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Case Report

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Synchronous Double Primary Lung Adenocarcinomas With *EGFR* L858R Point Mutation and *MET* Exon 14 Skipping Mutation

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Abstract

Various driver mutations and the corresponding molecular-targeted drugs have been detected and developed in non-small cell lung cancer. There were many cases in which surgical specimens had happened to find double primary cancers. However, to our knowledge, our case was the first report of synchronous double primary lung adenocarcinomas harboring epidermal growth factor receptor (*EGFR*) L858R and mesenchymal-to-epithelial transition (*MET*) exon 14 skipping mutations. A 75-year-old Japanese woman with chronic heart and renal failures was referred to our department because of a growing nodule in the right upper lung field on chest X-ray films. Chest computed tomography (CT) detected a nodule in the right S_1 and another nodule in the left S_{1+2}. Bronchoscopic biopsy diagnosed the right S_1 nodule as moderately differentiated adenocarcinoma. Oncomine Dx Target Test Multi-CDx system of the right S_1 adenocarcinoma detected *EGFR* L858R mutation. The 18^F-fluorodeoxyglucose positron emission tomography/CT showed abnormal uptakes both in the right S_1 and the left S_{1+2} nodules, and in the bilateral inferior paratracheal lymph nodes. We made a diagnosis of c-stage IIIA ($cT_{1b}N_2M_0$) of adenocarcinoma in the right S_1 and suspected another primary lung cancer in the left S_{1+2}. Considering her general conditions, comorbidities and wishes, we started osimertinib. The right S_1 cancer achieved partial response (PR), while the left S_{1+2} nodule and lymph nodes enlarged. Aspiration cytology from the left supraclavicular lymph node showed adenocarcinoma. The FoundationOne® Liquid CDx tumor profiling test detected not only *EGFR* L858R, but also *MET* exon 14 skipping mutation. We made a diagnosis of another primary adenocarcinoma from the left S_{1+2} nodule ($cT_{1b}N_3M_0$, c-stage IIIB) with *MET* mutation, and changed osimertinib to capmatinib. Although the left S_{1+2} cancer achieved and maintained PR by capmatinib, the right S_1 cancer increased, and several new metastases appeared. The subsequent switch from capmatinib to osimertinib could not control cancers. In this case, we tried to switch monotherapies from osimertinib to capmatinib for double primary adenocarcinomas harboring different two driver mutations, according to each cancer progression. The temporal and spatial heterogeneity reinforces the need for primary tissue biopsy if dual primaries are suspected. Temporally distinct liquid biopsies, not standard at present, may be considered.

Keywords: *EGFR* L858R point mutation; *MET* exon 14 skipping mutation; Synchronous double primary lung cancers; Multiple primary lung cancers; Adenocarcinoma; Osimertinib; Capmatinib

Introduction

Multiple primary lung cancer (MPLC) is uncommon, and the actual frequency of MPLCs remains unknown. According to the Surveillance, Epidemiology, and End Results (SEER) Program, MPLCs are classified into synchronous and metachronous by 2-month interval between the diagnoses of the first and second primary cancers [1]. The incidences of synchronous and metachronous MPLCs were 6.0% and 5.0% in a Japanese Surgical Registry [2]. In the case of multifocal lung cancers and identical histological types, it remains difficult to discriminate MPLCs from intrapulmonary metastases, decide the exact clinical stage and select the optimal treatment strategy in the clinical setting [3]. Based on the analyses of ground-glass nodules, the discrepancy rate of driver mutations in MPLCs was 80% to 92% [4, 5]. This discrepancy leads to different responses to molecular-targeted therapy and may present unique challenges to targeted drugs for MPLC patients.

Epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC) has been dramatically improved in prognosis by development of EGFR tyrosine kinase inhibitors (TKIs). Overall *EGFR* mutation frequency was 45% (range: 21-68%) in Japanese patients with adenocarcinoma histology [6]. Common mutations of exon 19 deletion and L858R point mutation in exon 21 accounted for 44.8% and 39.8% of *EGFR* mutations, respectively [7]. In the phase III FLAURA trial, the median progression-free survival (PFS) and overall survival (OS) were 18.9 and 38.6 months for osimerti-

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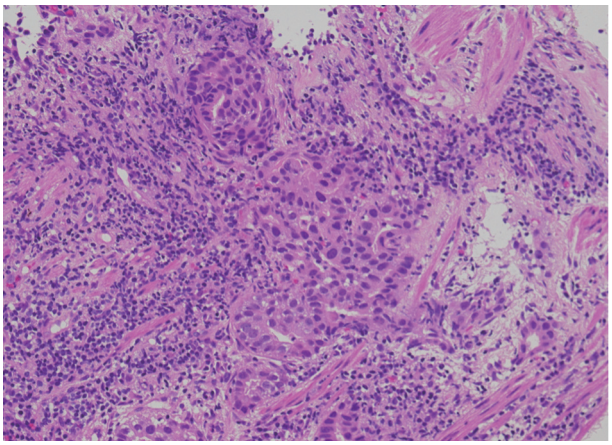

Figure 1. Histology of bronchoscopic specimen from the tumor in the right upper lobe (hematoxylin and eosin stain, magnification, × 200).

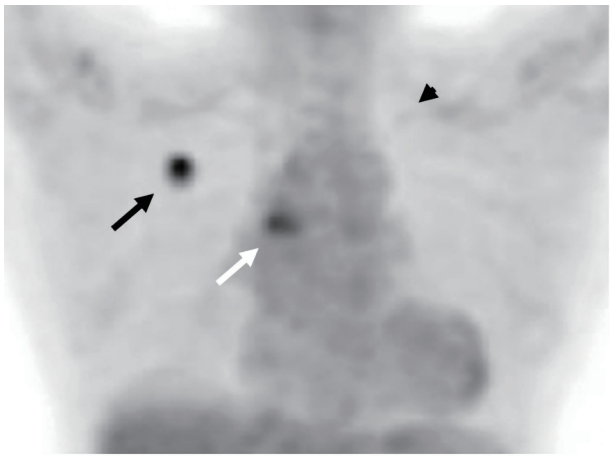

Figure 2. FDG-PET-CT showed the accumulation of FDG in the right S_1 (SUVmax: 7.1) (shown by black arrow) and in the left S_{1+2} (SUVmax: 2.1) (shown by black arrowhead), and in the bilateral inferior paratracheal lymph nodes (SUVmax: 4.49) (shown by white arrow). FDG-PET-CT: 18^F-fluorodeoxyglucose positron emission tomography-computed tomography.

nib, a third-generation EGFR-TKI, but 10.2 and 31.8 months for control regimen of gefitinib or erlotinib, first-generation EGFR-TKIs, respectively [8]. Compared with gefitinib and erlotinib, osimertinib tended to display milder adverse events, especially in skin rash and hepatic toxicity. Thus, osimertinib was approved by Japanese medical insurance in August 2018 as the first-line EGFR-TKI for inoperable or recurrent NSCLC.

On the other hand, mesenchymal-to-epithelial transition (*MET*) gene exon 14 skipping mutation accounts for 3-4% of lung adenocarcinoma [9]. As molecular-targeted antitumor drugs for *MET* mutation, capmatinib was approved by Japanese medical insurance in June 2020, based on the phase II trial of GEOMETRY mono-1 [10] study. For capmatinib in Japan, only FoundationOne CDx is currently approved as companion diagnostics. Capmatinib provided overall response rate of 41% and 68%, the median PFS of 5.4 and 12.4 months in pretreated and chemo-naive patients, respectively [10].

Herein, we report a rare patient with synchronous double primary lung adenocarcinomas harboring different driver mutations, *EGFR* L858R point mutation and *MET* exon 14 skipping mutation.

Case Report

Investigations

A 75-year-old Japanese woman was referred from the Cardiologic Department in our hospital in September 2020 because of a growing nodular shadow in the right upper lung field on chest X-ray films within 4 months' interval. Chest computed tomography (CT) detected a nodule with the diameter of 2.6 cm in the right S_1, another nodule in the left S_{1+2}, which consisted of a partly solid ground-glass nodule with the maximum diameter of 1.8 cm and a solid core with the diameter 1.3 cm, and localized gland glass opacities in both upper lobes and right lower lobe.

Her serum carcinoembryonic antigen level was elevated to 12.6 ng/mL. She was an ex-smoker with an 11-pack-year smoking history. She had been treated with angiotensin-converting enzyme inhibitor (enalapril maleate), diuretic (azosemide and spironolactone) and β-blocker (carvedilol) since October 2013 for chronic heart failure after acute myocardial infarction, with reduced ejection fraction (22%), elevated H-brain natriuretic peptide (161.9 pg/mL, with a normal range < 18.4 pg/mL) and New York Heart Association functional class IV symptoms. She also had chronic kidney disease stage Kidney Disease Improving Global Outcomes (KDIGO) G3b (estimated glomerular filtration rate 41 mL/min) after acute kidney injury transiently treated with continuous hemodialysis filtration in December 2017. Her Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS) was 2.

Diagnosis

Bronchoscopic biopsy pathologically diagnosed the right S_1 nodule as moderately differentiated adenocarcinoma (Fig. 1). Genetic testing of the right S_1 adenocarcinoma (Oncomine Dx Target Test multi-CDx system (ODxTT); Thermo Fisher Scientific, Waltham, MA, USA) detected *EGFR* L858R point mutation. The tumor proportion score of a programmed cell death ligand 1 was below 1%. 18^F-fluorodeoxyglucose positron emission tomography/CT showed abnormal uptakes in the nodules in the right S_1 (maximum standardized uptake value (SUVmax): 7.1) and in the left S_{1+2} (SUVmax: 2.1), and in the bilateral inferior paratracheal lymph nodes #4R and 4L (SUVmax, 4.49) (Fig. 2). Contrast-enhanced brain magnetic resonance imaging did not find brain metastasis. From the left S_{1+2} nodule, we tried neither trans-bronchoscopic biopsy nor CT-guided aspiration biopsy because of technically difficult specimen collection. From the slightly swollen para-tracheal lymph nodes, we did not try endobronchial ultrasound-guided trans-bronchial needle aspiration, because the lymph nodes were apparently too small for us to obtain some tissues or cells. We suspected the para-tracheal lymphadenopathy as mediasti-

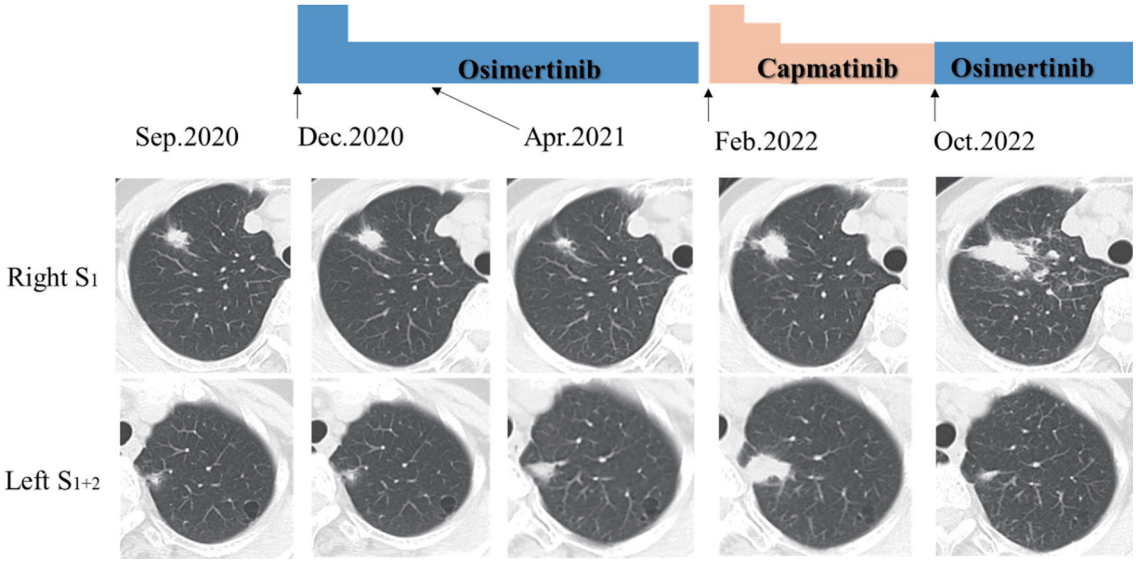

Figure 3. Chest computed tomography (CT) demonstrated nodular shadows in the right S_1 and the left S_{1+2} at the diagnosis (in September 2020). These nodules changed before and 4 months after osimertinib administration (partial response in the right S_1), and before and 8 months after capmatinib administration (partial response in the left S_{1+2} and progression disease in the right S_1).

nal metastases from the right S_1 cancer, and the S_{1+2} nodule as another primary lung cancer. We made a diagnosis of adenocarcinoma with c-stage IIIA ($cT_{1b}N_2M_0$) in the right S_1, and suspected unconfirmed another lung cancer with c-stage IA2 ($cT_{1b}N_0M_0$) in the left S_{1+2}.

Treatment

Considering her general conditions, comorbidities and unwillingness to receive invasive and aggressive treatment, we decided not to provide curative-intent chemoradiotherapy and surgery. We also decided not to provide radial radiotherapy to both primary tumors and mediastinal metastases for fear of wide range of irradiation, adverse event of radiation pneumonitis and then deterioration of her heart failure. Instead, we started osimertinib (80 mg/day, once daily) in December 2020. We reduced the dose of osimertinib down to 40 mg/day due to grade 2 of diarrhea 2 weeks after the initiation of osimertinib. The right S_1 cancer achieved partial response (PR) in April 2021, while the left S_{1+2} nodule enlarged against osimertinib (Fig. 3). The lymphadenopathies appeared in the left hilum in July 2021, and then in the left mediastinum and the left supraclavicular fossa in October 2021. Aspiration cytology from the left supraclavicular lymph nodes showed adenocarcinoma (Fig. 4). As a result of consultation to our otorhinolaryngologists, we gave up surgical biopsy from the supraclavicular lymph nodes at the risk of the surrounding large vessels. Thus, we suspected progression of another adenocarcinoma in the left S_{1+2} ($cT_{1b}N_3M_0$, c-stage IIIB). She refused cytotoxic chemotherapy at that time. The treatment choice became molecular target therapy or immune checkpoint inhibitor or best supportive care. Because we could not obtain enough tissue specimen for ODxTT genetic test and AmoyDx Pan Lung Cancer PCR Panel, we requested FoundationOne® Liquid CDx tumor profiling test (Foundation Medicine, Inc., USA). This genetic test detected not only *EGFR* L858R point mutation (allele frequency (AF); 0.0014), but also *MET* exon 14 skipping mutation (AF; 0.13) (Table 1). Following the recommendation from the expert panel, we started capmatinib (800 mg/day, twice daily) in February 2022. The left S_{1+2} nodule and multiple lymph metastases remarkably reduced and achieved PR 2 weeks after the initiation of capmatinib. This drug was gradually reduced to 400 mg/day due to repeated grade 2 of nausea and fatigue.

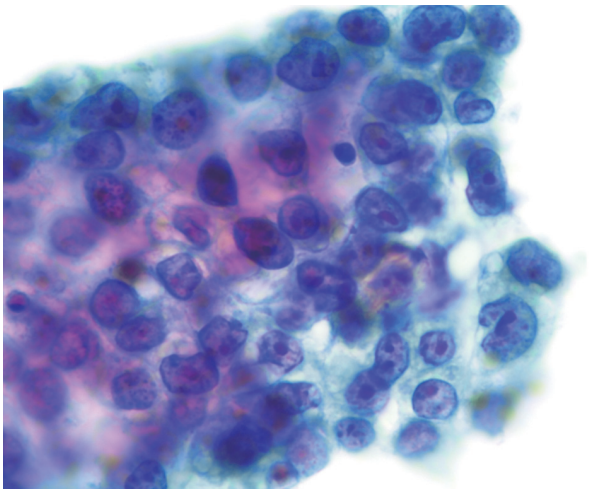

Figure 4. Cytology of fine-needle aspiration from the left supraclavicular lymph nodes (papanicolaou stain, magnification, × 400).

Follow-up and outcomes

Although the left S_{1+2} primary nodule and lymph node metasta-

Table 1. List of Positive Mutations Detected by FoundationOne® Liquid CDx Tumor Profiling Test

Gene	Mutation	Allele fraction
EGFR	L858R	0.0014
MET	Splice site 2888-21_2888-20 TT>AGA	0.13
TP53	Q331*	0.04
TP53	V143M	0.5
VHL	E10*	0.03

EGFR: epidermal growth factor receptor; *MET*: mesenchymal-to-epithelial transition; *TP53*; Tumor Protein P53; *VHL*: von Hippel Lindau.

ses in hilum, mediastinum, supraclavicular fossa and left axilla maintained reduction, the chest CT in May 2022 detected new lesions of diffuse intrapulmonary metastases and right pleural dissemination. She still refused cytotoxic chemotherapy and immune checkpoint inhibitor. We were also afraid of rapid growth of the tumor after discontinuation of capmatinib. Thus, we dared to continue capmatinib in spite of progression disease. While the tumor in the left S_{1+2} did not grow, the tumor in the right S_1 enlarged and then multiple liver metastases also appeared (Fig. 3). However, despite of switch from capmatinib to osimertinib in October 2022, new metastases appeared in the 9 - 12 thoracic vertebra, which was then irradiated for palliative pain control. After discontinuation of osimertinib and discharge from our hospital, she chose home palliative care service and died in January 2023.

Discussion

This case was the first report of synchronous double primary lung adenocarcinomas harboring different driver mutations, *EGFR* L858R point mutation and *MET* exon 14 skipping mutation.

Double mutations of *EGFR* and *MET* can be categorized into the following three patterns: 1) *EGFR*-mutant NSCLC acquired *MET* mutation during EGFR-TKIs; 2) a NSCLC harboring both *EGFR* and *MET* mutations; 3) double primary NSCLCs harboring different driver mutations. For pattern 1, MET amplification has been well known as an acquired resistance mechanism to EGFR-TKIs for *EGFR*-mutant NSCLC [11]. Whereas, there were only five cases of acquired *MET* exon 14 skipping mutation as a resistance mechanism to EGFR-TKIs for *EGFR*-mutant NSCLC (Table 2) [12-16]. Some of these cases had been successfully treated by addition of capmatinib [16] or crizotinib [13] to osimertinib or icotinib, respectively, or by switch from osimertinib to tepotinib [15] or crizotinib [14]. Thus, in the case of acquired *MET* mutation, addition of or switch to a MET-TKI may be an optimal option. For pattern 2, on the other hand, there were only four cases of NSCLCs initially and synchronously harboring this genetic combination of these two driver mutations (Table 3) [17-20]. Only one case had both *MET* exon 14 skipping mutation and amplification concomitantly [17], while *EGFR* mutation types varied among four cases. Two cases were successfully treated by combining afatinib and crizotinib [18, 20], one transiently responded to crizotinib monotherapy [17], while the other suddenly died 17 days after addition of crizotinib to osimertinib for unknown causes [19]. Treatment regimens and responses were various. Therefore, in the case of synchronous *EGFR* and *MET* mutations in one advanced tumor, combining two types of molecular-targeted drugs may be reasonable, but still be controversial in efficacy, adverse effects and costs. In the near future, a bispecific antibody targeting both EGFR and MET receptor alone or combined with an EGFR-TKI may be a potential candidate in this setting. For pattern 3, unlike these cases, our case was characterized by simultaneously coexisting two primary adenocarcinomas harboring different driver mutations. If our patient had been younger, better ECOG-PS and less comorbidities, the following two-stage strategy of sequential and curative-intent treatments might have been optimal: 1) in the initial stage for the right S_1 advanced cancer, chemoradiotherapy alone or optionally followed by consolidation of an immune-checkpoint inhibitor, or surgical resection followed

Table 2. Summary of the Previous Case Reports of Acquired *MET* Exon 14 Skipping Mutation as a Resistance Mechanism to EGFR-TKIs

Authors (publication year)	Age, sex	Histology	*EGFR* mutation	EGFR-TKIs (response, PFS)	*MET* mutation	Regimens after appearance of MET mutation
Xiang et al, 2023 [16]	53M	Ad	Ex19del	Erlotinib, osimertinib (PR, 28 mo)	Ex 14 skipping	Osimertinib + capmatinib (PR, 7 mo)
Takamori et al, 2022 [15]	76F	Ad	L858R + T790M	Osimertinib (PR, 14 mo)	Ex 14 skipping	Tepotinib (PR, 8 mo)
Pinquie et al, 2022 [14]	56M	Ad	L858R → L858R+T790M	Gefitinib/erlotinib (PR, 12 mo) → osimertinib (PD, 5 mo)	Ex 14 skipping	Crizotinib (PR, 4 mo)
Ou et al, 2022 [13]	63F	Ad	Ex18 G719D + Ex 21 L861Q	Icotinib (PR, 9 mo) → osimertinib (SD, 1 yr)	*CUX1-MET* fusion	Icotinib + crizotinib (PR, > 9 mo)
Jiao et al, 2021 [12]	33M	AdSq	*EGFR* p.S768_D770dup	Afatinib (PD, 1 mo) → anlotinib (PD, 1 mo)	Germline *MET* Ex 14 skipping	None

Ad: adenocarcinoma; AdSq: adenosquamous cell carcinoma; EGFR: epidermal growth factor receptor; Ex: exon; F: female; M: male; MET: mesenchymal-to-epithelial transition; mo: months, PD: progressive disease; PR: partial response; yr: years.

Table 3. Summary of the Previous Case Reports of Lung Cancers Harboring Coexistence of *EGFR* Mutation and *MET* Exon 14 Skipping Mutations

Authors (publication year)	Age, sex	Histology	Stage at diagnosis	*EGFR* mutation	*MET* mutation	Regimen (response, PFS)
Liu et al, 2023 [19]	82F	Ad	IV	Ex19 del + L858R	Ex 14 skipping	Osimertinib (PD) → osimertinib + crizotinib (death, 17 days)
Chen et al, 2022 [17]	69M	Ad	IIIB	Ex 20 insertion	Ex 14 skipping + amplification	Crizotinib (PR, 6 mo)
Zeng et al, 2019 [20]	60M	Ad	IV	Ex18 G750A	Ex 14 skipping	Afatinib + crizotinib (PR, > 3mo)
Kauffmann-Guerrero et al, 2019 [18]	53F	Ad	IIIB	Ex19 del	Ex 14 skipping	Afatinib (PD) → afatinib + crizotinib (PR, > 3mo)

Ad: adenocarcinoma; del: deletion; EGFR: epidermal growth factor receptor; Ex: exon; F: female; M: male; MET: mesenchymal-to-epithelial transition; mo: months: PD: progressive disease; PFS: progression-free survival; PR: partial response.

by adjuvant chemotherapy; and then 2) in the second stage for the left S_{1+2} early cancer, stereotactic body radio therapy or surgical resection. However, for frail cancer patients who seem intolerable for aggressive treatments, palliative chemotherapy may be optional. Thus, in the case of double primary cancers with different mutations, treatment strategy depends on various factors such as histology, stage, patient's conditions, etc.

In conclusion, we switched monotherapies from osimertinib to capmatinib for synchronous double primary adenocarcinomas harboring *EGFR* mutation and *MET* exon 14 skipping mutation, according to each cancer progression. The temporal and spatial heterogeneity in this case reinforces the need for primary tissue biopsy if dual primaries are suspected. Temporally distinct liquid biopsies, not standard at present, may be considered.

Learning points

The main take-away point is that treatment strategy for double primary cancers with different driver mutations depends on various factors such as histology, stage, patient's conditions, etc. We experienced a rare case of synchronous double primary lung adenocarcinomas harboring different driver mutations, *EGFR* L858R point mutation and *MET* exon 14 skipping mutation. We should take various factors into consideration of treatment choice.

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Financial Disclosure

None to declare.

Conflict of Interest

All authors have no conflict of interest to declare.

Informed Consent

Not applicable because the manuscript has been sufficiently deidentified to protect the patient.

Author Contributions

All authors were involved in diagnosis, treatment and management of the patient. S. Ando drafted the report. All authors read and critically reviewed the manuscript, and then approved the final submitted version.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

CT: computed tomography; ECOG-PS: Eastern Cooperative Oncology Group Performance Status Scale; EGFR: epidermal growth factor receptor; KDIGO: Kidney Disease Improving Global Outcomes; MET: mesenchymal-to-epithelial transition; MPLC: multiple primary lung cancer; NSCLC: non-small cell lung cancer; ODxTT: Oncomine Dx Target Test multi-CDx system; OS: overall survival; FDG-PET: 18^{F}-fluorodeoxyglucose positron emission tomography; PFS: progression-free survival; PR: partial response; TKI: tyrosine kinase inhibitor

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