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Case Report

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68-months progression-free survival with crizotinib treatment in a patient with metastatic ALK positive lung adenocarcinoma and sarcoidosis: A case report

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Abstract

Introduction: Lung cancer still ranks first among the most common and most lethal cancers today. The most common subtype is non-small cell lung cancer, and in this group, adenocarcinoma has the worst prognosis. EGFR, ROS1 and ALK-EML4 gene fusion mutations are common in non-small cell lung cancer.

Case report: A 62-year-old non-smoker patient applied in February 2014 for purulent sputum and pain in the chest. Computed tomography revealed a 39x33 mm mass in the right hilum, multiple parenchymal nodules in the bilateral lung and mediastinal multiple enlarged lymph nodes. The patient was admitted to the lung adenocarcinoma as a result of a biopsy from the mass in the hilum, and sarcoidosis was diagnosed by mediastinal lymph node biopsy.

Management & outcome: After 4 cycles of carboplatin-pemetrexed for the first line treatment, progression was detected. The patient did not have EGFR and ROS1 mutations. The patient with positive ALK fusion mutation started crizotinib treatment in July 2014. The patient's last response assessment was in March 2020, with 68-progression-free disease with crizotinib. No toxicity was observed except for Grade 1 weakness. No dose changes were made. The patient is still being followed up without brain metastasis under the treatment of crizotinib.

Discussion: In this article, we wanted to share our experience of crizotinib in a 68-months progression-free survival in a 62-years old non-smoking female patient with metastatic lung adenocarcinoma who is also diagnosed with sarcoidosis.

Keywords

Lung adenocarcinoma, crizotinib, ALK-rearrangement, sarcoidosis, progression-free survival

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Introduction

Today, despite the positive effects of targeting therapies and immunotherapy options, lung cancer continues to rank among the causes of death from cancer. The five-year survival rate of all lung cancer patients is reported to be 17%.[1] The prognosis of patients with lung cancer depends on multiple factors, including the stage of the disease and histological type.[1–3] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and in this group, histology of adenocarcinoma has a worse prognosis than other subtypes.[1–3]

The most common mutation in NSCLC has been reported to be epithelial growth factor receptor

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(EGFR) exon 19 deletions or exon 21 L858R point mutations, which is more common in non-smoking female adenocarcinoma.[2–4] Another important mutation is anaplastic lymphoma kinase (ALK) gene rearrangements.[4,5]

It has been reported that ALK gene rearrangements are found in approximately 5% in patients with NSCLC, especially adenocarcinoma histological subtype.[4,5] Some clinical features such as young onset and never or light-smokers have been described in patients with NSCLC who have ALK gene rearrangements positive.[4–6] Although crizotinib was the first multi-targeted tyrosine kinase inhibitor (TKI) against ALK rearrangements to be approved, several ALK-TKIs such as alectinib, ceritinib, brigatinib, and lorlatinib have been also developed for ALK-positive patients with NSCLC.[6–13]

In the literature, while only a few cases have shown long-lasting response to crizotinib especially over 5 years with initial rapidly response to it, in the majority of patients develops disease progression within 12 months because of the drug resistance.[14–16]

In this article, we aimed to discuss a 62-year-old never smoked female patient with metastatic lung adenocarcinoma and sarcoidosis because of a rare association and with 68-months progression-free survival with crizotinib.

Case description

A 62-year-old nonsmoker woman who has been using metformin and angiotensin converting enzyme inhibitor for about 8 years with the diagnosis of type 2 diabetes and hypertension, applied to the emergency department in February 2014 due to purulent sputum and pain in the chest.

In thorax computed tomography, several lymph nodes with a shortest axis of 10 mm in the mediastinum, a solid tumor mass of 39x33 mm in the right hilum localization, multiple metastatic nodules, the largest of which is measured as 9x6 mm in the upper segment of the left lower lobe, and multiple subpleural nodular lesions with a diameter of 7x6 mm in the right lung were detected (Figure 1).

Positron emission tomography/computed tomography with F-18 fluoro-fluorodeoxygulose (F18 FDG- PET/CT) revealed several lymph nodes with hypermetabolic involvement (SUVmax 3.6), the largest of which was 1.5 cm in diameter in the bilateral cervical region, as well as a hypermetabolic mass lesion (SUVmax 11.3) adjacent to the mediastinum and irregular contours located in the posterobasal segment of the right lobe.

When biopsy with bronchoscopy was considered non-diagnostic, cervical lymph node excisional biopsy was performed. In histologically examination, granuloma structures consisting of epitheloid histiocytes and some of them containing Langhans type multinuclear giant cells, and focal fibrinoid necrosis foci at the central of some granulomas were observed. The patient was diagnosed as sarcoidosis and malignancy. PPD test was accepted as anergy, with 0 mm. For a definitive diagnosis of malignancy, wedge resection was applied to the mass lesion in the lung by performing open thoracotomy, and also sampling from lymph nodes. As a result, the patient was diagnosed with non-small cell lung carcinoma in the subtype of adenocarcinoma and necrotizing type sarcoidosis (Figure 2).

EGFR and ROS1 mutations were negative in the patient. In contrast, ALK-EML4 fusion gene mutation was detected and the patient underwent 4 cycles of carboplatin-pemetrexed (3-weekly pemetrexed 500 mg/m^2 and carboplatin AUCx6) in first-line chemotherapy with the diagnosis of metastatic lung adenocarcinoma. Crizotinib (250 mg twice daily) treatment was initiated in the patient who was admitted to progression by developing left supraclavicular lymph node metastasis proven with lymph node biopsy in July 2014 after treatment response evaluation with F18-FDG PET/CT. During the treatment period, no toxicity was observed except for grade 1 weakness and no dose change was made. The patient was followed by F18-FDG PET/CT in 3-month periods from the beginning of the crizotinib to the treatment response assessment in March 2020. In the response evaluation with F18-FDG PET/CT in March 2020, the disease was considered stable (Figure 3). The treatment of crizotinib is still ongoing for the patient whose sarcoidosis is in remission.

Discussion

In this article, we discussed a 62-year-old female patient with ALK- positive metastatic lung adenocarcinoma and sarcoidosis at the time of diagnosis, which had 68-months progression-free survival with crizotinib treatment.

In the updated survival analysis of the Phase III PROFILE 1014 study of first-line crizotinib treatment of patients with ALK positive metastatic NSCLC, the 4-year predicted survival rate was reported to be 56.6%. In this analysis, it was emphasized that the effects of post-crizotinib treatments should not be overlooked in long-term progression-free survival results.[17]

ALK -positive NSCLC is a heterogeneous molecular subtype. It has been identified to have at least 27 ALK-fusion variants.[1–3] The most common of the several variants of EML4-ALK fusion is variant 1 (33%), where exon 13 of EML4 fused with 20 exons of ALK

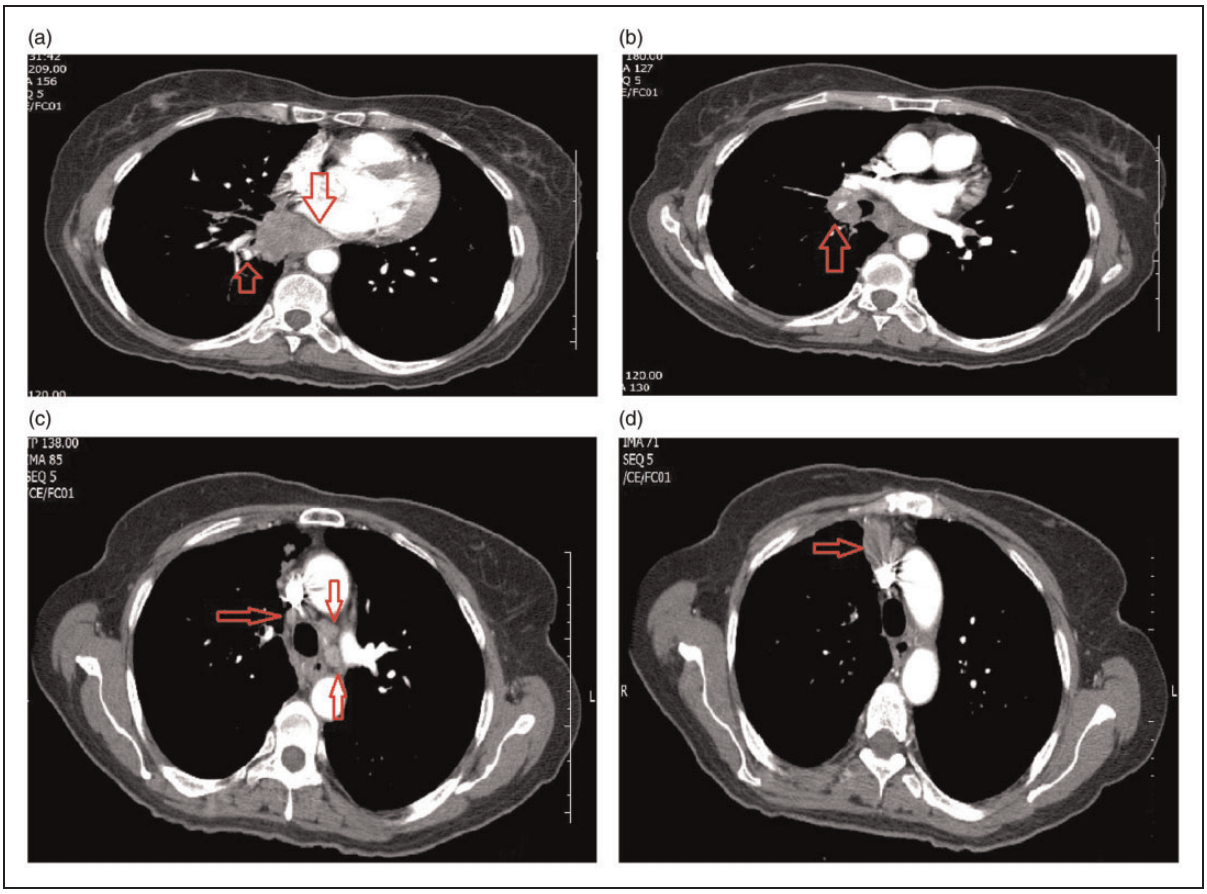

Figure 1. In the axial sections of the thorax computed tomography taken at the time of diagnosis: a malignant mass lesion extending to the subcarinal, paraaortic area is observed in the right hilar region (a), there are large lymph nodes in the right hilar, aortopulmonary, paratracheal, anterior mediastinal areas (b, c, d).

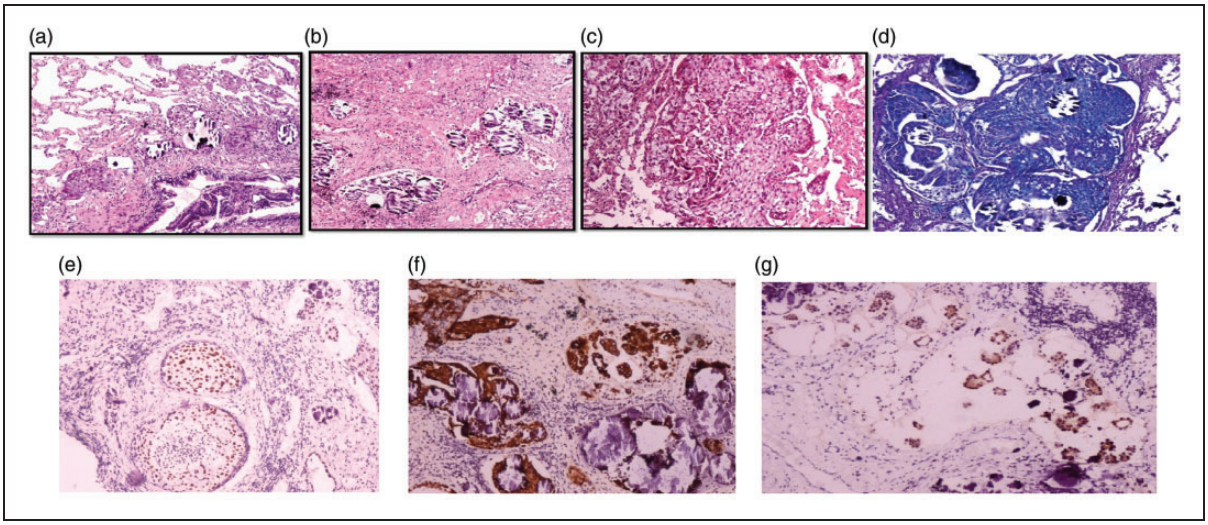

Figure 2. In the histopathological examination of the right lung lower lobe-wedge resection material, which was surgically excised; Atypical epithelial cells with light pleomorphic and hyper-chromatic nuclei, with cytoplasmic mucin in the lung parenchyma, with large areas of necrosis and granuloma structures containing a large number of Schaumann bodies, mostly cytoplasmic mucin in Alcian Blue staining (a–d). In the applied immunohistochemistry panel; tumor cells were stained positively with TTF-1 (e), Cytokeratin 7 (f) and ALK (g), but staining with CD 68 was not detected in cells with vacuolized cytoplasm. Based on the current findings, the case was evaluated to be compatible with primary lung adenocarcinoma with extensive lymphatic vascular involvement and concomitant necrotizing type sarcoidosis.

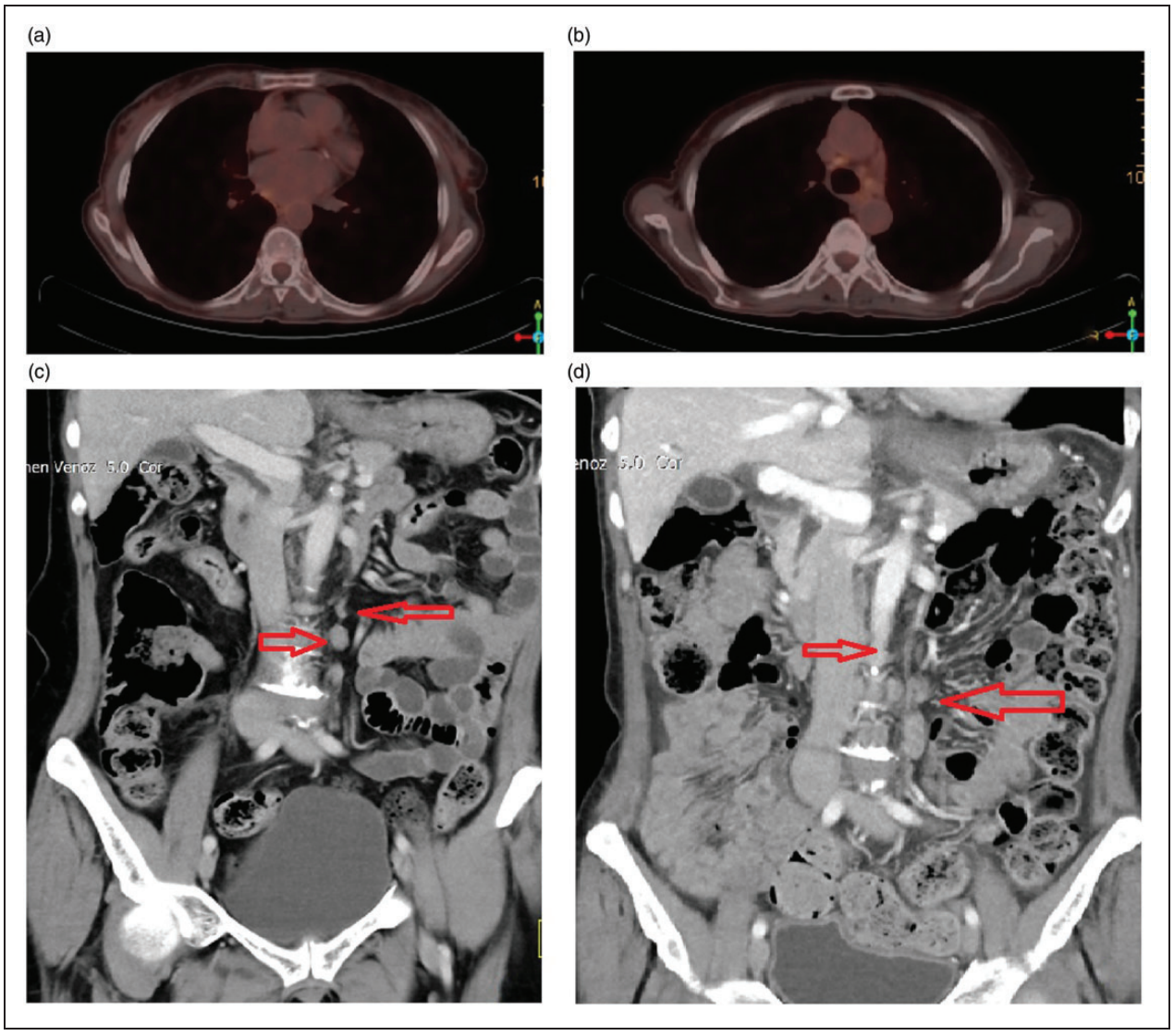

Figure 3. In the F18 FDG-PET/CT examination dated March 2020; It is seen that the mass observed in the right hilar region has disappeared (a). In the same examination, aortopulmonary, paratracheal lymph nodes appear to be persistent, although their size decreases (b). On CT images with coronal reformat; enlarged lymph nodes with paraaortic size, the largest of which are 20x11 mm in size, and their numbers remain stable (c, d).

(E13; A20). The second frequency variant is variant 3a/b (29%), where EML4 is fused to exon 6a or 6b to 20 exons of ALK (E6a/b; A20). In variant 2 (9%), EML4 20 exons fuse to 20 exons of ALK (E20; A20).[16] Molecular studies have shown that kinase activity in ALK positive NSCLC patients is abnormally activated by dimerization of ALK cytoplasmic different fusion partners (EML4, KIF5B, KLC1 or TFG).[14,16]

Crizotinib is a small molecule ALK inhibitor approved for the treatment of ALK-positive NSCLC.[7–9] Since the findings obtained from the clinical studies of crizotinib were 10.9 months after the first-line treatment and 7.7 months in the patients receiving the previous platinum-based regimen, it is believed that most of the patients treated with crizotinib will develop to progression within 1 year after treatment.[7–9]

Lung cancer patients with EGFR-TKI treated with EGFR mutations have sometimes been reported to respond well for a long time. In an analysis involving patients with EGFR mutations treated with EGFR-TKI by Li et al., the 5-year survival rate was reported to be 14.6%. In this analysis, long-term overall survival was found to be significantly correlated with the absence of extra-thoracic metastasis.[14]

When the literature was examined, it was seen that there were two advanced lung adenocarcinoma cases with PFS obtained for more than 5 years with crizotinib given as first-line treatment by Rangachari et al.[15]

In contrast, another case presented by Kosaka et al. is the first long-term case with complete response to crizotinib after postoperative recurrence.[16]

While the clinical and pathological details affecting the long-lasting PFS in 2 cases presented by Rangachari et al could not be reached, there is controversy regarding several variants of EML4-ALK fusion in the case presented by Kosaka et al.[15,16] However, Li et al. reported that patients with variant 2 had longer PFS than other variants.[14] Li et al. as well as Kosaka et al, the Ba/F3 cells expressing variant 2 were found to be compatible with in vitro studies showing higher sensitivity to crizotinib than cells expressing other variants.[14,16]

Another interesting situation in our patient was the simultaneous diagnosis of lung cancer and sarcoidosis. Sarcoidosis is a chronic, granulomatous, systemic disease which is often associated with pulmonary involvement and has unknown etiology.[17] Moreover, because of the chronic inflammatory process, sarcoidosis has been reported to be an factor in cancer etiopathogenesis in previous studies.[17,18] Additionally, because of the radiological and clinical features of pulmonary involvement at the time of diagnosis, it can often be confused with lung cancer.[19] However, there have been reports of patients diagnosed with sarcoidosis after the use of immunotherapies.[20–22] There is case reports of sarcoidosis developing in the follow-up of patients with malignant melanoma treated with immune check-point inhibitors such as nivolumab, ipilimumab, and pembrolizumab. Similarly, reports have been made that sarcoidosis is activated in patients using control point inhibitors for the treatment of Hodgkin lymphoma, renal cell carcinoma and sarcoma.[20–22]

The risk of developing brain metastasis is a worrying clinical situation in patients with lung cancer, as the life span increases. Approximately 17% of NSCLC patients have brain metastases when diagnosed, whereas almost 64% patients develop brain metastases after the diagnosis.[23,24] While the frequency of brain metastasis is 23.8% at the time of diagnosis in patients with positive ALK fusion, the incidence of brain metastasis is around 58.4% after 3 years of diagnosis. It has been reported that the median time to develop brain metastasis in patients with ALK fused lung adenocarcinoma is 27 months (range: 2-174). It is noteworthy that in patients with lung adenocarcinoma with ALK fusion mutation, approximately 74% of those treated with crizotinib develop brain metastasis. Indeed, the effects of the next generation drugs such as alectinib, ceritinib and brigatinib, to penetrate the blood-brain barrier and control brain metastases are more pronounced.[24] Our patient, who was neurologically asymptomatic, started to be monitored with a magnetic resonance every 6 months due to this concern and is still monitored without brain metastasis in March 2020.

In conclusion, we wanted to share our experience of the patient with stage 4 lung adenocarcinoma that we treated with a TKI, crizotinib, both to indicate that there was no sarcoidosis activation and to emphasize that we achieved progression-free survival for more than 5 years.

Declaration of Conflicting Interests

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References

1. Bade BC and Dela Cruz CS. Lung cancer 2019: Epidemiology, etiology, and prevention. *Clin Chest Med* 2020; 41: 1–24.
2. Campbell JD, Lathan C, Sholl L, et al. Comparison of prevalence and types of mutations in lung cancers among black and white populations. *JAMA Oncol* 2017; 3: 801–809.
3. Chen Z, Teng X, Zhang J, et al. Molecular features of lung adenocarcinoma in young patients. *BMC Cancer* 2019; 19: 777.
4. Rose-James A and Tt S. Molecular markers with predictive and prognostic relevance in lung cancer. *Lung Cancer Int* 2012; 2012: 729532.
5. Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. *Proc Natl Acad Sci USA* 2008; 105: 19893–19897.
6. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; 363: 1693–1703.
7. Kim DW, Ahn MJ, Shi Y, et al. Results of a global phase II study with crizotinib in ALK-positive non small cell lung cancer NSCLC. *J Clin Oncol* 2012; 30: abstr 7533.
8. Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013; 368: 2385–2394.
9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014; 371: 2167–2177.
10. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017; 377: 829–838.
11. Geater SL, Orlov S, Cortinovis D, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer

(ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 2017; 389: 917–929.
12. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol* 2017; 35: 2490–2498.
13. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol* 2017; 18: 1590–1599.
14. Li Y, Zhang T, Zhang J, et al. Response to crizotinib in advanced ALK-rearranged non-small cell lung cancers with different ALK-fusion variants. *Lung Cancer* 2018; 118: 128–133.
15. Kosaka T, Yajima T, Yamaki E, et al. Long-term complete response in a patient with postoperative recurrent ALK-rearranged lung adenocarcinoma treated with crizotinib: a case report. *Mol Clin Oncol* 2019; 11: 309–312.
16. Rangachari D, Le X, Shea M, et al. Cases of ALK-rearranged lung cancer with 5-year progression-free survival with crizotinib as initial precision therapy. *J Thorac Oncol* 2017; 12: e175–e177.
17. Wu YL, Lu S, Lu Y, et al. Results of PROFILE 1029, a phase III comparison of first-line crizotinib versus chemotherapy in East Asian patients with ALK-positive advanced non-small cell lung cancer. *J Thorac Oncol* 2018; 13: 1539–1548.
18. Grados A, Ebbo M, Bernit E, et al. Sarcoidosis occurring after solid cancer: a nonfortuitous association of 12 cases and review of the literature. *Medicine (Baltimore)* 2015; 94: e928.
19. Spiekermann C, Kuhlencord M, Huss S, et al. Coexistence of sarcoidosis and metastatic lesions: a diagnostic and therapeutic dilemma (review). *Oncol Lett* 2017; 14: 7643–7652.
20. Fakhri G, Akel R, Salem Z, et al. Pulmonary sarcoidosis activation following neoadjuvant pembrolizumab plus chemotherapy combination therapy in a patients with non-small cell lung cancer: a case report. *Case Rep Oncol* 2017; 10: 1070–1075.
21. Reuss JE, Kunk PR, Stowman AM, et al. Sarcoidosis in the setting combination ipilimumab and nivolumab immunotherapy: a case report & review of literature. *J Immunother Cancer* 2016; 4: 94.
22. Paydas S. Pulmonary sarcoidosis induced by the anti-PD1 monoclonal antibody pembrolizumab or post-immunotherapy granulomatous reaction: which is more appropriate terminology? *Ann Oncol* 2016; 27: 1650–1651.
23. Nishino M, Soejima K and Mitsudomi T. Brain metastases in oncogene-driven non-small cell lung cancer. *Transl Lung Cancer Res* 2019; 8: S298–S307.
24. Petrelli F, Lazzari C, Ardito R, et al. Efficacy of ALK inhibitors on NSCLC brain metastases: a systematic review and pooled analysis of 21 studies. *PLoS One* 2018; 13: e0201425.