Lung Cancer 145 (2020) 167–172

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Ophthalmological assessment of crizotinib in advanced non-small-cell lung cancer

Benjamin J. Solomon[a,*], Elizabeth E. Kim[b], Maria Winter[c], Katherine Monti[d,1], Yiyun Tang[c], Keith D. Wilner[c], Sherry Wang[c], Sai-Hong Ignatius Ou[e]

[a] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[b] Pfizer, New York, NY, USA
[c] Pfizer Oncology, La Jolla, CA, USA
[d] Rho, Inc., Chapel Hill, NC, USA
[e] Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange, CA, USA

ARTICLE INFO

Keywords:
Crizotinib
Ophthalmology
Visual disturbances
NSCLC
TKI

ABSTRACT

Objectives: During crizotinib clinical evaluation, visual disturbances, generally of grade 1 severity, were frequently reported adverse events (AE). Consequently, ophthalmologic assessments were included in a patient subgroup enrolled in PROFILE 1001 (NCT00585195), a phase 1, open-label, single-arm trial of crizotinib in patients with advanced non-small-cell lung cancer and are reported here.

Materials and methods: At least 30 patients were required to undergo ophthalmologic assessments, including: best-corrected visual acuity (BCVA), refractive error, pupil size, slit-lamp anterior segment biomicroscopy, intraocular inflammation, intraocular pressure, retinal fundoscopic exams, fundus photography, ocular characteristics, and optical coherence tomography (OCT). Scheduled assessments included those at baseline, Cycle 1 Day 15, Cycle 3 Day 1 (C3D1), annually during treatment, and end of treatment (28 days after last crizotinib dose).

Results: Thirty-three patients completed all required ophthalmologic assessments through C3D1, and 22 (66.7 %) had abnormal findings on ≥1 ophthalmologic test. Clinically important changes were ≥2-line loss in BCVA in 10 patients (30.3 %), > ± 1.25-diopter change in refractive error in 3 patients (9.1 %), > ± 2-mm change pupillary diameter change in 3 patients (9.1 %), and > 50 μm increase in OCT center point thickness in 7 patients (21.2 %). Three patients (15 %) reported clinically significant abnormalities in anterior segment biomicroscopy (grade 1 cataract [n = 2], grade 1 Visual Impairment [n = 1]). No permanent treatment discontinuations were associated with ophthalmologic findings changes. Twenty-four patients (72.7 %) reported ≥1 ocular all-causality treatment-emergent AE (TEAE); none required dose reduction or permanent discontinuation, but 2 required temporary dosing interruption. Although TEAEs and ophthalmologic findings may not have occurred concurrently, of 24 patients with ≥1 all-causality ocular TEAE, 18/24 (75.0 %) had ≥1 abnormal ophthalmologic finding and 6/24 (25 %) had none; and of 9 patients without an all-causality ocular TEAE, 4/9 (44.4 %) had ≥1 abnormal ophthalmologic finding and 5/9 (55.6 %) had none. Of the 18 patients with ≥1 abnormal ophthalmologic finding, 9 (50 %) had preexisting ocular conditions.

Conclusion: During crizotinib treatment, ophthalmologic changes from baseline did not appear to be associated with patient-reported ocular TEAEs. Abnormal ophthalmologic findings occurred in the context of preexisting conditions for a number of patients. No ophthalmologic changes from baseline or ocular all-causality TEAEs required permanent treatment discontinuation.

1. Introduction

Crizotinib is a first-generation, orally administered small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), MET (also known as hepatocyte growth factor receptor) and ROS1. Crizotinib is approved for patients with *ALK*-positive non-small-cell

* Corresponding author at: Department of Medical Oncology, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC 3000, Australia.
E-mail address: ben.solomon@petermac.org (B.J. Solomon).
[1] Now retired.

https://doi.org/10.1016/j.lungcan.2020.04.010
Received 10 December 2019; Received in revised form 7 April 2020; Accepted 9 April 2020
0169-5002/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

lung cancer (NSCLC) in over 90 countries and *ROS1*-positive NSCLC in over 70 countries [1].

In preliminary and updated analyses of a single-arm trial of crizotinib in patients with *ALK*-positive advanced NSCLC, predominantly grade 1 or 2 visual disturbances were among the most common adverse events (AEs), including, but not limited to, light trails, flashes or brief image persistence. These mild-to-moderate ocular AEs occurred in 41 % and 64 % of patients, respectively, in the 2 analyses [2,3]. Visual disturbances continued to be one of the most frequently reported AEs with crizotinib, occurring in 60–71 % and 82 % of patients with *ALK*- or *ROS1*-positive NSCLC, respectively [4–6]. The frequency of visual disturbances led regulatory authorities in both the United States and European Union to institute a postmarketing requirement to conduct specialized ophthalmologic assessments among patients treated with crizotinib. Although the ocular all-causality AEs were generally grade 1 or 2 in severity and non-serious, their relatively high incidence in patients treated with crizotinib suggested that a comprehensive characterization of these events would be beneficial.

The purpose of this prospective subgroup analysis was to determine if there were specific objective ophthalmologic findings present among patients with advanced NSCLC treated with crizotinib and whether any such findings correlated with symptomatic reports of visual disturbances.

2. Methods

2.1. Study design and patients

The design of the ongoing, multicenter, multinational, open-label, phahalmologic assessments to evaluate possible causes of ocular AEs. Patients with NSCLC received 10 specific ophthalmologic tests (see section entitled *Ophthalmologic Tests*). These assessments were to occur at baseline, Cycle 1 Day 15 (C1D15), Cycle 3 Day 1 (C3D1), annually thereafter while on treatment, and at the end of treatment, defined as 28 days after the last crizotinib dose. Patients in the *ALK*-negative NSCLC cohort were treated on a 21-day cycle, whereas patients in all other cohorts were treated on a 28-day cycle. Accordingly, scheduled C3D1 assessments fell on Study Day 43 (1 day after two 21-day cycles had been completed) or Study Day 57 (1 day after two 28-day cycles), depending on the patient cohort.

2.2. Study population

The 10-test-evaluable population was defined as those patients in the Intent-To-Treat population who completed assessments at screening, C1D15 and C3D1 for all 10 ophthalmologic tests. Results in the present analysis are presented for the 10-test-evaluable population.

2.3. Ophthalmologic tests

Ophthalmologic tests included: 1) best-corrected visual acuity (BCVA; patients were given credit for reading a line if at least 3 letters on the line were read correctly. A decrease in BCVA of ≥ 2 lines from baseline was considered clinically important); 2) refractive error associated with BCVA (a change in spherical or cylindrical refraction power of $\pm$ 1.25 diopters relative to baseline was considered clinically important); 3) pupil size (pupillary diameter for both eyes was measured under standard lighting conditions and was recorded to the nearest mm using standard rounding rules. A change in pupil diameter of greater than $\pm$ 2 mm was considered clinically important); 4) slit-lamp biomicroscopy of the anterior segment (at each scheduled visit, any abnormalities of the lids, conjunctiva, sclera, cornea, anterior chamber, iris, or lens of either eye were to be reported and graded as mild, moderate or severe); 5) intraocular inflammation (for each eye, the shift in aqueous humor cell count from baseline to maximum on study was determined. Baseline to maximum on-study aqueous flare was also assessed on a per-eye basis); 6) intraocular pressure (IOP; for each assessment time, the average IOP of 2 readings was used as the data value for summary. The test was performed twice for each eye on a given visit; if test results deviated by > 2 mmHg from each other, a third reading was to be obtained. A change to > 22 mmHg was considered to be clinically important); 7) fundoscopy of the posterior segment (ophthalmoscopy was to be performed on both eyes after dilation of the pupils to examine the vitreous body, retina macula, peripheral retina (non-macula), and optic nerve head. At each visit, any abnormalities and pathologic findings were to be recorded and graded as mild, moderate or severe); 8) dilated fundus photography of the macula, peripheral retina (non-macula) and optic nerve head (at each visit, any abnormalities and pathologic findings were to be recorded and graded as mild, moderate or severe); 9) optical coherence tomography (OCT) of the vitreous body and macula (images of the fovea of both eyes were to be taken using a spectral domain OCT. Assessments included examination of vitreous body and macula. Central retinal thickness [in μm] as given by the OCT device was recorded, and any abnormalities and pathological findings were to be reported and graded as mild, moderate or severe. An increase [worsening] from baseline [i.e., measurement at screening] in OCT center point thickness of > 50 μm was defined as being clinically important); and 10) ocular characteristics including eye color and documentation of nevi or freckles on the iris or conjunctiva bulbi (using a slit lamp, the iris color of each eye was to be recorded as homogeneous [gray, blue, green or brown], blue-gray, yellow-brown, green-brown, blue-brown or gray-brown. In addition, the presence or absence of any nevi and/or freckles on the bulbar conjunctiva and, separately, on the iris was to be recorded).The investigators referred the patients to board-certified ophthalmologists to perform the ophthalmologic testing. The ophthalmologists submitted the test results and findings to the investigative site for data entry into the electronic case report form.

2.4. Safety

Presence and causality of all AEs, including ocular AEs, were assessed and reported by the investigator. Abnormal findings were evaluated in the context of the totality of each patient's medical history. All-causality treatment-emergent AEs (TEAEs) were defined as AEs that occurred for the first time after the first dose of crizotinib on C1D1, as well as preexisting events that worsened in severity after C1D1. Treatment-related AEs (TRAEs) were AEs assessed by the investigator as having a possible causal relationship to crizotinib. Ocular AEs were eye disorders classified by the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0) as being in the system organ class of Eye Disorders or Sponsor-defined cluster terms of Vision Disorder and Visual Loss. A cluster term was an aggregation of selected preferred terms created because the frequency of certain medical concepts or conditions may be underestimated by reliance on individual MedDRA preferred terms. Patients having AEs coded to ≥ 1 preferred term within a cluster term were counted once for that cluster term, and those with > 1 AE coded to any preferred term not included in a cluster term were counted once for each of those preferred terms. AEs were recorded at the highest grade observed. The Vision Disorder cluster term included the AE Preferred Terms of chromatopsia, diplopia, halo vision, photophobia, photopsia, vision blurred, visual acuity reduced, visual brightness, visual impairment, visual perseveration or vitreous floaters. Visual Loss cluster term included the AE preferred terms of amaurosis, amaurosis fugax, blindness, blindness cortical, blindness day, blindness transient, blindness unilateral, hemianopia, hemianopia heteronymous, hemianopia homonymous, night blindness, optic atrophy, optic ischemic neuropathy, optic nerve disorder, optic neuropathy, quadrantanopia, retinopathy, sudden visual loss, toxic optic neuropathy, tunnel vision, visual cortex atrophy, visual field defect or visual pathway disorder.

2.5. Statistical analysis

Analysis of the ophthalmologic assessments was conducted on the 10-test-evaluable population. The baseline values and post-baseline changes from baseline at C1D15 and C3D1 were summarized for each eye (right/left) separately using univariate descriptive statistics for refractive error, pupillary diameter, intraocular pressure and center point thickness. Categorical methods were used to summarize, for each eye separately and together, the most extreme change from baseline observed at any post-baseline visit (C1D15, C3D1, end of treatment [EOT], annual examinations, and unplanned visits) for each of the following: the number of lines in BCVA, the biomicrochanges from baseline at C1D15 and C3D1 were summarized for each eye (right/left) separately using univariate descriptive statistics for refractive error, pupillary diameter, intraocular pressure and center point thickness. Categorical methods were used to summarize, for each eye separately and together, the most extreme change from baseline observed at any post-baseline visit (C1D15, C3D1, end of treatment [EOT], annual examinations, and unplanned visits) for each of the following: the number of lines in BCVA, the biomicroscopy parameters, in the fundoscopy parameters, the color fundus parameters, and the OCT parameters (excluding centerpoint). The aqueous humor cell count changes from baseline to maximum cell count observed at any post-baseline visit (C1D15, C3D1, EOT, annual examinations, and unplanned visits) were cross-tabulated separately for each eye. Summaries of ocular characteristics (change in color—yes/no, change in nevi or freckles—yes [by location, iris or conjunctiva]/no) were similarly summarized by eye and overall. A cross-tabulation was provided indicating the number/percentage of patients who had an ophthalmologic examination abnormality on study (yes/no) and by whether these patients were reported to have an ocular all-causality TEAE on study. The frequency and percentage of patients with ocular TEAEs of all causality were tabulated by grade for the 10-test-evaluable population; TEAE severity was graded according to the National Cancer Institute Common Terminology Criteria in Adverse Events (Version 3.0).

3. Results

3.1. Patients

A total of 33 patients were included in the 10-test-evaluable population. As of February 29, 2016, 11 patients (33.3 %) in the 10-test-evaluable population remained on treatment and 22 (66.7 %) had discontinued; disease progression (n = 15) was the most common reason for discontinuation. No patients with all-causality ocular TEAEs permanently discontinued treatment or required dose reduction; however, 2 patients required temporary dose interruption (one each of Grade 1 and 2 cataract). In the 10-test-evaluable population, the median age was 67 years. The majority of patients were female (57.6 %) and most were either white (54.5 %) or Asian (39.4 %) (Table 1).

3.2. Ocular assessments in the 10-test-evaluable population

3.2.1. Visual acuity

A majority of patients (n = 23 [69.7 %]) had a ± 1-line change from baseline in BCVA in either eye, which was considered no change from baseline in visual acuity (Table 2). Nine patients (27.3 %) had a 2-line loss in at least 1 eye, and 1 patient (3.0 %) with a diagnosis of bilateral cataracts had a 3-line loss in at least 1 eye. Although these changes were considered clinically important, none resulted in permanent discontinuation of crizotinib.

3.2.2. Refractive error

Changes from baseline in refractive error at the two post-baseline assessment times were on average minimal (Table 3); however, three patients (3; 9.1 %) had refractive error measurements that were greater than ± 1.25 diopter change from baseline. While clinically important, none of these changes resulted in permanent discontinuation from the study.

Table 1
Patient demographics.

	10-Test-Evaluable Population (N = 33)
Sex, n (%)	
Male	14 (42.4)
Female	19 (57.6)
Age, years	
Median (range)	67 (25–87)
Race, n (%)	
White	18 (54.5)
Black	1 (3.0)
Asian	13 (39.4)
Korean	11 (33.3)
Chinese	2 (6.1)
Other[a]	0
Other	1 (3.0)[b]

n, number of patients in the indicated category; N, number of patients in the population.
[a] Additional details on "other" race were not collected for Asian patients.
[b] One patient was Hispanic.

Table 2
Worst change from baseline in best-corrected visual acuity; 10-test evaluable population.

Change in Line, n (%)	Right Eye (N = 33)	Left Eye (N = 33)	Overall[a] (N = 33)
Total	33 (100.0)	33 (100.0)	33 (100.0)
≥3-line loss	1 (3.0)	0	1 (3.0)
2-line loss	4 (12.1)	6 (18.2)	9 (27.3)
± 1 line[b]	28 (84.8)	26 (78.8)	23 (69.7)
> 1-line increase	0	1 (3.0)	0

n, number of patients with the indicated worst post-baseline assessment; N, total number of patients in the population.
[a] Overall included worst change from baseline among both eyes. [b] A change of ± 1 line was considered no change from baseline in visual acuity.

3.2.3. Pupillary diameter

Changes from baseline in pupillary diameter at the 2 post-baseline assessment times were on average minimal (Table 3); however, a clinically important change from baseline in pupillary diameter greater than ± 2 mm occurred in 3 patients (9.1 %), but did not result in any permanent discontinuations of crizotinib.

3.2.4. Biomicroscopy of the anterior segment

Slit-lamp anterior segment biomicroscopy revealed no patients with new or worsening of findings of the lids, conjunctivae, sclera, cornea or anterior chamber of either eye. New or worsening findings were observed in 2 patients with iris change and 4 patients with lens change (Table 4), representing a total of 5 patients (15.2 %). Three of these 5 patients had changes that were considered to be clinically significant and/or were reported as ocular TEAEs by the investigator (grade 1 cataract in 2 patients, both considered to be unrelated to crizotinib, and grade 1 treatment-related visual impairment in 1 patient). However, none of these patients discontinued crizotinib treatment because of these events.

3.2.5. Intraocular inflammation

Thirty-two (97.0 %) of 33 patients had intraocular inflammation measurements with no change from baseline in aqueous humor cell count during treatment. Aqueous humor cell counts improved in one patient from 11 to 20 cells (right eye) and 6 to 10 cells (left eye) at baseline to 1 to 5 cells for both eyes during the on-treatment assessment

Table 3
Baseline ophthalmic assessments and changes at cycle 1, day 15 and cycle 3, day 1; 10-test-evaluable population.

Ophthalmologic Assessment	Right Eye (N = 33)	Left Eye (N = 33)
Refractive Error		
Baseline		
Mean (SD), diopters	−0.12 (2.66)	−0.06 (2.70)
Median (range), diopters	0.50 (−10.38 to 3.50)	0 (−10.25 to 4.00)
C1D15		
Mean change from baseline (SD), diopters	0 (0.37)	−0.06 (0.35)
Median change from baseline (range), diopters	0 (−1.13 to 1.00)	0 (−1.37 to 0.50)
C3D1	C3D1	
Mean change from baseline (SD), diopters	0.01 (0.64)	0.02 (0.52)
Median change from baseline (range), diopters	0 (−1.88 to 2.13)	0 (−0.88 to 2.25)
Pupillary Diameter		
Baseline		
Mean (SD), mm	3.06 (1.03)	3.12 (1.08)
Median (range), mm	3.00 (1.0 to 6.0)	3.00 (1.0 to 6.0)
C1D15		
Mean change from baseline (SD), mm	0 (0.83)	0 (0.83)
Median change from baseline (range), mm	0 (−2.0 to 3.0)	0 (−2.0 to 3.0)
C3D1		
Mean change from baseline (SD), mm	−0.18 (0.83)	−0.21 (0.87)
Median change from baseline (range), mm	0 (−2.5 to 2.0)	0 (−2.5 to 2.0)
Intraocular Pressure		
Baseline		
Mean (SD), mmHg	14.30 (2.81)	14.93 (2.91)
Median (range), mmHg	14.00 (8.5 to 19.7)	15.00 (9.5 to 21.0)
C1D15		
Mean change from baseline (SD), mmHg	−0.29 (2.44)	−0.44 (2.54)
Median change from baseline (range), mmHg	0 (−7.0 to 4.3)	0 (−6.5 to 4.3)
C3D1		
Mean change from baseline (SD), mmHg	−0.23 (2.86)	−0.45 (2.70)
Median change from baseline (range), mmHg	−0.50 (−5.5 to 6.7)	−0.50 (−5.0 to 5.5)
Optical Coherence Tomography (center point thickness)		
Baseline		
Mean (SD), μm	254.1 (34.04)	257.1 (40.59)
Median (range), μm	254.0 (196 to 354)	247.0 (204 to 399)
C1D15		
Mean change from baseline (SD), μm	−3.8 (34.12)	−4.2 (28.68)
Median change from baseline (range), μm	0.0 (−109 to 58)	0.0 (−107 to 62)
C3D1		
Mean change from baseline (SD), μm	0.3 (32.42)	5.7 (32.13)
Median change from baseline (range), μm	1.0 (−123 to 75)	2.0 (−89 to 76)

C1D15, cycle 1, day 15; C3D1, cycle 3, day 1; N, total number of patients in the population; SD, standard deviation.

Table 4
Worst finding on treatment for ophthalmologic assessments[a]; 10-test-evaluable population.

Ophthalmologic Assessment, n (%)	Right Eye (N = 33)	Left Eye (N = 33)	Overall[b] (N = 33)
Biomicroscopy of the Anterior Segment			
Iris change			
New/worsening finding	2 (6.1)	2 (6.1)	2 (6.1)
No change	31 (93.9)	31 (93.9)	31 (93.9)
Improvement of finding	0	0	0
Lens change			
New/worsening finding	4 (12.1)	4 (12.1)	4 (12.1)
No change	29 (87.9)	29 (87.9)	29 (87.9)
Improvement of finding	0	0	0
Fundoscopy			
Vitreous body change			
New/worsening finding	1 (3.0)	0	1 (3.0)
No change	32 (97.0)	33 (100.0)	32 (97.0)
Improvement of finding	0	0	0
Retina non-macula (peripheral) change			
New/worsening finding	1 (3.0)	1 (3.0)	1 (3.0)
No change	32 (97.0)	32 (97.0)	32 (97.0)
Improvement of finding	0	0	0
Optic nerve head change			
New/worsening finding	1 (3.0)	0	1 (3.0)
No change	32 (97.0)	33 (100.0)	32 (97.0)
Improvement of finding	0	0	0
Color Fundus Photography			
Retina macula change			
New/worsening finding	0	0	0
No change	33 (100.0)	33 (100.0)	33 (100.0)
Improvement of finding	0	0	0
Retina non-macula (peripheral) change			
New/worsening finding	0	0	0
No change	33 (100.0)	33 (100.0)	33 (100.0)
Improvement of finding	0	0	0
Optic nerve head change			
New/worsening finding	1 (3.0)	0	1 (3.0)
No change	32 (97.0)	33 (100.0)	32 (97.0)
Improvement of finding	0	0	0
Optical Coherence Tomography			
Vitreous Body Change			
New/worsening finding	0	0	0
No change	33 (100.0)	33 (100.0)	33 (100.0)
Improvement of finding	0	0	0
Retina Macula Change			
New/worsening finding	0	0	0
No change	33 (100.0)	33 (100.0)	33 (100.0)
Improvement of finding	0	0	0

n, number of patients in the indicated assessment category; N, total number of patients in the population.

[a] There were no changes detected by biomicroscopy of the anterior segment (lids, conjunctiva, sclera or anterior chamber).

[b] Overall included worst postbaseline assessment among both eyes.

period (Supplementary Table 1). There were no instances of aqueous flare reported for any patient at baseline or during the on-treatment assessments.

3.2.6. Intraocular pressure

Changes from baseline in IOP at the two post-baseline assessment times were on average minimal (Table 3). The IOP across multiple readings revealed no clinically important changes (increase > 22 mmHg) from baseline in either eye for any patient during the on-treatment assessment period.

3.2.7. Fundoscopy

New or worsening findings, by retinal fundoscopic examinations, in the vitreous body, peripheral retina (non-macula) or optic nerve head occurred in 3 patients (9.1 %; Table 4); these were not considered by the investigators to be clinically significant and did not result in permanent discontinuation of crizotinib.

3.2.8. Color fundus photography

There were no observed changes from baseline in color fundus photographs of the macula and peripheral retina (non-macula) (Table 4). One patient had a new or worsening finding in the optic nerve head (Table 4), which was not considered by the investigator to be clinically significant and did not result in permanent discontinuation of crizotinib.

3.2.9. Optical coherence tomography

There were no new or worsening findings in OCT of the vitreous body or retina macula in either eye in any patient during the on-

treatment assessment period (Table 4). Overall, mean and median changes from baseline in OCT center point thickness of either eye were small (Table 3); however, a total of 7 patients (21.2 %) showed increases from baseline in OCT center point thickness during the study that were considered to be clinically important (> 50 μm) and secondary to baseline eye pathology, but none of these changes resulted in permanent discontinuation of crizotinib.

3.2.10. Ocular characteristics

With regard to ocular characteristics, 4 patients (12.1 %) reported changes in iris color during the on-treatment assessment period, whereas most patients (n = 29 [87.9 %]) had no change in either eye. No patients reported changes on the conjunctiva bulbi. Two patients (6.1 %) reported changes in iris nevi and/or freckles, which were also detected during the biomicroscopy examination (Supplementary Table 2). None of these changes in iris color, nevi or freckles were recorded as AEs, were considered clinically significant by the investigator, or resulted in permanent discontinuation of crizotinib.

3.3. Ocular AEs

Twenty-four patients (72.7 %) in the 10-test-evaluable population had ≥1 ocular all-causality TEAE (Table 5). The most common ocular TEAE was Vision Disorder, which occurred in 21 patients (63.6 %) (Table 6). For these 21 patients, the most common ocular TEAE within the cluster term of Vision Disorder was Visual Impairment (n = 15). Two ocular TEAEs, both grade 2, were reported for the cluster term Visual Loss in one patient (blindness cortical and visual field defect); one patient had an all-causality TEAE of Visual Loss that was considered to be disease related, thus, not treatment related.

3.3.1. Evaluation of ocular TEAEs and ophthalmologic assessments

Although TEAEs and ophthalmologic findings may not have occurred concurrently, of 24 patients with ≥1 all-causality ocular TEAE, 18/24 (75.0 %) had ≥1 abnormal ophthalmologic finding and 6/24 (25 %) had none; and of 9 patients without an all-causality ocular TEAE, 4/9 (44.4 %) had ≥1 abnormal ophthalmologic finding and 5/9 (55.6 %) had none (Table 5). Patients with an ocular TEAE but no abnormal ophthalmologic test results (n = 6) had the following ocular TEAEs: visual impairment (n = 5), photopsia (n = 1) and ocular hyperemia (n = 1).

3.3.2. Clinically relevant abnormal ocular findings and patient history

Of the 24 patients with all-causality ocular TEAEs, 18 also had at least 1 abnormal ophthalmologic examination result, indicating clinically relevant abnormal ocular findings. Of these 18 patients, half (n = 9) had preexisting eye condition(s) at baseline that could have contributed to the reported eye abnormalities (Supplementary Table 3).

Table 5
Ophthalmologic examination results versus ocular TEAEs (all causality); 10-test-evaluable population.

	Presence of Eye Disorder AEs (All-Causality)[a]		
	Yes (n = 24)	No (n = 9)	Overall[a] (N = 33)
Abnormality by ophthalmologic assessment, n (%)			
Yes[b]	18 (75.0)	4 (44.4)	22 (66.7)
No	6 (25.0)[c]	5 (55.6)	11 (33.3)

[a] AEs for eye disorders included those with a system organ class of Eye Disorder as well as the preferred terms associated with the cluster terms of Vision Disorder and Visual Loss, as summarized in the methods.
[b] Patients with an abnormality for ≥1 of the ophthalmologic assessments. AEs, adverse events; n, number of patients in the indicated category; N, total number of patients in the population.
[c] Patients with an ocular AEs but no abnormal ophthalmologic test results (n = 6) had the following ocular AEs: visual impairment (n = 5), photopsia (n = 1) and ocular hyperemia (n = 1).

Table 6
Summary of ocular TEAEs (all causality); 10-test-evaluable population (N = 33).

AEs[a], n (%)	Grade 1	Grade 2	Grade 3–5	Total
Any ocular AE	22 (63.6)	2 (6.1)	0	24 (72.7)
Vision Disorder[b]	20 (60.6)	1 (3.0)	0	21 (63.6)
Visual impairment	15 (45.5)	0	0	15 (45.5)
Photopsia	3 (9.1)	0	0	3 (9.1)
Blurred vision	1 (3.0)	1 (3.0)	0	2 (6.1)
Vitreous floaters	2 (6.1)	0	0	2 (6.1)
Diplopia	0	1 (3.0)	0	1 (3.0)
Cataract	2 (6.1)	1 (3.0)	0	3 (9.1)
Eye pruritis	1 (3.0)	0	0	1 (3.0)
Ocular hyperemia	1 (3.0)	0	0	1 (3.0)
Optic disc hemorrhage	1 (3.0)	0	0	1 (3.0)
Visual Loss[c]	0	1 (3.0)	0	1 (3.0)
Blindness cortical	0	1 (3.0)	0	1 (3.0)
Visual field defect	0	1 (3.0)	0	1 (3.0)
Vitreous degeneration	1 (3.0)	0	0	1 (3.0)

[a] The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) was used.
[b] This cluster term includes the following preferred terms; chromatopsia, diplopia, halo vision, photophobia, photopsia, vision blurred, visual acuity reduced, visual brightness, visual impairment, visual perseveration and vitreous floaters.
[c] This cluster term includes the following preferred terms; amaurosis or amaurosis fugax or blindness or blindness cortical or blindness day or blindness transient or blindness unilateral or hemianopia or hemianopia heteronymous or hemianopia homonymous or night blindness or optic atrophy or optic ischaemic neuropathy or optic nerve disorder or optic neuropathy or quadrantanopia or retinopathy or sudden visual loss or toxic optic neuropathy or tunnel vision or visual cortex atrophy or visual field defect or visual pathway disorder. AE, adverse event; n, number of patients having at least 1 of the indicated ocular AEs; N, total number of patients in the population.

4. Discussion

Although 22 of 33 patients (66.7 %) experienced at least one change during the on-treatment assessment period in some of the specialized ophthalmologic assessments (BCVA, refractive error, pupil size, slit lamp biomicroscopy, intraocular inflammation, IOP, fundoscopy, color fundus photography, OCT and ocular characteristics) following treatment with crizotinib, most of these changes were not considered to be clinically significant by the investigators. The present findings are thus consistent with previous reports, where the majority of ocular events with crizotinib treatment have been of low-grade severity and were presumed by the Investigator to be of low clinical significance [3–5,7].

For the cases in the present study that were reported as TEAEs by the investigator, a number of patients had preexisting eye conditions (e.g., cataract, lenticular opacities, detachment of retinal pigment epithelium, macular fibrosis, maculopathy, retinal degeneration, retinal hemorrhage, retinal neovascularization, vitreous detachment, vitreous floaters, meibomian gland dysfunction, eyelid dermatochalasis, blepharitis, ocular rosacea, ocular vascular disorder and photophobia) that could have contributed to the reported eye abnormalities. While 18 of the 24 patients in the 10-test-evaluable population with ocular all-causality TEAEs also had at least one on-treatment abnormality on an objective ophthalmologic assessment, 4 of the 9 patients in this population with no ocular all-causality TEAEs reported new or worsening ophthalmologic abnormalities. Therefore, there did not appear to be a relationship between patients who reported ocular all-causality TEAEs and objective ophthalmologic test assessments of eye abnormalities during the on-treatment assessment period. However, a simultaneous

temporal occurrence between findings for TEAEs and those abnormal ophthalmologic test assessments was not examined. It should be noted, in the context of considering the relationship between preexisting findings and those during the on-treatment assessment period, that the time frame during which the patients were assessed was of relatively short duration and early in the course of patient exposure to crizotinib, whereas the TEAEs were recorded over the entire treatment period until data cutoff.

The overall rate of ocular TEAEs seen in this study was consistent with those seen in previous clinical trials of patients with *ALK*-positive NSCLC treated with crizotinib [3–5,7]. Rates of ocular TEAEs with crizotinib are higher than those seen with other ALK inhibitors (e.g., alectinib, brigatinib and ceritinib) in similar patient populations [8–10]. Because of differences in the detailed activity profiles of crizotinib and these other ALK inhibitors, off-target effects as a mechanism accounting for the elevated ocular TEAE rates seen with crizotinib relative to other ALK inhibitors is possible; however, ocular TEAEs appear to be relatively uncommon with other ROS1 and MET inhibitors [11,12].

One limitation of this ocular safety analysis is the relatively small patient sample size (N = 33) In addition, the impact of preexisting ocular comorbidities on the development of ocular TEAEs and abnormal ophthalmologic examination results requires further study. A strength is that, to the authors' knowledge, this is the first prospective study to evaluate a potential association of the results of objective ophthalmologic test assessments with the ocular TEAEs reported by a large number of patients treated with crizotinib.

In conclusion, the lack of association in this analysis between changes detected by formal ophthalmologic examination and patient-reported ocular TEAEs suggests that patients initiating crizotinib do not require additional ophthalmologic examinations. Patients with preexisting ocular conditions should continue their regular ophthalmic eye care while on crizotinib therapy and for those patients who develop ocular symptoms in the context of ongoing crizotinib treatment, an ophthalmologic examination should be conducted. These data provide new information on the ocular safety profile of crizotinib, which should aid clinicians managing ocular disorders in the context of patients receiving crizotinib therapy.

Funding

This study was sponsored by Pfizer Inc.

Data availability

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Declaration of Competing Interest

BJ Solomon reports grants and personal fees from Pfizer and personal fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche/Genentech, Loxo Oncology and Gritstone Oncology. EE Kim reports personal fees from Pfizer, outside the submitted work. M Winter and K Wilner report personal fees from Pfizer. K Monti reports personal fees from Rho and Pfizer. Y Tang and S Wang report personal fees and other from Pfizer. SHI Ou reports personal fees from Foundation Medicine Inc, personal fees from Roche, Pfizer, AstraZeneca, Takeda/ARIAD, and Merck, and personal fees and other from Turning Point Therapeutics.

Acknowledgements

Medical writing support was provided by Jonathan Raksin and Julian Martins of inScience Communications (Philadelphia, PA, USA) and was funded by Pfizer Inc.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.04.010.

References

[1] XALKORI® (crizotinib), US Prescribing Information, Pfizer Inc., New York, NY, 2018 February.
[2] E.L. Kwak, Y.J. Bang, D.R. Camidge, Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer, N. Engl. J. Med. 363 (18) (2010) 1693–1703.
[3] D.R. Camidge, Y.J. Bang, E.L. Kwak, Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study, Lancet Oncol. 13 (10) (2012) 1011–1019.
[4] A.T. Shaw, D.W. Kim, K. Nakagawa, Crizotinib versus chemotherapy in advanced ALK-positive lung cancer, N. Engl. J. Med. 368 (25) (2013) 2385–2394.
[5] B.J. Solomon, T. Mok, D.W. Kim, Y.L. Wu, First-line crizotinib versus chemotherapy in ALK-positive lung cancer, N. Engl. J. Med. 371 (23) (2014) 2167–2177.
[6] A.T. Shaw, S.H. Ou, Y.J. Bang, Crizotinib in ROS1-rearranged non-small-cell lung cancer, N. Engl. J. Med. 371 (21) (2014) 1963–1971.
[7] F. Blackhall, D. Ross Camidge, A.T. Shaw, Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer, ESMO Open 2 (3) (2017) e000219.
[8] T. Hida, H. Nokihara, M. Kondo, Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial, Lancet 390 (10089) (2017) 29–39.
[9] A.T. Shaw, T.M. Kim, L. Crino, Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial, Lancet Oncol. 18 (7) (2017) 874–886.
[10] S.N. Gettinger, L.A. Bazhenova, C.J. Langer, Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial, Lancet Oncol. 17 (12) (2016) 1683–1696.
[11] D. Liu, M. Offin, S. Harnicar, Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of NTRK, ROS1, and ALK fusion-positive solid tumors, Ther. Clin. Risk Manag. 14 (2018) 1247–1252.
[12] M. Schmidinger, R. Danesi, Management of adverse events associated with cabozantinib therapy in renal cell carcinoma, Oncologist 23 (3) (2018) 306–315.

University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Solomon, BJ; Kim, EE; Winter, M; Monti, K; Tang, Y; Wilner, KD; Wang, S; Ou, S-HI

Title:
Ophthalmological assessment of crizotinib in advanced non-small-cell lung cancer

Date:
2020-07-01

Citation:
Solomon, B. J., Kim, E. E., Winter, M., Monti, K., Tang, Y., Wilner, K. D., Wang, S. & Ou, S. -H. I. (2020). Ophthalmological assessment of crizotinib in advanced non-small-cell lung cancer. LUNG CANCER, 145, pp.167-172. https://doi.org/10.1016/j.lungcan.2020.04.010.

Persistent Link:
http://hdl.handle.net/11343/273816

File Description:
Published version

License:
CC BY-NC-ND