Answering Reviewers

Q1: You must add in the discussion if you can more references about this cancerous transformation that have been well evolued after 3rd generation TKI introduction.

Thank you very much for your advice! After 10.5 months of 1st generation TKI (Gefeitinib) treatment, the chest imaging showed enlargement of the main lesion in the right upper lung accompanied by two lung metastases and secondary drug resistance of the tumor. Afterwards, T790M mutation was confirmed by ddPCR of peripheral blood, and the main lesion in the right upper lung continued to increase after the 3rd generation TKI (Osimertinib) treatment. It suggested that before 3rd generation TKI treatment, the right upper lung lesions may have undergone tumor type transformation, but the metastatic tumors in both lungs responded well to the 3rd generation TKI treatment and almost completely subsided, which could be conjectured that there were adenocarcinoma cells with T790M mutation in the metastatic lesions in both lungs. This dramatic performance also fully confirmed the complexity of secondary drug resistance due to the heterogeneity of tumor cells.

Q2：You cannot generalize from one case that the 3rd line TKI had apported an objective and good results because you've had associated carboplatine and etoposide. this encouraging result should be taken with caution.

Thank you very much for your opinion! After 3 months of 3rd generation TKI treatment, the right upper lung lesion continued to progress, and small cell lung cancer transformation was confirmed by lung biopsy. The next-generation sequencing (NGS) indicated that T790M mutation disappeared, and the 3rd generation TKI had no value for continued use. Therefore, Carboplatin combined with etoposide chemotherapy used for small-cell lung cancer was replaced and good therapeutic effect was achieved.

Q3: You had submitted the patient to 4 series of biopsy. In my opinion it's to aggressive. You must develop the dna method of circulating cells to detect any tumor mutation.

Thank you very much for your advice! While DNA method of circulating cells is an effective and dynamic method to monitor tumor gene mutations，but it cannot replace the value of pathological diagnosis. After several biopsies，we not only identified the mutations of the tumor drug resistance gene, but also found a pathological evolution from adenocarcinoma to small cell carcinoma and eventually to compound lung cancer. The complex pathological mechanism of secondary drug resistance was effectively revealed.