often report visual disturbances as flashes of light or trailing lights in their peripheral vision, overlapping shadows, or after-images, most commonly occurring during adaptation to changes in lighting conditions (dim or bright) [20]. In PROFILE 1005, the proportions of patients reporting visual effects diminished with increasing time on crizotinib treatment: cycle 2, 65%; cycle 3, 58%; cycle 4, 55%; and cycle 5, 50% [21]. In general, visual disturbances were reported as transient (either <30 s or 30–60 s) and as either not or a little bothersome, with little or no impact on their activities of daily living (Fig. 2) [21].

Electroretinography studies in rats have provided evidence of a direct effect of crizotinib on retinal function, specifically a decreased rate of dark adaptation [22]. Since visual disturbances are generally transient, are not found to be bothersome, and do not affect patients' quality of life, they do not require specific intervention. However, ophthalmologic and/or neurologic evaluation should also be considered if visual disturbances persist or worsen in severity during crizotinib treatment in order to exclude unrelated retinal pathology, optic nerve pathology, or CNS involvement of underlying NSCLC. Treating physicians should discuss visual disturbances with their patients prior to initiating crizotinib treatment, and patients should be aware that this might potentially interfere with certain activities (e.g. when driving in the dark).

2.3. Gastrointestinal toxicity

Crizotinib-associated gastrointestinal toxicities include nausea (47–57%), vomiting (39–47%), diarrhea (41–60%), and constipation (28–42%) [4,11,12,14]. These are generally mild or moderate (grade 1/2); across clinical studies to date, fewer than 1% of each of these toxicities were grade 3/4. Nausea and vomiting generally occur early in treatment, with a median time to first onset of 2–3 days (range 1–518). During treatment, the prevalence of common treatment-related grade 1 gastrointestinal AEs decreased over time [11].

Gastrointestinal toxicities can usually be managed with supportive care rather than crizotinib dose reduction or interruption; however, in rare cases, dose reduction may be necessary. As specified in the Summary of Product Characteristics (SmPC), there is only a minor food effect on the absorption of crizotinib; hence, it can be administered with and without food [8]. Some physicians report that vomiting may occur more frequently in the morning and can be ameliorated by taking crizotinib with or after meals and/or with concomitantly administered antiemetics, such as metoclopramide. Serotonin 5-HT₃ receptor antagonists (for example, ondansetron) should be used with caution because they can prolong the QT interval, which is an AE observed with crizotinib (see Section 2.4). Diarrhea can generally be managed with loperamide or codeine phosphate. If dose reduction is warranted, crizotinib should be reduced to 200 mg twice daily [8]. If further reduction is necessary, the dose should be modified to 250 mg once daily [8].

2.4. Cardiac toxicity

Bradycardia and QTc prolongation have been observed with crizotinib treatment [8,14,17]. While QTc prolongation is observed with other kinase inhibitors [23], bradycardia is relatively unique to crizotinib [17]. In a retrospective analysis of 42 crizotinib-treated patients enrolled in PROFILE 1001 and PROFILE 1005, the average on-treatment heart rate reduction relative to baseline was 26.1 beats per minute (bpm) [17]. Additionally, 69% of patients experienced at least one episode of sinus bradycardia (heart rate ≤ 60 bpm), although this was asymptomatic in all cases. Mean time to the lowest heart rate was 18.6 weeks. Patients at higher risk for sinus bradycardia were older (55.8 years vs. 47.8 years; $p = 0.0336$) and had a lower pretreatment heart rate (mean, 77.9 vs. 100.6 bpm; $p = 0.002$) [17].

In terms of QTc prolongation, 1.4% of 1167 patients were found to have a QTc ≥ 500 ms, and 4.4% of 1136 patients had an increase from baseline QTc of ≥ 60 ms as measured by automated machine-read electrocardiogram (ECG) [24]. A pharmacokinetic–pharmacodynamic analysis suggested a crizotinib concentration-dependent increase in the QTc [24].

At the current time, the clinical significance and long-term effects of crizotinib-associated bradycardia and QTc prolongation are not fully understood. However, crizotinib should be used cautiously in patients who have a history of or predisposition for QTc prolongation [8]. Moreover, the risk of QTc prolongation may be increased because of electrolyte disturbances secondary to vomiting, diarrhea, or impaired renal function. ECG monitoring should be considered in patients with a history of cardiac disease, and in those taking medications with the potential for QTc prolongation. In high-risk patients, measuring QTc under optimal conditions (possibly in triplicate) at baseline and during treatment might be advisable. Symptoms such as dizziness, palpitations, syncope, seizures, or unexplained loss of consciousness, as well as electrolyte imbalance (e.g. caused by gastrointestinal toxicity), may also be considered triggers for additional ECG monitoring. In the case of grade 3 QT prolongation (≥ 501 ms on at least two separate ECGs [25]), treatment should be temporarily discontinued until recovery to grade

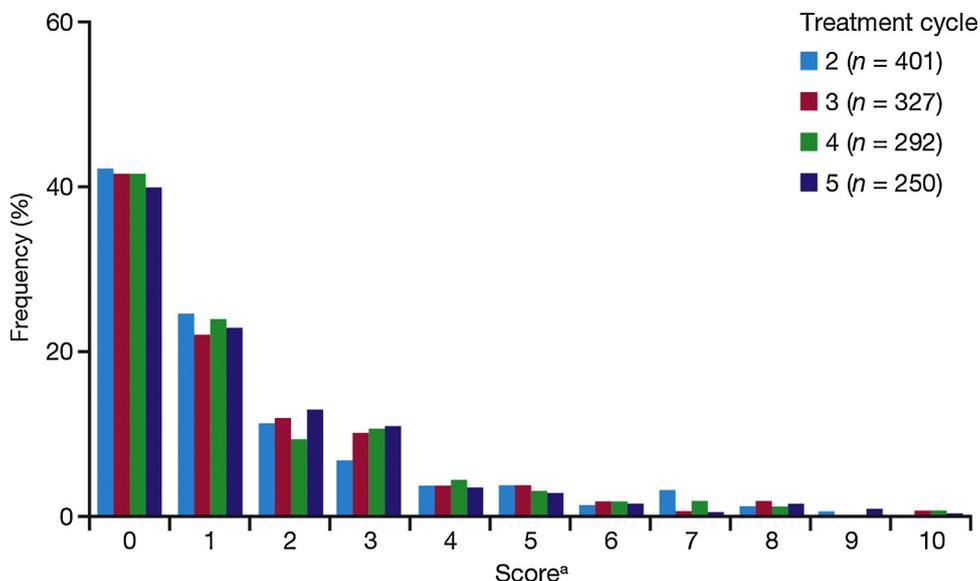


Fig. 2. Patient-reported impact of visual disturbances with crizotinib on activities of daily living in PROFILE 1005. ^a0, no effect; 10, completely prevented activities of daily living. Adapted from Besse B et al., 2012 [21] with the author's permission.

≤1, resumed at 200 mg twice daily, and permanently discontinued if QT prolongation recurs or if a grade 4 event is observed [8].

Bradycardia may lead to clinical symptomatology, including dizziness, syncope, hypotension, and fatigue, particularly in the elderly or in patients also receiving antihypertensive medications. Therefore, use of concomitant medications associated with bradycardia (e.g. beta blockers) should be carefully evaluated prior to and during crizotinib treatment. According to the current US prescribing information [24], crizotinib should be withheld in the event of symptomatic bradycardia until recovery to asymptomatic bradycardia or a heart rate ≥60 bpm, and concomitant medications known to cause bradycardia, as well as antihypertensive medications, should be evaluated. If contributing concomitant medication is identified and discontinued or dose-adjusted, crizotinib can be resumed at the previous dose upon recovery to asymptomatic bradycardia or a heart rate ≥60 bpm. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose-modified, crizotinib can be resumed at a reduced dose upon recovery to asymptomatic bradycardia or a heart rate ≥60 bpm [24]. In cases of life-threatening bradycardia, crizotinib should be permanently discontinued unless a contributing concomitant medication is identified. In this case, crizotinib can be resumed at 250 mg once daily upon recovery to asymptomatic bradycardia or a heart rate of ≥60 bpm with frequent monitoring [24].

2.5. Hepatotoxicity

Elevated ALT levels were reported in 38% of crizotinib-treated patients in PROFILE 1007, and 16% of crizotinib-treated patients had grade 3/4 ALT elevations [14]. Detailed laboratory analysis of blood samples from over 1000 patients from PROFILE 1001 and PROFILE 1005 showed frequent liver enzyme elevations (Table 2 [18]), generally occurring in the first 2 months of treatment [4,11,12,18]. ALT and AST elevations were evident in 70.9% and 61.3% of cases, respectively, and were grade 3 or 4 in 7.4% and 3.2% of cases, respectively [18]. In this analysis, temporary discontinuations or dose reductions due to hepatic AEs occurred in 5.3% of patients. Although permanent discontinuations were necessary in 1.3% of patients, transaminase elevations were generally reversible, allowing patients to continue at the same or a lower dose [18]. As

of March 31, 2013, a total of 16 cases of severe, possibly drug-induced liver injury (elevation of ALT to ≥3 × upper limit of normal [ULN] and concurrent or subsequent elevation of total bilirubin to ≥2 × ULN in the absence of biliary obstruction, hemolysis, or any evident or likely explanation of these findings other than crizotinib treatment) have been reported from clinical studies, spontaneous sources, or compassionate use (Pfizer Inc., data on file).

Severe hepatic impairment, as defined by a bilirubin of >3 × ULN regardless of ALT/AST, is listed as a contraindication in the SmPC, based on the above-mentioned liver toxicity and in the absence of systematic data in this population [8]. A clinical study of crizotinib in severely hepatically impaired patients is currently ongoing. Monitoring of liver enzymes and total bilirubin every week for the first 2 months of crizotinib therapy (with monthly monitoring and as clinically indicated thereafter) should be performed, as specified in the SmPC [8]. Furthermore, patients should be educated about signs and symptoms of drug-induced liver injury and hepatic failure.

Initiation and withdrawal of crizotinib treatment should be made on a case-by-case basis and take into account clinical factors, as well as laboratory data. For example, a patient with elevated total bilirubin may benefit from crizotinib if the higher total bilirubin levels are caused by biliary obstruction due to liver metastases. Most patients in whom significantly elevated hepatic enzymes are observed after starting crizotinib can be successfully re-challenged with a lower dose following recovery after dose interruption. The SmPC recommends withholding treatment until recovery to grade ≤1, resuming at 200 mg twice daily in the case of grade 3/4 ALT or

Table 2
Hepatic laboratory abnormalities with crizotinib in PROFILE 1001 and PROFILE 1005 (N = 1054) [18].

Parameter	n ^b	Proportion of patients by CTCAE ^a grade, %				
		Grade 1	Grade 2	Grade 3	Grade 4	Grades 1–4
ALT	1004	50.7	12.8	5.8	1.6	70.9
AST	1005	51.4	6.7	2.7	0.5	61.3
AP	1004	53.0	9.5	2.3	0	64.7
TBL	1005	2.1	1.1	0.4	0	3.6

ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; CTCAE, Common Terminology Criteria for Adverse Events; TBL, total bilirubin.

^a PROFILE 1001, CTCAE v3.0; PROFILE 1005, CTCAE v4.0.

^b Number of patients with available laboratory data.

AST elevation with concurrent grade ≤ 1 total bilirubin elevation; and permanent discontinuation for patients with grade ≥ 2 ALT or AST elevation with concurrent grade ≥ 2 total bilirubin elevation (in the absence of cholestasis or hemolysis) [8]. To date, no factors associated with an increased risk of developing crizotinib-induced hepatotoxicity have been identified.

2.6. Hypogonadism

A rapid reduction in testosterone levels has been observed within 14–21 days of crizotinib treatment. This was found to be reversible after stopping crizotinib [19]. In one report, mean total testosterone levels were 25% below the lower limit of normal (LLN) in 27 of 32 crizotinib-treated patients (84%) versus 29% above LLN in six of 19 non-crizotinib-treated patients (32%; $p = 0.0012$). In addition to reductions in the levels of two major testosterone-binding proteins (albumin and sex hormone-binding globulin), levels of luteinizing hormone and follicle-stimulating hormone levels also declined rapidly, suggesting that crizotinib may have a centrally mediated effect [26]. In total, 84% and 79% of crizotinib-treated patients with low free and low total testosterone levels, respectively, manifested symptoms consistent with androgen deficiency [26]. Notably, in addition to sexual dysfunction, fatigue may be a common symptom of low testosterone.

As a consequence of these observations, the potential for hypogonadism should be discussed with male patients prior to initiating crizotinib treatment. Monitoring testosterone levels in patients with potential symptoms of hypogonadism was suggested by the advisory board, along with referral of patients with low levels to an endocrinologist, without changing the crizotinib dosage. Testosterone replacement therapy may be recommended by endocrinologists, although the risk–benefit ratio should be carefully considered [27].

2.7. Other adverse events

Approximately 30% of crizotinib-treated patients experience grade 1/2 edema, which was associated with a rather late onset (median onset, 85 days) [11]. Peripheral edema is most commonly observed, particularly in women, although facial and periorbital edemas have also been reported. In some patients, crizotinib-induced edema appears to be amenable to standard medical or physiotherapeutic interventions. While low-grade edema may be a common and bothersome event, in the vast majority of cases it does not necessitate dose reduction or treatment interruption.

Neutropenia has been reported in 9–14% of crizotinib-treated patients participating in clinical trials [12] and is also a common grade 3/4 AE (6–13%) [12], leading to dose reductions in a small number of cases [11]. For any grade 3/4 hematologic toxicity except lymphopenia, the SmPC recommends withholding treatment until recovery to grade ≤ 2 , resuming on the same dosing schedule for patients who had grade 3 hematologic toxicity or at 200 mg twice daily for those with grade 4 toxicity [8].

In approximately 1–2% of patients, crizotinib has been associated with pneumonitis or interstitial lung disease, which can be severe, life-threatening, or fatal [4,8]. However, symptoms indicative of pneumonitis may be disease- rather than drug-related and may be caused by NSCLC progression, infection, prior radiation effects, or other pulmonary diseases. Any decision to stop crizotinib treatment should therefore be made on a case-by-case basis. If treatment-related pneumonitis is diagnosed, crizotinib should be permanently discontinued [8], and standard treatment of interstitial lung disease should be considered.

Complex renal cysts have been reported in 4% of crizotinib-treated patients [24]. However, a blinded radiologic review of computed tomography images of 255 crizotinib-treated patients

revealed new renal cysts in almost 10% of patients (Pfizer Inc., data on file). There were no reports of associated renal impairment, and urinalyses were typically normal. Aspirations and biopsies, when performed, were generally not diagnostic, and to date, no evidence of malignancy has been found. In some cases, local extension of cysts into adjacent tissues necessitated percutaneous drainage procedures; however, most patients were able to continue crizotinib without dose modification. In a small retrospective analysis, treatment with crizotinib was shown to be related to a reversible reduction of the glomerular filtration rate by approximately 20%. This did not, however, have clinical implications [28].

3. Optimizing duration of treatment

Acquired resistance is a common feature of tyrosine kinase inhibitor (TKI) therapy due to the selection pressure for clones with reduced sensitivity to the drug. A number of small studies have investigated the molecular mechanisms of acquired resistance to crizotinib and have unveiled a striking heterogeneity of molecular events underlying this process [29–31]. In 25–43% of cases, secondary point mutations have been identified in *ALK*, conferring resistance to crizotinib. An in vitro mutagenesis screen of crizotinib in NSCLC cells identified similar mutations [32]. Other mechanisms of acquired resistance include *ALK* copy-number gain (with or without additional *ALK* mutation), as well as *ALK*-non-dominant mechanisms including point mutation of *KRAS*, *EGFR*, and amplification of *KIT* [29–31]. Furthermore, separate cases of coexistence of *ALK*-dominant and non-dominant mechanisms of resistance have been identified in patients (*ALK* mutation with *KIT* amplification and *ALK* copy-number gain with *EGFR* mutation) [30,31]. In a significant number of cases the mechanism of resistance is unknown.

Different clinical scenarios of progression under crizotinib treatment have been observed: (1) rapid symptomatic progression, (2) formation of a single new lesion or increased size of a single lesion that was previously under control (oligoprogression), and (3) slow asymptomatic growth of multiple lesions that were formerly controlled with crizotinib. In this context it is interesting that cessation of TKI therapy in NSCLC with activating *EGFR* mutations has been documented to cause disease flare in 23% of patients with acquired resistance to *EGFR* TKIs following washout of the drug [33]. Although this phenomenon has not been systematically evaluated for *EML4-ALK* translocations and crizotinib, two case reports document a similar phenomenon following crizotinib withdrawal at disease progression in patients with *ALK*-positive metastatic NSCLC [34,35].

Single new or newly growing lesions can potentially be controlled by local treatment such as stereotactic radiotherapy or even surgery when all other disease areas remain controlled by crizotinib [36]. When alternative signaling pathways get activated, the tumor remains at least partly driven by the *ALK* rearrangement. In both cases, withdrawal of crizotinib bears the risk of restarted or enhanced tumor proliferation since aberrant *ALK* remains the major oncogenic driver.

In a small series of patients ($n = 25$), Weickhardt et al. demonstrated a median additional 6.2 months of PFS when erlotinib or crizotinib were continued beyond a progression event, which was treated locally (surgery or radiotherapy). Interestingly, there was a trend toward a larger benefit for patients who had progression the CNS only [37]. In a follow-up analysis of crizotinib-treated patients with *ALK*-positive NSCLC, Gan and coauthors showed that local control of up to 4 newly growing lesions outside the CNS with local ablative approaches allowed an additional median 5.5 months of PFS with crizotinib, which was also associated with a longer overall survival. Although not statistically significant, this approach appeared to be more successful for patients with 1 or 2 progression lesions compared to 3 or 4 [36]. In

addition, Ou and coauthors showed longer survival among those patients who stayed on crizotinib post-Response Evaluation Criteria in Solid Tumors (RECIST)-defined progressive disease (PD) [38]. In this retrospective analysis involving 194 patients from PROFILE 1001 and PROFILE 1005, overall survival was significantly longer among patients who continued crizotinib treatment beyond RECIST-defined PD than among those who did not, both from the time of PD (median 16.4 vs. 3.9 months, respectively; $p < 0.0001$) and from initiation of crizotinib treatment (median 29.6 vs. 10.8 months; $p < 0.0001$) [38]. Additional reports have also suggested continued clinical benefit in this setting [11,39]. Although all of these analyses are retrospective and subject to a potential selection bias, they provide evidence that there is substantial value from continued crizotinib for individual patients who are candidates for local therapy at a progression event. The advisory board consensus opinion was that crizotinib should be continued for as long as the patient derives benefit from treatment. The decision to stop treatment should not be based only on radiography but should take the clinical situation into consideration. Treatment should be discontinued when symptomatic and/or rapid progression occurs and if other treatment options are available, such as chemotherapy or novel agents in clinical trials.

Ideally, treatment plans for patients with disease progression on crizotinib should be individualized based upon clinical profiles, including the magnitude of prior response, number and location of metastatic sites, and remaining tumor burden. In select cases of oligometastatic progression, integration of crizotinib and other local therapeutic options such as surgery, radiofrequency ablation, and radiotherapy should be considered. In addition, treatment of isolated brain metastases with radiotherapy or local ablative therapy with subsequent continued crizotinib therapy has shown promise [37,39]. For single liver metastasis, surgery or local ablation may be appropriate therapies depending upon tumor volume. Similarly, extent of disease influences the management of patients with bone metastases, with continued crizotinib and intermittent irradiation probably being appropriate for patients with single lesions only. Once a local recurrence is controlled using other modalities, crizotinib remains effective in controlling the primary disease in many cases. However, clinical studies assessing the benefit derived from crizotinib in combination with local therapy in a prospective setting are warranted to enable definitive recommendations to be made.

In early clinical trials, the second generation ALK inhibitors ceritinib and alectinib have demonstrated marked activity in ALK-positive NSCLC after failure of crizotinib with an ORR of 56% and 55%, respectively [40,41]. Based on these data, ceritinib has recently been approved by the US FDA for the treatment of patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib. Following failure of crizotinib, ceritinib and alectinib can be a treatment option when access to these compounds is available. Unless it has been used in the first-line before crizotinib, pemetrexed is the otherwise preferred medical treatment in the resistance situation based on accumulating evidence of its efficacy in ALK-positive NSCLC [14]. If pemetrexed was used before, docetaxel is another option. Cases of successful re-challenge with crizotinib have been described after chemotherapy [42].

4. Conclusion

The rapid development of crizotinib from experimental compound to approved therapy has had a major impact on the lives of patients with ALK-positive NSCLC. However, a consequence of such rapid approval is limited experience and information concerning management of AEs and long-term therapy management. This report summarizes consensus opinion developed during a European Crizotinib Therapy Management Advisory Board meeting. The

opinion was that crizotinib was generally well tolerated. AEs were mostly mild to moderate in severity, and appropriate monitoring and supportive therapies were considered effective in avoiding the need for dose interruption or reduction in most cases.

Mild visual disturbances are the most common side effect associated with crizotinib and, while rarely bothersome, patients should be advised to exercise caution when driving or operating machinery; if symptoms worsen, further investigation may be appropriate. ECG monitoring is recommended to assess possible QTc prolongation as well as bradycardia in crizotinib-treated patients. This is particularly important for patients with a history of cardiac disease, those taking medications with a potential for QT prolongation, or those with clinically relevant symptoms. Due to cases of severe hepatotoxicity observed in a small number of crizotinib-treated patients, regular monitoring of liver function is important. In cases of severe hematologic toxicity, treatment interruption may be necessary for some patients.

Based on available clinical data, it is evident that patients may have prolonged benefit from crizotinib after RECIST-defined PD. Therefore, crizotinib should be continued for as long as the patient derives benefit. Local recurrences can be managed using other modalities, and in many cases crizotinib continues to provide effective disease control. Crizotinib should be discontinued upon rapid progression and/or clinical deterioration.

Continued data collection, information sharing, and clinical trials are essential to optimize AE management and crizotinib treatment, as well as to manage the impact of the heterogeneous mechanisms associated with crizotinib resistance.

Conflict of interest statement

Denis Moro-Sibilot has served in a consultancy/advisory role for Pfizer, Roche, Boehringer-Ingelheim, Eli Lilly, AstraZeneca, and Novartis. Oliver Gautschi and Paul Germonpré have served in a consultancy/advisory role for Pfizer. Ekaterini Boleti and Nicola Steele have served in a consultancy/advisory role for and received honoraria from Pfizer. Enriqueta Filip has served in a consultancy/advisory role for Lilly, GSK, Pfizer, Roche, and Boehringer-Ingelheim. Edurne Arrriola has served in a consultancy/advisory role for Pfizer and Boehringer-Ingelheim. Jesme Fox has served in a consultancy/advisory role for Pfizer, Boehringer-Ingelheim, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, Amgen, Novartis, Roche, and GSK. Patrick Schnell and Arne Engelsberg are Pfizer employees and hold Pfizer stock. Jürgen Wolf has served in a consultancy/advisory role for and received honoraria and research funding from Pfizer. Federico Cappuzzo, Harry J.M. Groen, and Peter Meldgaard have no conflicts of interest to disclose.

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