Response Rate and Outcomes in Crizotinib Treated Advanced *ALK*-positive NSCLC Patients

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BACKGROUND

- Crizotinib is an oral tyrosine kinase inhibitor with superior response rates and proven efficacy against anaplastic lymphoma kinase (*ALK*)–rearranged tumors as compared with standard chemotherapy.[1]
- Crizotinib was approved in the United States (US) in August 2011 for the treatment of *ALK*-positive advanced non-small cell lung cancer (NSCLC).
- The clinical experience of crizotinib-treated patients with *ALK*-positive NSCLC has not been widely assessed outside of clinical trials.

OBJECTIVE

- The objective of the current study was to assess the treatment patterns and outcomes of patients with *ALK*-positive advanced NSCLC treated with crizotinib in regular clinical practice.

METHODS

- **Study design:** Retrospective cohort study
- **Data source:** Medical chart abstraction performed in 2014 by a pooled sample of 147 oncologists in the US (n = 107) and Canada (n = 40)
- **Patient inclusion criteria:**
  - Diagnosed with metastatic NSCLC and confirmed *ALK* gene rearrangement
  - Age ≥ 18 years at diagnosis of *ALK*-positive NSCLC
  - Initiated crizotinib treatment as first- or later-line therapy between August 1, 2011 and March 31, 2013 (for US patients) or April 1, 2012 and March 31, 2013 (for Canadian patients)
  - Complete medical record from crizotinib initiation until ≥ 3 months after last crizotinib dose (if patient died less than 3 months after last dose, the patient record was still eligible)
- **Patient exclusion criteria:**
  - Treated with crizotinib as part of a clinical trial
  - Patient was ROS1-positive
- **Study endpoints:**
  - Objective response rate (ORR) was defined as the proportion of patients achieving a best clinical response to crizotinib of either complete response or partial response.
  - Progression-free survival (PFS) was defined as time from crizotinib initiation until the earlier of:
    - Clinical progression or death occurring during crizotinib treatment (up to and including 2 weeks after switch to/initiation of a new therapy, if a new therapy was initiated)
    - Death occurring between 2 and 14 weeks after crizotinib completion, if there was no initiation of a new therapy during this period
  - Patients without a progression event (as defined above) were censored at the earlier of initiation of a new therapy, death occurring more than 14 weeks after crizotinib completion, or end of available medical records.
  - Overall survival (OS) was defined as time from crizotinib initiation until death; patients still alive at the time of data collection were censored at the date of the last available medical record.
- **Data collection:**
  - A secure web-based case report form was developed and used by physicians for data entry.
  - All data were deidentified and anonymized.
  - Institutional review board (IRB) approvals were obtained in the US and Canada.
- **Analyses:**
  - Descriptive analyses were conducted to assess treatment patterns and ORR.
  - PFS and OS were descriptively analyzed using Kaplan-Meier methods.
  - Analyses were stratified by the setting (first line vs. second line or later) in which crizotinib was initiated.

RESULTS

Characteristics of the Participating Physicians

- Medical oncology was the predominant (74.8%) specialty among these physicians.
- The physicians had, on average, approximately 15 years of practice experience.

Patient Demographic and Clinical Characteristics

- Data were extracted from 212 patient records in the US (n = 147) and Canada (n = 65).
- Mean (standard deviation [SD]) age at *ALK*-positive, metastatic NSCLC diagnosis was 58.9 (9.5) years, and a majority of patients were male (69%), White/Caucasian (79%), and current or former smokers (67%) (Table 1).
- Most patients presented with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (75%) and adenocarcinoma histology (90%) at initial diagnosis.
- Cough, fatigue, and dyspnea were the most common symptoms present (71%, 65%, and 55%, respectively) at the time of metastatic NSCLC diagnosis.
- At the time of medical record abstraction, 37% of patients were deceased.

Crizotinib Treatment Patterns

- Approximately 65% (n = 137) of patients initiated crizotinib as first-line therapy, and mean (SD) duration of crizotinib treatment in the overall cohort was 8.7 (4.9) months. (Table 2).
- The most common starting dose of crizotinib was 250 mg twice daily (79.7% of patients).
- Most patients (90%) had no changes (reduction or escalation) in crizotinib dose.
- Disease progression following initial response was the most frequently reported (59%) reason for treatment discontinuation overall; this result varied somewhat based on line of crizotinib initiation, with slightly higher rates reported for patients receiving crizotinib in first line (66%) than patients receiving crizotinib in second line or later (49%).
- Rates of disease progression with no initial response were relatively low (14%).
- Following crizotinib completion, 35% of patients received additional systemic chemotherapy; 38% received no additional cancer-directed therapy in the follow-up period.

Crizotinib Response Rate and Outcomes

- The estimated crizotinib ORR was 66% for the overall cohort (69% for first-line initiators vs. 60% for second/later-line initiators) (Figure 1).
- Based on Kaplan-Meier estimation, 1- and 2-year survival rates from crizotinib initiation were 82% (95% CI, 77%-87%) and 49% (95% CI, 39%-49%), respectively (Figure 2).
- Median PFS from crizotinib initiation was 9.5 months (95% confidence interval [CI], 8.7-10.1 months), in the overall cohort.
- Median OS from crizotinib initiation was 23.4 months (95% CI, 19.5 months to not reached), or ~2 years (95% CI, 1.6 years to not reached), for the overall cohort.

Figure 1. Response Rate During Crizotinib Treatment

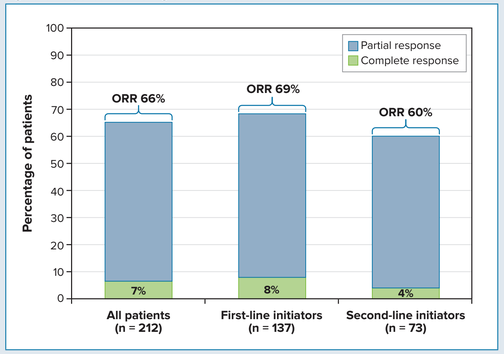
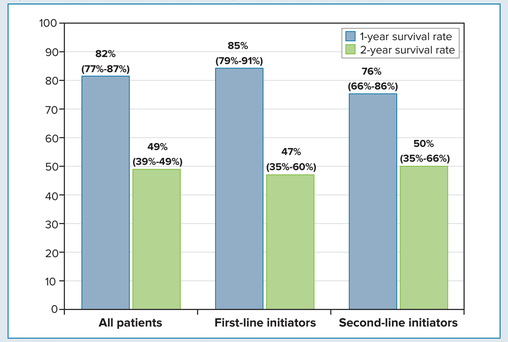


Figure 2. Kaplan-Meier Survival Estimates by Line of Crizotinib Treatment



Note: 95% confidence interval shown in parentheses.

Table 1. Demographic and Clinical Characteristics

	All Patients (n = 212)	Setting of Crizotinib Initiation (n = 210)[a]		
		First Line (n = 137)	Second Line or Later (n = 73)	P Value
Age (years) at diagnosis,[b] mean [SD]	58.9 [9.5]	59.6 [9.0]	57.6 [10.1]	0.1343
Male, n (%)	146 (68.9)	93 (67.9)	51 (69.9)	0.7685
Ethnicity, n (%)				
White/Caucasian	167 (78.8)	103 (75.2)	62 (84.9)	0.3828
African/black	22 (10.4)	16 (11.7)	6 (8.2)	
Asian or Pacific Islander	22 (10.4)	17 (12.4)	5 (6.8)	
Unknown	1 (0.5)	1 (0.7)	—	
Smoking status at diagnosis,[b] n (%)				
Current or former smoker	141 (66.5)	84 (61.3)	56 (76.7)	0.0875
Never smoked	68 (32.1)	51 (37.2)	16 (21.9)	
Unknown	3 (1.4)	2 (1.5)	1 (1.4)	
ECOG performance status at diagnosis,[b] n (%)				
0-1	159 (75.0)	107 (78.1)	51 (69.9)	0.1076
2-4	53 (25.0)	30 (21.9)	22 (30.1)	
Symptoms present at diagnosis,[b] n (%)				
Chest pain/discomfort	55 (25.9)	38 (27.7)	17 (23.3)	0.4849
Dyspnea	117 (55.2)	79 (57.7)	38 (52.1)	0.4358
Cough	150 (70.8)	102 (74.5)	48 (65.8)	0.1839
Fatigue	137 (64.6)	83 (60.6)	54 (74.0)	0.0524
Other symptoms	11 (5.2)	4 (2.9)	7 (9.6)	0.0388
Patient had no symptoms	9 (4.2)	6 (4.38)	3 (4.1)	0.9267
Vital status at date of medical record abstraction, n (%)				
Alive	124 (58.5)	82 (59.9)	40 (54.8)	0.6998
Deceased	79 (37.3)	50 (36.5)	29 (39.7)	0.6998
Unknown	9 (4.2)	5 (3.6)	4 (5.5)	0.6998
Median duration (months) of observation, from crizotini[b] initiation until record abstraction	16.5	16.5	16.5	0.2170

[a] Line of crizotinib initiation was unknown for 2 patients.

[b] "At diagnosis" refers, more specifically, to "at diagnosis of *ALK*-positive metastatic NSCLC."

Table 2. Crizotinib Treatment Patterns

	All Patients (n = 212)	Setting of Crizotinib Initiation (n = 210)[a]		
		First Line (n = 137)	Second Line or Later (n = 73)	P Value
Initial crizotinib total daily dose prescribed, n (%)				
200 mg bid	32 (15.1)	22 (16.2)	8 (11.0)	0.0452
250 mg bid	169 (79.7)	111 (81.6)	58 (79.5)	
200 mg qd	8 (3.8)	3 (2.2)	4 (5.5)	
250 mg qd	3 (1.4)	—	3 (4.1)	
Crizotinib total daily dose changes, n (%)				
Had ≥ 1 dose reduction	15 (7.1)	7 (5.1)	8 (11.0)	0.1207
Had ≥ 1 dose escalation	6 (2.8)	2 (1.5)	4 (5.5)	0.0980
Had no changes (reduction or escalation) in dose	190 (89.6)	126 (92.6)	61 (83.6)	0.0413
Unknown	1 (0.5)	2 (1.5)	—	0.4329
Median duration (months) of crizotinib treatment, from initiation to last observed dose	8.7	9.0	8.5	0.1008
Reason(s) for final discontinuation of crizotinib, n (%)				
Death	2 (3.1)	1 (2.4)	1 (4.3)	0.6737
Disease progression following initial response	126 (59.4)	90 (66.2)	36 (49.3)	0.0175
Disease progression following no initial response	29 (13.7)	14 (10.3)	14 (19.2)	0.0722
Treatment-related toxicity or side effects	10 (4.7)	2 (1.5)	8 (11.0)	0.0022
Patient request	41 (19.3)	25 (18.4)	15 (20.5)	0.7044
Other reason	8 (3.8)	4 (2.9)	4 (5.5)	0.3619
Unknown	6 (2.8)	3 (2.2)	2 (2.7)	0.7432
Other cancer-directed treatment modalities received after crizotinib discontinuation/ completion, n (%)				
None	81 (38.2)	49 (35.8)	32 (43.8)	0.4258
Surgery	2 (0.5)	1 (0.7)	—	0.9455
Radiotherapy	38 (17.9)	21 (15.3)	17 (23.3)	0.4884
Chemotherapy	75 (35.4)	58 (42.3)	17 (23.3)	0.3274
Other *ALK* inhibitor in clinical trials	10 (4.7)	5 (3.6)	5 (6.8)	0.3100
Targeted therapy	21 (9.9)	16 (11.7)	5 (6.8)	0.4748
Other	2 (0.5)	1 (0.7)	2 (2.7)	0.2252

bid = twice daily; qd = once daily.

a Line of crizotinib initiation was unknown for 2 patients.

LIMITATIONS

- Patients selected for study inclusion represented a "convenience" sample, in that the records were obtained from physicians who were willing and available to participate in the study. Results therefore may not be fully generalizable, and additional studies are needed to confirm our findings.
- Information captured by the study's data-collection form was limited to information available in the patients' medical records held by the physicians participating in the study.
- In retrospective studies, response criteria are not dictated by a protocol and assessments (imaging studies) are not done on a uniform schedule, so results regarding this endpoint may not be directly comparable to those observed in clinical trials.
- Finally, data were entered into the data-collection form directly by the treating physicians and therefore may have been subject to entry errors and resulting inaccuracies in reporting.

CONCLUSIONS

- Response rates for crizotinib-treated patients in real-world settings seem to align with data reported from previous clinical studies[2] and a small number of retrospective observational studies.[3,4]
- The *ALK*-positive metastatic NSCLC patients studied here have a reasonably high ORR (> 60%), as well as a 1-year survival rate of approximately 75% to 80%.
- Our data provide further support for the potential of crizotinib to have a major positive effect on the lives of patients with *ALK*-positive NSCLC.

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