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Letter to the Editor

Combination therapy of erlotinib/crizotinib in a lung adenocarcinoma patient with primary *EGFR* mutation plus secondary *MET* amplification and a novel acquired crizotinib-resistant mutation *MET* G1108C

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A 36-year-old non-smoking Chinese woman was diagnosed as stage IV lung adenocarcinoma and pneumonia by chest computed tomography (CT) scan (Fig.1A) and biopsy in June 2016. CT scan and brain enhanced Magnetic Resonance Imaging (MRI) showed left pleural effusion and multiple metastases in lymph nodes, liver and brain. The patient adopted chest drainage and was given pemetrexed and nedaplatin for treatment. However, the disease massively progressed after two weeks post treatment (Fig 1A).

An immediate peripheral ctDNA analysis was performed based on next-generation sequencing (NGS). The results showed L858R mutation (allele frequency, AF, 58%) and copy number amplification (log ratio, LR, 1.32) of epidermal growth factor receptor (*EGFR*). Thus the patient was switched to receive erlotinib 150mg/day in July 2016. The patient demonstrated significantly decreased tumor biomarkers (Fig.1B) and improved clinical symptoms within ten days post erlotinib treatment. After three months, MRI detected complete responses of brain metastases, and CT detected partial responses of lung and liver lesions free of pleural effusion.

The patient maintained stable disease for about six months. However, metastasis in right adrenal occurred in November 2016. Clinical symptoms and chest CT revealed disease progression a month later together with multiple bone metastases. Apart from the continually present *EGFR* L858R mutation (AF 74.94%) and amplification (LR 2.68), the secondary ctDNA analysis revealed copy number amplification of *MET* (LR 2.77), considered responsible for erlotinib resistance[1]. Subsequently, the patient was treated with erlotinib (150 mg/d) and crizotinib (250 mg/d) in January 2017, based on the confirmed safe use by a phase I clinical trial[2]. Four weeks after the combination therapy, cough was significantly relieved and a dramatic response was observed in lung (Fig. 1A). Yet the combination therapy resulted in severe side effects including vomiting and rash.

Nine weeks post combination therapy, nevertheless, the patient again showed progressed symptoms. The following ctDNA analysis demonstrated three novel mutations: *NRAS* Q61H (AF 4.06%), *KRAS* G12D (AF 0.64%), and *MET* G1108C (AF 7.84%), in addition to *EGFR* L858R mutation (AF 33.91%) and amplification (LR 1.68). *NRAS* Q61H and *KRAS* G12D are capable of conferring erlotinib-resistance[3]. Interestingly, the novel acquired *MET* G1108C mutation is located within the kinase domain next to the binding site of crizotinib. Steric stabilization and increased hydrophilic of cysteine residue may influence drug binding, resulting in crizotinib-resistance (Fig.1C). In April 2017, the patient suffered from severe pneumonia and infection and finally died.

Discussion

The patient has shown free brain lesions since October 2016, indicating a great benefit of erlotinib for brain metastases. However, high levels of *EGFR* mutation and amplification were detected throughout the therapy, implying other TKIs could be considered for the continued treatment when patient's brain metastases disappeared. Upon detecting *EGFR* mutations with concurrent *MET* amplification, we observed dramatic response post to the combination therapy of erlotinib/crizotinib. Yet due to paucity of the drugs targeting the upcoming *MET* resistant mutation and *RAS* mutations, we were unable to control the aggressive recurrence of this case. The development of new drugs for treating these mutations is required. Of note, disease monitoring via ctDNA sequencing is crucial for targeted therapy in lung adenocarcinoma.

References

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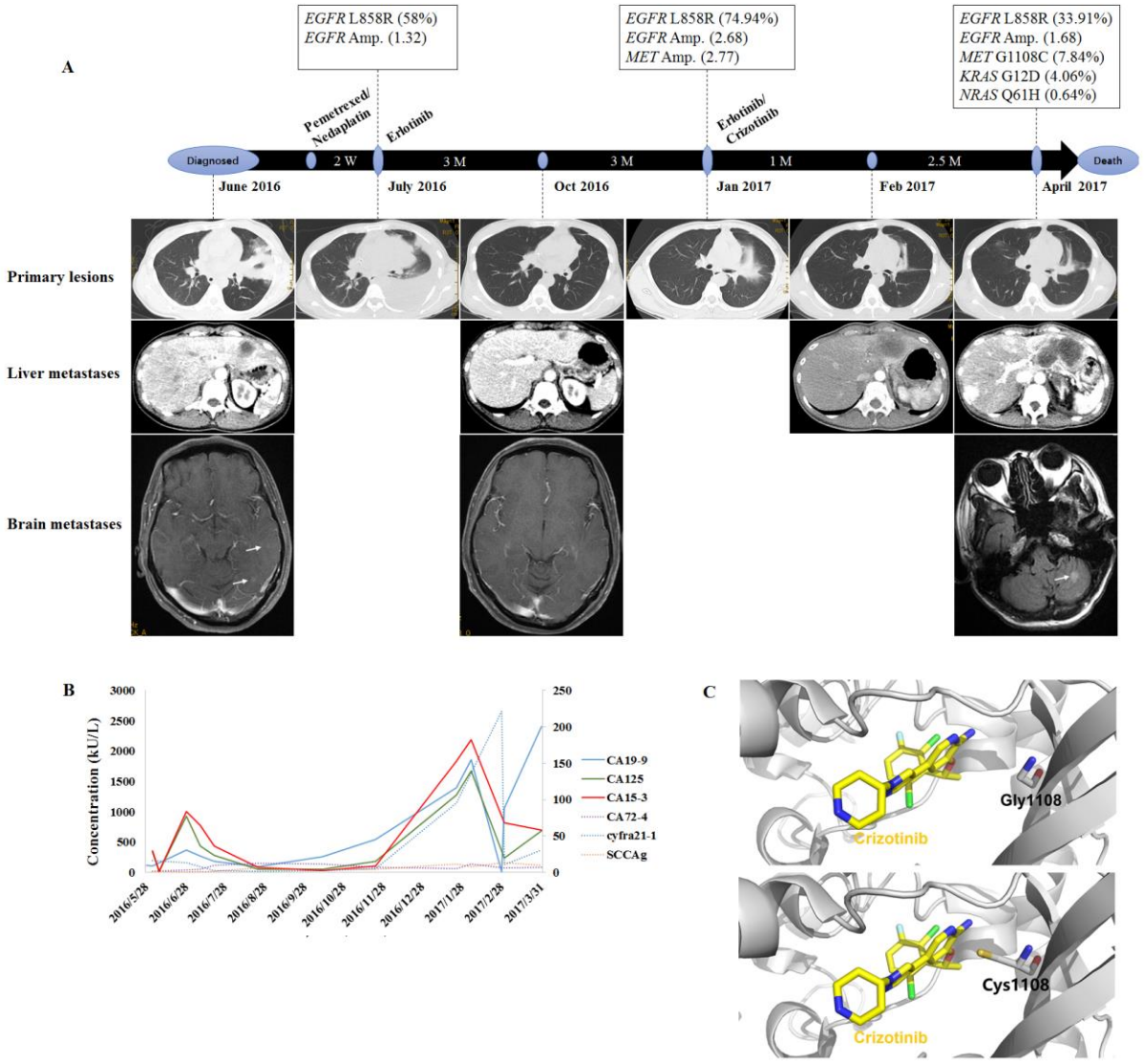

Figure 1. Course of the disease. A, Course of the disease with driver mutations, treatment history and CT images. B, Concentration variations (Y axis) of serum tumor markers over time (X axis), i.e. CA19-9, CA125, CA15-3, CA72-4, cyfra21-1 and SCCAg. Solid lines correspond to left Y-axis, and dotted lines correspond to right Y-axis. Normal reference ranges (kU/L): CA19-9 (0-37), CA125 (0-35), CA15-3 (0-31.3), CA72-4 (0-6.9), cyfra21-1 (0-3.3), SCCAg (0-1.5). C, Predicted structures of wild type *MET* or *MET* G1108C mutation with crizotinib using phymol.