Crizotinib in MET Exon 14-Mutated or MET-Amplified in Advanced Disease Non-Small Cell Lung Cancer: A Retrospective, Single Institution Experience

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Keywords
C-MET · Non-small cell lung cancer · Crizotinib (Xalkori\textsuperscript{®}) · Tyrosine kinase inhibitors · Immunotherapy

Abstract
Introduction: Non-small cell lung cancer (NSCLC) accounts for most lung cancers and is a leading cause of cancer-related deaths in the USA. Alterations in c-MET, a tyrosine kinase receptor, have been involved in many cases of NSCLC progression and metastasis. Crizotinib and other tyrosine kinase inhibitors (TKIs) have been used in NSCLC treatment with limited success. Methods: In this retrospective observational study, we analyzed data from patients diagnosed with lung cancer at Soroka University Medical Center between January 2015 and January 2020. We investigated patient characteristics, including disease-associated mutation type and median survival in response to different TKI treatments. Results: A total of 780 patients with lung cancer were included in the study, 134 of whom had small cell lung cancer and 646 had NSCLC. Of the NSCLC patients, 403 were diagnosed with advanced or metastatic disease, and 374 underwent molecular testing. We identified 16 patients with either c-MET mutations or amplifications who were treated with crizotinib. Of these patients, 7 expressed a c-MET exon 14 skipping mutation while the remaining 9 patients expressed c-MET amplification. Among the patients with a c-MET exon 14 skip mutation, the overall survival was 22.8 months and the median progression-free survival (PFS) on crizotinib treatment was 12.4 months. Of the patients with c-MET amplification, the median overall survival was 5.4 months and the median PFS with crizotinib treatment was 2.6 months. Discussion and Conclusions: We analyzed the data of a series of cases describing patients diagnosed with different stages of NSCLC, having either a c-MET exon 14 skipping mutation or an amplification mutation, and treated with various TKIs, including crizotinib. We investigated the characteristics of these patient groups in accordance with mutation types and compared median survival between patient groups. Crizotinib was found to be an optimal treatment for NSCLC harboring c-MET exon 14 skipping mutations.

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Introduction

Lung cancer remains the leading cause of cancer-related deaths in the USA and is a significant health care concern throughout the world [1]. Over two-thirds of lung cancer patients diagnosed are over the age of 65 years-old, with approximately 3% diagnosed under the age of 45 years-old [2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Histologically, NSCLC is divided into adenocarcinoma, squamous cell carcinoma ( SCC), and large cell carcinoma [3]. NSCLC is often insidious, producing no symptoms until the disease is widely advanced, contributing to the poor prognosis of lung carcinoma [4–6]. NSCLCs may be caused by mesenchymal-epithelial transition (MET) gene amplification or the c-MET exon 14 skipping mutation.

The discovery of molecular targeted mutations has changed the treatment landscape of NSCLC. At present, about 40–50% of lung adenocarcinomas harbor one of these mutations, including the new targeted mutation. The most common mutations are epidermal growth factor receptor (EGFR), KRAS G12C, and anaplastic lymphoma kinase (ALK), while the less common mutations are MET, HER II, ROS1, BRAF, and other rare mutations such as NTRK. EGFR mutations exist in up to 17% of all lung adenocarcinomas, with a higher prevalence among females and non-smokers (Fig. 1). Osimertinib is an oral, third-generation, irreversible EGFR tyrosine kinase inhibitor (EGFR-TKI) that inhibits both EGFR-TKI-sensitizing and EGFR T790M-resistant mutations. Osimertinib treatment has shown 80% activity with a median progression-free survival (PFS) of 18.9 months [7]. The KRAS p.G12C variant is part of the KRAS mutation family, with a prevalence of approximately 13% in lung adenocarcinomas [8]. Sotorasib is a small molecule that specifically and irreversibly inhibits KRAS G12C. Sotorasib administration has shown promising results in previously treated patients with a response rate of 37% and a median duration of response of 11.1 months [9]. ALK gene rearrangements, which result in the EML4-ALK fusion oncogene, are another common alteration found in around 7% of advanced NSCLCs, mainly in light smokers or non-smokers and younger female patients. Alectinib and lorlatinib are second- and third-generation highly selective and potent ALK inhibitors, respectively, that inhibit tumor proliferation with activity against several ALK mutations [10, 11]. Lorlatinib has shown high activity in this group of patients with a response rate of 76% and a 1-year PFS of 78%. Additionally, an intracranial response rate of 82% has been reported due to the highly efficient penetration of the blood-brain barrier by this drug [12]. Other rare mutations have also been investigated in phase I/II clinical trials and several targeted therapies have shown promising activity [13].

MET factor (c-MET) is a tyrosine kinase receptor located on the cell surface that is activated when bound by its ligand or proto-oncogene and is responsible for vital cellular activities including cell proliferation, survival, motility, invasion and morphogenesis, wound healing, and tissue homeostasis [14]. Mutations in the c-MET receptor are known to be involved in the formation, metastasis, and invasion of various malignant tumors. It is known that c-MET is directly linked to NSCLC with related overexpression of p140-beta, while c-MET expression in SCLC is more heterogenous [15]. c-MET alterations in NSCLC are found in up to 2–3% of NSCLC cases (Fig. 1) and include point mutations, amplification, fusion, and protein overexpression [16]. MET exon 14 skipping mutations lead to reduced degradation of the MET receptor, resulting in the activation of the MET signaling pathway and, ultimately, tumorigenesis [17]. MET amplification is the carcinogenic driver where the MET/CEP7 ratio is increased due to the increased replication number of the MET gene [18].

c-MET amplification is indicative of a poor prognosis; however, patients with higher levels of amplification have been shown to be more responsive to systemic treatment [19]. c-MET amplification also plays a crucial role in resistance to targeted therapies [20]. c-MET alterations may

Fig. 1. Existing mutations in adenocarcinoma of the lung [7].
therefore be responsible for interfering with desirable treatment outcomes [21]. For these reasons, c-MET has long been an attractive anti-tumor drug target [22]. Crizotinib (Xalkori®) is the first small molecular TKI approved by the USA Food and Drug Administration (FDA) for the treatment of ALK NSCLC [21]. It is also currently recommended by the National Comprehensive Cancer Network (NCCN) for treating MET-mutated NSCLC, with capmatinib as an additional treatment option [23].

This recommendation is based on the positive results seen in the Profile 1001 study which recruited 18 MET-mutated NSCLC patients and treated them with Crizotinib. Crizotinib administration resulted in a 44% response rate, including patients who had amplified c-MET [24, 25].

Capmatinib, the other NCCN-recommended treatment option, is a highly selective c-MET inhibitor, which was tested in phase I/II clinical trials with response rates between 18% and 63% in c-MET positive, c-MET immunohistochemistry +3 and c-MET overexpressed NSCLC. The median PFS (mPFS) was 5.4 and 9.7 months in pretreated and naïve NSCLC patients, respectively [26, 27]. The most common adverse events of capmatinib are peripheral edema, nausea, vomiting, and increased creatinine level. In the above-mentioned trial, 67% of patients experienced grade 3–4 toxicity.

In this study, we present a series of cases describing patients diagnosed with advanced or metastatic NSCLC having c-MET alterations (mutations and amplifications) treated with various TKIs, including crizotinib. We investigated the characteristics of this study population and the different mutation types present, and compared the median survival of these patients. The analyzed cases exemplify crizotinib as an optimal treatment for cancers harboring certain c-MET mutations.

**Materials and Methods**

This was a single institution retrospective, observational study without intervention. The study received Institutional Review Board approval (no.0316 on December 02, 2021).

The study included patients who were admitted to Soroka Medical Center between January 2015 and January 2020. The following were the inclusion criteria.

**Patients Aged 18 Years or Older**

Patients diagnosed with lung cancer (any histology and any stage).

**No Concomitant Cancer Other Than Lung Cancer**

Treated only in Soroka Medical Center or have a full follow-up history in Soroka Medical Center’s records. Each patient admitted to Soroka Medical Center Oncology Institute is presented and discussed in a multidisciplinary team as required. This team includes a general medical and radiation oncologist, imaging and nuclear physician, pulmonologist, pathologist, and thoracic surgeon. The discussion is based on the patients’ status, pathology, and imaging. Each patient is assigned a primary physician who is responsible for the treatment course.

Patients with advanced or metastatic NSCLC are treated mainly by medical oncologists, and the treatment plan is based in general on the NCCN recommendations. Routine molecular profiling is performed for each patient when possible. We identified a total of 16 patients with stage IV NSCLC, who were treated with TKIs due to c-MET alteration (i.e., exon 14 skipping mutation or c-MET amplification).

Patients with lung cancer that were admitted to Soroka Medical Center between January 2015 and January 2020 (n = 780)

- Patients with non-small-cell lung cancer (n = 646)
- Patients with small-cell lung cancer (n = 134)
- Patients with advanced or metastatic (Stage 4) lung cancer (n = 403)
- Patients with local (Stage 1–3) lung cancer (n = 243)

- Patients with adenocarcinoma (n = 208)
- Patients with other types of carcinoma (n = 26)
- Patients with squamous cell carcinoma (n = 166)
- Patients with sarcomatoid carcinoma (n = 3)

374 Patients underwent molecular testing

- Patients with C-MET exon 14 skipping mutation (n = 7)
- Patients with C-MET amplification (n = 9)

Fig. 2. Flow diagram of the single-center, retrospective, observational lung cancer study.
During the study period, 780 patients with lung cancer were admitted to Soroka Medical Center Oncology Institute (Fig. 2), out of which 134 patients had small cell lung cancer and 646 patients had NSCLC. Of the patients with NSCLC, 403 patients were diagnosed with advanced or metastatic disease (stage IV) and 243 were diagnosed with local disease (stage 1–3). Of the patients with metastatic disease, 208 patients were diagnosed with adenocarcinoma, 166 patients with SCC, 3 with sarcomatoid carcinoma, and 26 with either large cell carcinoma or adenosquamous cell carcinoma. Of the 403 patients with NSCLC, advanced or metastatic disease, 208 patients were diagnosed with adenocarcinoma, 166 patients with SCC, 3 with sarcomatoid carcinoma, and 26 with either large cell carcinoma or adenosquamous cell carcinoma. Of the 403 patients with NSCLC, advanced or metastatic disease, 374 underwent molecular testing. We identified 16 patients with a defect in c-MET (Table 1) who were treated with crizotinib due to either a c-MET exon 14 skipping mutation or c-MET amplification.

Of the 16 patients with a defect in c-MET, 7 patients expressed the c-MET exon 14 skipping mutation with a median age of 67 and an age range of 48–78 years (Table 2). The remaining 9 patients expressed c-MET amplification and had a median age of 63 with a range of 50–70 years (Table 2).

### Table 1. NSCLC patient demographics and disease characteristics

| Characteristic                        | N = 16 (%) |
|--------------------------------------|------------|
| Age at diagnosis, years              |            |
| Median                               | 65         |
| Mean                                 | 60.5 (SD)  |
| Range                                | 48–78      |
| Sex                                  |            |
| Male                                 | 9 (56)     |
| Female                               | 7 (44)     |
| Smoking history                      |            |
| Yes                                  | 10 (62.5)  |
| No                                   | 6 (37.5)   |
| Brain metastasis at diagnosis        |            |
| Present                              | 4 (25)     |
| Absent                               | 12 (75)    |
| Histology profile                    |            |
| Adenocarcinoma                       | 12 (75)    |
| SCC                                  | 3 (18.75)  |
| Sarcomatoid                          | 1 (6.25)   |
| Type of mutation                     |            |
| c-MET Exon 14 Skipping               | 7 (44)     |
| c-MET Amplification                  | 9 (56)     |

N, number of patients; SD, standard deviation; SCC, squamous cell carcinoma.

### Table 2. Crizotinib-treated NSCLC patient disease characteristics and treatment outcomes by c-MET mutation type

| Type of mutation characteristic | Amplification, N = 9 (%) | Exon 14 – skip, N = 7 (%) |
|--------------------------------|--------------------------|---------------------------|
| Age at diagnosis, years         |                          |                           |
| Median                          | 63 (55.6)                | 67 (77.8)                 |
| Range                           | 50–70                    | 48–78                     |
| Sex                             |                          |                           |
| Male                            | 5 (55.6)                 | 4 (57.2)                  |
| Female                          | 4 (44.4)                 | 3 (42.8)                  |
| Smoking history                 |                          |                           |
| Yes                             | 7 (77.8)                 | 3 (42.8)                  |
| No                              | 2 (22.2)                 | 4 (57.2)                  |
| Brain metastasis at diagnosis   |                          |                           |
| Present                         | 1 (11.1)                 | 3 (42.8)                  |
| Absent                          | 8 (88.9)                 | 4 (57.2)                  |
| Histology profile               |                          |                           |
| Adenocarcinoma                  | 6 (66.7)                 | 6 (85.8)                  |
| SCC                             | 3 (33.3)                 | 0                         |
| Sarcomatoid                     | 0                        | 1 (14.2)                  |
| TKI mPFS, months                | 2.6                      | 12.4                      |
| TKI mOS, months                 | 5.4                      | 22.8                      |

N, number of patients; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor; mPFS, median progression-free survival; mOS, median overall survival.

Of the 7 patients with the exon 14 skipping mutation, four (57.2%) were male, four (57.2%) did not have a history of smoking, and four (57.2%) did not have brain metastasis present at diagnosis (Table 2). Six of the patients with the exon 14 skipping mutation received whole brain irradiation, while the remaining patients continued to be monitored. Of the 9 patients with the amplification mutation, five (55.6%) were male, seven (77.8%) had a history of smoking, and eight (88.9%) did not have brain metastasis at the time of diagnosis (Table 2).

All 16 patients were subcategorized according to the histopathological findings. Seven patients (85.8%) with the c-MET exon 14 skipping mutation had the histopathological findings of adenocarcinoma and 1 patient (14.2%) had sarcomatoid carcinoma (Table 2). With regard to the patients with the c-MET amplification mutation, six (66.7%) had histopathological findings of adenocarcinoma, and three (33.3%) had SCC (Table 2).

The course of treatment for all NSCLC patients harboring the c-MET exon 14 skipping mutation and c-MET amplification mutation is presented in Figure 3. For the patients who started chemotherapy before undergoing molecular testing (due to aggressive metastatic disease), treatment was modified based on mutation type results.
both types of mutations, overall survival (OS) and the mPFS on TKI treatment were recorded. Among the 9 patients harboring c-MET amplification, the median OS was 5.4 months (range 1–17 months) and the mPFS with crizotinib treatment was 2.6 months (range 1–9 months). Among the 7 patients with c-MET exon 14 skipping, the OS was 22.8 months (range 3–52 months) and the mPFS on crizotinib treatment was 12.4 months (range 0–33 months).

Discussion

Lung cancer is still the leading cause of cancer-related death in patients worldwide. It is for this reason that detection and personalized treatment plans are vital to improve outcomes for patients with NSCLC. Treatment of these patients is based on molecular profiling and PDL1 testing. NSCLC is treated based on its driver mutation by receptor monoclonal antibodies (mAb) or small-molecule TKIs. While the treatment of EGFR- and ALK-mutated NSCLC is well established, the treatment of other mutations, especially the more rare ones, is still under investigation. This is due to the rarity of these mutations and the lack of phase III clinical trial-related data. Effective treatments for MET amplification in NSCLC are also still being studied and include HGF antagonists, anti-HGFR mAb, anti-MET mAb, and MET TKIs such as tivantinib, cabozantinib, and crizotinib [28].

Crizotinib and capmatinib have been studied in patients with c-MET mutations; however, the results show a wide range of discrepancies [24–27]. Based on these studies, both agents have a response rate of approximately 40–50%. While capmatinib has shown a mPFS between 5 and 9 months, the mPFS for crizotinib could not be calculated. About 67% of the patients who received capmatinib developed grade 3/4 toxicity, while in the crizotinib group, most of the reported toxicity was mild to moderate being grade 1/2. One grade 3 treatment-related adverse event (edema) and no grade 4/5 treatment-related adverse events were reported following crizotinib administration [25].

The present single-center retrospective analysis compared the efficacy rates of crizotinib treatment between NSCLC patients harboring the c-MET amplification mutation and the exon 14 skipping mutation. Crizotinib has been shown to have clinical activity in patients with NSCLC with the c-MET amplification and the c-MET exon 14 skipping mutation. The median overall and PFS rates of crizotinib with respect to each c-MET mutation separately are yet to be reported. Based on this study, crizotinib treatment in patients with the c-MET exon 14 skipping mutation appears to prolong survival to a greater extent compared to those with the c-MET amplification mutation. It is unclear why the c-MET exon 14 skipping mutation has a different response to crizotinib than the de-novo c-MET amplification, but MET gene amplification could serve as a resistance mechanism secondary to EGFR-TKIs, possibly contributing to this difference [29].

Crizotinib is a type Ia MET TKI that blocks the binding of ATP by binding MET in its catalytically active conformation at the aspartic acid-phenylalanine-glycine (DFG) motif, and in doing so, prevents phosphorylation/activation of the receptor [29–32]. The NCCN...
guidelines indicate crizotinib to be a potentially useful therapy in certain circumstances for patients with the MET exon 14 skipping mutation NSCLC [22]. Other proposed treatments include selective MET inhibitors such as capmatinib, tepotinib, and savolitinib [33]. Numerous novel agents are under clinical investigation for MET exon 14 skipping mutation treatment including amivantamab, APL-101, cabozantinib, capmatinib, glumetinib, telisotuzumab vedotin, and tepotinib, amongst others [33].

In a study of patients with high-risk central nervous system (CNS) dissemination of ALK positive NSCLC, one third of patients treated with crizotinib had CNS failure [34]. This can be explained by poor CNS drug penetration through the blood-brain barrier. Crizotinib is not able to effectively cross the blood-brain barrier and cannot reach high concentrations in cerebrospinal fluid [34]. This is a limitation that allows for CNS spread without inhibition. Next-generation ALK inhibitors such as ceritinib, brigatinib, and lorlatinib have demonstrated promising activity in the CNS [34]. Although the majority of NSCLC patients in this study harboring the MET exon 14 skipping mutation had brain metastasis during diagnosis, resulting prognoses were still better than those patients bearing c-MET amplifications.

It should also be noted that the patient with the longest survival time in the c-MET amplification group was given multiple drug treatments, while 7 other patients were given 1 month of combined carboplatin-pemetrexed followed by crizotinib. Chemotherapy is possibly a better alternative when it comes to the MET amplification mutation because of crizotinib’s low response to TKIs due to resistance [29]. Awad et al. [35] measured the median OS of metastatic patients with and without treatment of MET inhibitors and found that patients who did not have MET inhibitor treatment (such as crizotinib, glesatinib, capmatinib, and ABBV-399) had a median survival of 8.1 months, while patients treated with MET inhibitors had a median survival of 24.6 months. Twenty-two patients administered with crizotinib had a mPFS of 7.4 months [35]. In the present study, the vast majority of patients with the c-MET exon 14 skipping mutation had adenocarcinoma, while 67% of patients with the c-MET amplification mutation presented with adenocarcinoma and 33% presented with lung SCC.

The limitations regarding this study are the small sample size, the retrospective design, and the internal heterogeneity among the patient groups. Only 4 patients received crizotinib in a first-line setting, whereas remaining patients received the drug as a second-line treatment following chemotherapy. Although we found that crizotinib is successful in treating NSCLC with c-MET exon 14 skipping mutations, a larger sample size is required to confirm this. This finding is evident despite the higher number of patients with brain metastasis in the NSCLC c-MET mutation group of patients compared to the c-MET amplification group of patients. Further research should be done on the effect of TKI drugs on different NSCLC histological profiles within each subset of the c-MET mutation group to understand whether there is a stronger therapeutic effect when targeting a specific mutation. A larger sample size with a constant treatment option may reveal an increased efficacy rate of crizotinib.

Conclusions

In this paper, we presented a series of cases describing patients diagnosed with different stages of NSCLC with either the c-MET exon 14 skipping mutation or the amplification mutation, treated with various TKIs, including crizotinib. We investigated the characteristics of these patient groups in accordance with mutation types and compared median survival between patient groups. We found crizotinib to be the optimal treatment for NSCLC harboring c-MET exon 14 skipping mutations.

Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Soroka Medical Center as clinical and epidemiological characteristics of patients with thoracic tumors (Helsinki code of ethics 0316-21 and approved on December 02, 2021). The Institutional Review Board of Soroka Medical Center decided that written informed consent was not required because the waiver or alteration will not adversely affect the rights and welfare of the subjects and this research could not practically be carried out without the waiver or alteration.

Conflicts of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Walid Shalata, Alexander Yakobson, and Abed Agbarya: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Sarah Weissemann, Elron Oscar, Muhammed Iraqi, Waleed Kian, and Nir Peled: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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