



# Managing treatment-related adverse events associated with Alk inhibitors

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## ABSTRACT

Anaplastic lymphoma kinase (*ALK*) rearrangements have been identified as key oncogenic drivers in a small subset of non-small-cell lung cancers (NSCLC). Small-molecule Alk kinase inhibitors such as crizotinib have transformed the natural history of NSCLC for this subgroup of patients. Because of the prevalence of NSCLC, *ALK*-positive patients represent an important example of the paradigm for personalized medicine. Although Alk inhibitors such as crizotinib are well tolerated, there is a potential for adverse events to occur. Proactive monitoring, treatment, and education concerning those adverse events will help to optimize the therapeutic index of the drugs. The present review summarizes the management of treatment-related adverse events that can arise with Alk inhibitors such as crizotinib.

## KEY WORDS

Anaplastic lymphoma kinase inhibitors, *ALK*, crizotinib, adverse events, lung cancer

## 1. INTRODUCTION

The use of targeted therapies for subsets of molecularly-defined cancers has been a paradigm shift in cancer treatment. In non-small-cell lung cancer (NSCLC), the shift was first seen with the discovery that mutations in the epidermal growth factor receptor predicted responsiveness to epidermal growth factor receptor tyrosine kinase inhibitors. Although those inhibitors are generally well tolerated, they have a unique side effect profile that differs from that of traditional cytotoxic therapy. Given the effectiveness of targeted therapies, patients will often be taking the agents for long periods of time. It is therefore imperative to optimize the management of treatment-related adverse events (AES) and thus in turn to enhance the patient's quality of life.

In 2007, anaplastic lymphoma kinase (*ALK*) gene rearrangements were identified in NSCLC<sup>1,2</sup>. Although

*ALK* had previously been identified in subsets of anaplastic large-cell lymphomas<sup>3</sup> and inflammatory myofibroblastic tumours<sup>4</sup>, its identification in NSCLC was what prompted the investigation of Alk inhibition as a therapeutic strategy.

Roughly 4% of nonsquamous NSCLC is *ALK*-driven. Given the prevalence of NSCLC, estimates suggest that several hundred patients with advanced *ALK*-positive NSCLC will be diagnosed annually in Canada<sup>5</sup>. In bringing a new class of therapeutics into the clinic, it is essential that the multidisciplinary team be familiar with management of the AES that can arise—especially in the case of a therapy that will be used in a very specific subgroup of patients and with which clinicians may have limited experience<sup>6</sup>.

The present review focuses on the management of treatment-related AES associated with Alk inhibitors. It focuses on NSCLC, given that most of the available data relate to that disease and that the other populations in which Alk inhibitors have shown benefit are relatively rare tumours. Similarly, the focus of the discussion is crizotinib, because that agent is currently the only Alk inhibitor approved by the U.S. Food and Drug Administration and Health Canada; however, we also highlight emerging data concerning second-generation Alk inhibitors.

## 2. ALK AND CRIZOTINIB: AN OVERVIEW

Preclinical studies have highlighted the importance of *ALK* as an oncogenic driver in NSCLC and the associated sensitivity to Alk inhibition<sup>1,7</sup>. Patients with *ALK* rearrangements tend to be younger at diagnosis (median age: approximately 50 years), are typically never-smokers (in the crizotinib studies, never-smokers constituted roughly two thirds of the cohort), and have adenocarcinoma histology<sup>8-10</sup>. In Canada, patients are currently screened for *ALK* by immunohistochemistry, with fluorescence *in situ* hybridization used for confirmation.

Crizotinib is a small-molecule receptor tyrosine kinase inhibitor initially designed to target c-Met,

but subsequently found to be active against Alk. A phase I trial in advanced *ALK*-positive NSCLC (PROFILE 1001) demonstrated an impressive 60.8% response rate, a disease control rate of 82.5% at 8 weeks, and progression-free survival of 9.7 months<sup>8</sup>. A global phase II study in a similar patient population (PROFILE 1005) confirmed that remarkable clinical activity<sup>9</sup>. A phase III study in advanced *ALK*-positive NSCLC progressing on a first-line platinum-based doublet compared crizotinib with standard second-line chemotherapy using pemetrexed or docetaxel (PROFILE 1007)<sup>10</sup>. That study demonstrated significant improvements in response rate and progression-free survival in favour of crizotinib, but no overall survival benefit was observed, presumably because of crossover. Results from a first-line study in advanced *ALK*-positive NSCLC comparing crizotinib with platinum–pemetrexed combination chemotherapy [PROFILE 1014 (search for NCT01154140 at <http://clinicaltrials.gov/>)] are awaited. On the basis of the data from PROFILE 1001 and 1005, crizotinib received accelerated approval from the U.S. Food and Drug Administration and Health Canada.

Despite the impressive activity of crizotinib, resistance is generally inevitable<sup>11,12</sup>. One approach to overcoming resistance is the development of next-generation Alk inhibitors<sup>13</sup>. The newer agents are generally more potent than crizotinib and structurally distinct. As such, they may be associated with different AE profiles. Data on the efficacy of second-generation Alk inhibitors is limited mainly to phase I and II studies. For example, data presented on LDK378 (Novartis, Basel, Switzerland) at the 2013 annual meeting of the American Society of Clinical Oncology showed a response rate of 57% in crizotinib-treated patients<sup>14</sup>. Several excellent reviews on the current understanding of *ALK*-positive NSCLC and approaches to overcoming resistance are available<sup>13,15</sup>.

### 3. CRIZOTINIB PHARMACOLOGY

#### 3.1 Pharmacokinetics

The oral bioavailability of crizotinib is 43%, and absorption is slightly reduced (14%) when the drug is administered with a high-fat meal. Nonetheless, crizotinib can be taken with or without food. The tissue distribution of the drug is wide, and plasma protein binding *in vitro* is 91%<sup>16</sup>.

The solubility of crizotinib is pH-dependent: a high (less acidic) pH reduces solubility. Medications such as proton pump inhibitors, histamine H2 blockers, and antacids may therefore have an effect on bioavailability, although the clinical relevance of this interaction is unknown. Results of a drug–drug interaction study involving crizotinib and esomeprazole (search for NCT01549574 at <http://clinicaltrials.gov/>) have not yet been reported. Patients in the clinical trials were allowed to take all the foregoing medications while on treatment with crizotinib.

#### 3.2 Drug Interactions

Crizotinib is metabolized predominantly by CYP3A, and so co-administration with strong inhibitors of CYP3A4 such as ketoconazole increases the area under the curve of crizotinib and should be avoided. Moderate inhibitors of CYP3A4 should be used with caution, and crizotinib toxicity should be monitored. Patients taking crizotinib should avoid grapefruit juice, a strong CYP3A4 inhibitor. Conversely, strong inducers of CYP3A4 such as rifampin and St. John's Wort reduce plasma concentrations of crizotinib and should therefore be avoided.

Crizotinib has been identified as a CYP3A4 and CYP2B6 inhibitor, potentially increasing plasma concentrations of co-administered drugs. Caution should be exercised with the concomitant use of CYP3A-metabolized drugs with narrow therapeutic indices, especially when associated with cardiac arrhythmias<sup>16</sup>.

The use of crizotinib with heart-rate-lowering and QT-interval-prolonging drugs is discussed in detail in the “Specific AEs of Crizotinib” section.

#### 3.3 Dosing

The recommended dose of crizotinib is 250 mg taken orally twice daily. If dose reduction is necessary, 200 mg taken orally twice daily can be used. If further reduction is required, the dose can be modified to 250 mg taken orally once daily.

Because crizotinib is metabolized in the liver, hepatic impairment can lead to higher drug concentrations. In studies, patients were excluded if their serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) was more than 2.5 times the upper limit of normal (or more than 5 times if related to the underlying malignancy) or if total bilirubin was more than 1.5 times the upper limit of normal. In patients with significant hepatic dysfunction, crizotinib should be used with caution.

No dose modification is required for patients with mild-to-moderate renal dysfunction (creatinine clearance > 30 mL/min). The recommended dose in patients with severe renal impairment (creatinine clearance < 30 mL/min) not requiring dialysis is 250 mg orally once daily.

#### 3.4 Central Nervous System Penetration

The central nervous system (CNS) is a common site of progression in *ALK*-positive, crizotinib-treated NSCLC patients. A number of reports describe patients who continued to respond systemically, but who progressed in the CNS<sup>17,18</sup>. One possible explanation comes from a pharmacokinetic analysis in a single patient showing poor cerebrospinal fluid penetration<sup>19</sup>. Routine surveillance of the CNS should therefore be considered in all crizotinib-treated patients. Patients who develop CNS metastases as an isolated site of progression can

often undergo CNS radiation and continue crizotinib to control systemic disease<sup>20</sup>. Second-generation Alk inhibitors have shown promising activity in the CNS, and further data will be forthcoming<sup>21</sup>.

#### 4. OVERVIEW OF ADVERSE EFFECTS OF ALK INHIBITORS

##### 4.1 Crizotinib

Crizotinib is generally well tolerated, with most AEs being grade 1 or 2. Those AEs include visual disorders, gastrointestinal effects (nausea, diarrhea, vomiting, constipation), edema, and fatigue. Visual disturbance is a unique side effect associated with changes in ambient lighting—for example, moving from a dark to a light room. Patients commonly describe trails or flashes of light in their peripheral vision that are typically mild and short-lived (discussed in more detail later in this article). Table I describes the AEs commonly seen across the key studies (in which the safety profile of crizotinib is quite consistent). Nausea, vomiting, and diarrhea tend to occur early in treatment (median time to onset: 2–5 days); visual effects occur slightly later (median time to onset: 14 days); and peripheral edema occurs later on (median time to onset: 85 days). Over time, the visual and gastrointestinal effects tend to improve. Patients on treatment for more than 6 months did not have any new AEs or issues related to prolonged exposure<sup>8</sup>. Management of specific AEs is described in greater detail in the “Specific AEs of Crizotinib” section.

The occurrence of grades 3 and 4 toxicities was relatively uncommon. In PROFILE 1005, the most frequently described grades 3 and 4 AEs were elevated alanine aminotransferase (3.9%) and neutropenia (5.5%). Other rare, but potentially serious, toxicities include pneumonitis. The rate of treatment-related AEs resulting in permanent discontinuation of the drug was 3% in PROFILE 1001, 5% in PROFILE 1005, and 6% in PROFILE 1007<sup>8–10</sup>.

Although the possibility of serious AEs from crizotinib is relatively low, proactive monitoring is important to mitigate the risk. Table II describes the key toxicities and suggests parameters to monitor. Table III describes the recommended dose modifications for crizotinib-related AEs.

##### 4.2 Second-Generation Alk Inhibitors

Several second-generation Alk inhibitors are currently in phase I and II testing. In the phase II study of LDK378, which involved 130 patients, the most common AEs were nausea (73%), diarrhea (72%), vomiting (58%), and fatigue (41%). The most frequent grades 3 and 4 AEs were alanine aminotransferase elevation (19%), aspartate aminotransferase elevation (10%), and diarrhea (8%)<sup>14</sup>. In a phase II study of CH5424802 (Chugai Pharmaceutical, Tokyo, Japan) involving 46 patients, AEs were typically grades 1 and 2, and included dysgeusia (30%), increased aspartate aminotransferase (28%), increased bilirubin (28%), increased creatinine (26%), rash (26%), and constipation (24%). Visual disorders were rare<sup>22</sup>. Further studies will help to elucidate the differences

TABLE I All grades of treatment-related adverse events seen in at least 10% of patients in PROFILE 1001<sup>8</sup>, PROFILE 1005<sup>9</sup>, and PROFILE 1007<sup>10</sup>

Adverse event	Occurrence (%) in					
	PROFILE 1001 (n=149)		PROFILE 1005 (n=901)		PROFILE 1007 (n=172)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Visual effects	64	0	52	<1	60	0
Nausea	56	<1	47	<1	55	1
Diarrhea	50	0	41	1	60	0
Vomiting	39	<1	39	<1	47	1
Peripheral edema	30	0	23	<1	31	0
Constipation	28	<1	28	<1	42	2
Dizziness	21	0	11	0	22	1
Decreased appetite	16	0	19	<1	27	2
Fatigue	16	1	18	2	27	2
Increased ALT	12	4	16	4	NR <sup>a</sup>	NR <sup>a</sup>
Dysgeusia	11	0	17	0	26	0
Increased AST	10	3	12	1	NR <sup>a</sup>	NR <sup>a</sup>

<sup>a</sup> Reported as cluster term “elevated aminotransferase levels,” the all-grade occurrence was 38%, and the grade 3 or 4 occurrence was 16%. ALT = alanine aminotransferase; NR = not reported; AST = aspartate aminotransferase.

TABLE II Recommended monitoring for patients on crizotinib<sup>16</sup>

<i>Toxicity</i>	<i>Baseline testing</i>	<i>Ongoing monitoring</i>
Hepatotoxicity	AST, ALT, ALP, bilirubin	Every 2 weeks during the first 2 months, then monthly and as clinically indicated More frequent testing for grade 2, 3, or 4 elevation
Hematologic effects	Complete blood count and differential	Monthly and as clinically indicated More frequently if grade 3 or 4 abnormalities observed, or if fever or infection occurs
Cardiac (QTc prolongation and bradycardia)	Concomitant medication list, physical exam (heart rate and blood pressure), electrocardiogram, electrolytes	Concomitant medication list Physical exam (heart rate and blood pressure) Periodic monitoring for patients at risk for abnormalities with electrocardiogram and electrolytes
Ophthalmologic	None	If persistent or severe symptoms, consider ophthalmologic evaluation
Pneumonitis	None	As clinically indicated by symptoms and imaging
Hypogonadism	In men: serum testosterone	If symptomatic: serum testosterone

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase.

in side-effect profile between crizotinib and the second-generation Alk inhibitors.

## 5. SPECIFIC AES OF CRIZOTINIB

### 5.1 Visual Effects

The most common side effect of crizotinib is visual disturbance. Typically, this disturbance occurs early (median time to onset of less than 2 weeks). The visual effects are predominantly grade 1, and in the PROFILE 1001 and 1005 trials, no patients required dose interruptions or reductions because of them<sup>8,23</sup>. Ophthalmologic assessment was carefully performed in the PROFILE 1005 study, and no clinically meaningful changes were found.

In patients treated on PROFILE 1005, a visual symptom assessment questionnaire was completed on day 1 of each cycle. Over time, the visual effects occurred less frequently. Patients typically reported visual events in the morning or evening. The most common symptoms included the appearance of shimmering, flashing, or trailing lights; appearance of streamers, strings, or floaters; and overlapping shadows or afterimages. The events were short-lived, typically lasting less than 1 minute. Most patients reported that the visual effects were not at all or only a little bothersome. Similarly, they indicated no or minimal impact of visual effects on activities of daily living<sup>23</sup>.

In clinical practice, patients on crizotinib do not require baseline or routine ophthalmologic assessments. However, if visual changes worsen in severity,

ophthalmologic evaluation should be considered. A practical question about ability to drive often comes up at crizotinib start. No specific data address that question, but the product monograph recommends that caution should be exercised during driving or operating machinery by patients who experience vision disorders. We typically advise patients to observe how their vision is affected in low light conditions and, if they are significantly affected (a minority of patients), to refrain from driving at those times of day until symptoms improve.

### 5.2 Liver Enzyme Abnormalities

Abnormalities in liver enzymes are frequently observed with crizotinib, and in some cases, significant elevations can occur. A pooled analysis of PROFILE 1001 and 1005 that included more than 1000 patients treated with crizotinib calculated the overall incidence of liver enzyme abnormalities (Table IV)<sup>24</sup>.

Most patients who experience liver enzyme elevation do so within the first 2 months of treatment. However, liver enzyme elevation can occur later on as well. Transaminase elevations are usually reversible, and patients are typically able to resume treatment at the same or a lower dose. Temporary discontinuation or dose reduction because of a hepatic adverse event occurred in 5.3% of all patients. Permanent discontinuation because of a hepatic adverse event occurred in 1.3% of patients<sup>24</sup>.

Based on those findings, it is important to monitor liver enzymes while patients are on crizotinib,

TABLE III Dose modifications for crizotinib related adverse events<sup>16</sup>

Toxicity	CTCAE grade	Toxicity description	Dosing
Hematologic toxicity	Grade 3	ANC: <1.0 to 0.5×10 <sup>9</sup> /L Platelets: <50.0 to 25.0×10 <sup>9</sup> /L	Withhold until recovery to grade 2 or lower. Resume at same dose schedule.
	Grade 4	ANC: <0.5×10 <sup>9</sup> /L Platelets: <25.0×10 <sup>9</sup> /L	Withhold until recovery to grade 2 or lower. Resume at 200 mg twice daily <sup>a</sup> .
Hepatotoxicity	Grade 3 or 4 ALT or AST elevation and Grade 1 or lower total bilirubin	AST and ALT Grade 2: >3.0 to 5.0×ULN Grade 3: >5.0 to 20.0×ULN Grade 4: >20.0×ULN	Withhold until recovery to grade 1 or lower. Resume at 200 mg twice daily <sup>b</sup> .
	Grade 2, 3, or 4 ALT or AST elevation and concurrent grade 2, 3, or 4 total bilirubin elevation <sup>c</sup>	Bilirubin Grade 2: >1.5 to 3.0×ULN Grade 3: >3.0 to 10.0×ULN Grade 4: >10.0×ULN	Permanently discontinue.
Pneumonitis	Any grade <sup>d</sup>		Permanently discontinue.
QTc prolongation	Grade 3 <sup>e</sup>	QTc ≥ 500 ms	Withhold until recovery to baseline or to a QTc ≤ 480 ms Resume at 200 mg twice daily <sup>b,f</sup>
	Grade 4	QTc ≥ 500 ms and life-threatening signs or symptoms	Permanently discontinue.

<sup>a</sup> In case of recurrence, hold until recovery to grade 2 or lower, and then resume at 250 mg daily. Permanently discontinue in case of further grade 4 recurrence.  
<sup>b</sup> In case of recurrence, hold until recovery to grade 1 or lower, and then resume at 250 mg daily. Permanently discontinue in case of further grade 3 or 4 recurrence.  
<sup>c</sup> In the absence of cholestasis or hemolysis.  
<sup>d</sup> In the absence of disease progression, other pulmonary disease, infection, or radiation effect.  
<sup>e</sup> On at least 2 separate electrocardiograms.  
<sup>f</sup> Ensure that hypokalemia, hypomagnesemia, and hypocalcemia are corrected.

CTCAE = U.S. National Cancer Institute Common Terminology Criteria for Adverse Events; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

especially within the first 2 months. Symptoms of liver dysfunction should prompt assessment for possible drug-induced liver injury. Tables II and III detail parameters to monitor and dose modifications.

### 5.3 Gastrointestinal Effects

The main gastrointestinal effects of crizotinib include nausea, diarrhea, vomiting, and constipation. Grades 1 and 2 nausea or vomiting were commonly seen in the clinical trials (Table I). For many patients, taking crizotinib with food is a helpful strategy for alleviating the nausea<sup>8</sup>. Nausea and vomiting can be prevented and treated using anti-emetics such as metoclopramide or dimenhydrinate. Prochlorperazine and 5-HT<sub>3</sub> receptor

antagonists such as ondansetron should be avoided or used with caution because of the risk of QT prolongation. Aprepitant has not been studied with crizotinib, and as a CYP3A4 substrate and inhibitor, it might lead to increased crizotinib toxicity.

Grades 1 and 2 diarrhea and, to a lesser extent, constipation can both be seen with crizotinib (Table I). Once infectious causes for diarrhea have been excluded, standard nonpharmacologic measures (dietary adjustment and hydration) and antidiarrheal medications such as loperamide can be used. Management of constipation includes dietary modification and standard laxatives.

Patients receiving crizotinib also experienced dysgeusia (Table I). That effect—usually a metallic

TABLE IV Incidence of hepatic laboratory abnormalities among 1054 patients in PROFILE 1001 and PROFILE 1005<sup>24</sup>

Level of abnormality	Patients (%) experiencing elevation in			
	ALT	AST	ALP	Bilirubin
>3×ULN	15.2	7.7	8.9	0.4
>5×ULN	7.4	3.2	2.3	0.2
>10×ULN	3.0	1.5	0.6	0
>20×ULN	1.6	0.5	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN = upper limit of normal.

taste or lack of taste—is common with chemotherapy. In this case, patients reported an accentuation of sweet or sour taste, together with a diminished taste for hot or spicy food. Importantly, although gastrointestinal effects are frequently seen with crizotinib, they tend to improve over time and grade 3 or 4 AES are rare<sup>8</sup>.

#### 5.4 Cardiac Effects

Crizotinib is associated with two main cardiac effects: QT interval prolongation and bradycardia. For patients starting crizotinib, baseline evaluation should include physical examination (heart rate and blood pressure), electrocardiography, and blood work (electrolytes). The evaluation should be repeated periodically, with the frequency depending on the patient's risk for cardiac complications. Electrolyte abnormalities (specifically potassium, calcium, and magnesium) should be corrected. The patient's medication lists should be up to date, and concomitant medications should be analyzed for their potential to cause QT prolongation and to lower heart rate, as well as for their potential to cause electrolyte abnormalities. If co-administration of such drugs is unavoidable, monitoring should occur more frequently. Table III describes management of QT prolongation.

Although QT prolongation was observed in patients on crizotinib, no associated arrhythmias were observed<sup>25</sup>. Crizotinib should be used with caution in patients with a predisposition to QT prolongation or in those on concomitant QT-prolonging medications.

Bradycardia, typically grade 1 or 2, was reported in 5% of patients receiving crizotinib. Heart rate decrease is a pharmacodynamic effect of crizotinib, averaging 2.5 fewer beats per minute with every 100 ng/mL increase in the serum concentration of crizotinib<sup>26</sup>. In the PROFILE 1005 trial, a heart rate decrease by a mean of 15.9 bpm was measured on day 22 of crizotinib treatment<sup>16</sup>. In a retrospective analysis of patients from a single institution enrolled in the PROFILE 1001 and 1005 trials, most patients experienced at least 1 episode of an absolute decrease in heart rate of more than 10 bpm from baseline

before treatment. Importantly, patients with sinus bradycardia were asymptomatic and had no associated electrocardiographic changes such as PR or QT prolongation. An exploratory analysis looked at the correlation between heart rate decrease and clinical response, and further study is required. The exact mechanism of this phenomenon is not known. Some hypothesize that it might be related to c-Met inhibition<sup>25</sup>. Concurrent heart-rate-lowering medications such as beta-blockers or non-dihydropyridine calcium channel blockers should be used with caution in patients receiving crizotinib.

#### 5.5 Pneumonitis

Pulmonary toxicity from crizotinib is a rare, but potentially life-threatening, adverse reaction. This rare toxicity has been seen with other small-molecule tyrosine kinase inhibitors, including gefitinib and erlotinib. In PROFILE 1001 and 1005, severe pneumonitis was seen in 1.6% (4 of 255) of patients<sup>16</sup>. Typically, the event happened within 2 months after initiation of treatment. Cases of fatal crizotinib-induced pneumonitis have occurred<sup>27</sup>.

Because of the high incidence of baseline pulmonary disease, radiation-related changes, infectious complications, and presence of progressive malignancy, a diagnosis of drug-induced pneumonitis can be difficult to make in lung cancer patients. However, in patients with unexplained pulmonary symptoms, crizotinib-induced pneumonitis has to be considered in the differential diagnosis. Crizotinib should be permanently discontinued in patients who are diagnosed with treatment-related pneumonitis. Successful crizotinib re-treatment has been described with the addition of steroid premedication, but further data are required to evaluate the safety of that maneuver<sup>28</sup>.

#### 5.6 Hypogonadism

Hypogonadism occurs quite commonly in patients with advanced cancer, and it is often underdiagnosed and rarely treated<sup>29</sup>. Low testosterone in cancer patients has been correlated with fatigue, sexual disinterest, and decreased quality of life<sup>30</sup>. Given that a large number of patients treated with crizotinib are young adults who will be on therapy for relatively long periods of time, such symptoms can be even more distressing.

Total testosterone levels were low in a cohort of crizotinib-treated patients compared with patients with advanced NSCLC not taking crizotinib (84% vs. 32%). The exact mechanism of this difference has not been fully elucidated. Changes appeared to be both rapid and reversible on commencement and cessation of dosing. In a small cohort of patients, testosterone replacement with topical gel has been shown to normalize testosterone levels and to improve symptoms<sup>31</sup>.

Until further data emerge, men starting on crizotinib should have baseline testosterone levels determined in an early-morning blood sample. In patients who have symptoms of hypogonadism, serum testosterone should be checked. If the level is low, endocrinology referral should be arranged to discuss the pros and cons of testosterone replacement therapy<sup>31</sup>.

### 5.7 Peripheral Edema

Peripheral edema occurs in up to one third of patients taking crizotinib, being the main cumulative effect of this agent (Table 1). Occurrences are typically grade 1 or 2<sup>8</sup>. The mechanism is unknown, although edema is also an effect seen with other Met inhibitors<sup>32</sup>. No specific recommendations have been made for managing edema related to crizotinib, but conservative measures such as leg elevation, compression stockings, and dietary salt modification can be considered. Diuretics can be tried in refractory or more severe cases.

### 5.8 Rare Complications of Crizotinib

Complex renal cysts were seen very infrequently in patients treated with crizotinib. There was no associated renal impairment, and the significance of these occurrences is unknown<sup>16</sup>.

Esophageal disorders—almost exclusively grade 1 or 2—were reported in 11% of patients on PROFILE 1001 and 4% of those on PROFILE 1005. One published case of grade 3 esophagitis resolved with crizotinib discontinuation<sup>33</sup>.

## 6. SUMMARY

The field of oncology has entered an era of molecularly targeted therapy. Compared with cytotoxic chemotherapy, agents such as crizotinib offer the promise of improved outcomes with fewer toxicities. Given that these agents often target multiple pathways, it is important to recognize both on-target and off-target effects so as to anticipate and treat toxicities that arise. Proactive management of AEs helps to optimize the therapeutic index of targeted therapies and enhances quality of life for patients.

## 7. CONFLICT OF INTEREST DISCLOSURES

JR has received honoraria from Hoffmann–La Roche, Pfizer, and Boehringer Ingelheim. NL has received honoraria from Hoffmann–La Roche, Pfizer, and Novartis.

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