ORIGINAL ARTICLE

Transient Asymptomatic Pulmonary Opacities During Osimertinib Treatment and its Clinical Implication

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ABSTRACT

Introduction: Osimertinib is an oral, potent, irreversible third-generation EGFR tyrosine kinase inhibitor approved for the treatment of T790M-positive NSCLC patients who failed first- or second-generation EGFR tyrosine kinase inhibitors. Interstitial lung disease (ILD) is a rare complication with osimertinib, occurring in 1% to 3% of patients. Recently, a relatively high incidence of transient asymptomatic pulmonary opacities (TAPOs), which are different from ILD, has been described. However, its clinical implication has not been fully determined yet.

Methods: We retrospectively analyzed 74 EGFR T790M mutant NSCLC patients treated with osimertinib. Serial computed tomographic findings were reviewed by a thoracic radiologist independently, and TAPO was classified according to its radiologic pattern. We also analyzed the correlation of TAPO with clinical outcomes.

Results: Among 74 patients, TAPOs were found in 15 (20.3%). The median time to TAPO development was 24.0 weeks (range, 1 to 72 weeks) and the median duration of TAPO was 6.0 weeks (range, 5 to 24 weeks) during continued osimertinib treatment. The most common radiological patterns of TAPO include cryptogenic organizing pneumonia and/or simple eosinophilic pneumonia. There was no significant difference in patient characteristics between TAPO-positive and -negative groups. The duration of exposure to osimertinib was significantly longer in TAPO-positive than -negative groups (25.0 months versus 13.0 months, $p = 0.009$). The median progression-free survival and the median overall survival was numerically longer in TAPO-positive than -negative groups (22 months versus 15 months for progression-free survival, $p = 0.293$; 37 months versus 24 months for overall survival, $p = 0.059$), respectively.

Conclusions: TAPOs are frequently observed with osimertinib treatment and may be mistaken for isolated pulmonary progression or drug-induced ILD. Given the lack of serious clinical deterioration, it is reasonable to continue osimertinib with regular computed tomographic–scan follow-up. For further clinical validation of TAPOs, long-term follow-up and large studies are warranted.

Keywords: Transient asymptomatic pulmonary opacities; Osimertinib

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, despite improvements in survival.[1,2] The EGFR tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of NSCLC patients with activating EGFR mutation.[3,4] However, almost all patients treated with first- or second-generation EGFR TKIs

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develop acquired resistance, and T790M is the most common resistance mechanism accounting for 50% to 60% of resistance.[5] Osimertinib is an oral, potent, irreversible third-generation EGFR TKI approved for the treatment of T790M-positive NSCLC patients who failed first- or second-generation EGFR TKIs.[6,7] As the use of EGFR TKIs is increasing, serious complications such as acute lung injury or interstitial lung disease (ILD) have been reported.[8-10] A recent analysis reported that the overall incidence of all-grade ILD events was 1.6% among patients treated with first- or second-generation EGFR TKIs with a 13.0% mortality rate.[11] Although the underlying pathogenesis is still unclear, the risk factors associated with ILD include history of tobacco smoking, previous ILD, poor European Cooperative Oncology Group (ECOG) performance status, and old age. Besides, EGFR TKI has been reported to increase interstitial pneumonia by increasing interleukin 6 in cancer cells.[12] Similar to other TKIs, osimertinib is associated with side effects such as pneumonitis and ILD with a 2% to 3% incidence.[13] Usually, these severe side effects may lead to permanent drug discontinuation. Recently, Noonan et al.[14] reported novel interesting findings, so-called transient asymptomatic pulmonary opacities (TAPOs) that have not been reported previously. These opacities are asymptomatic, localized, and spontaneously disappeared in most of cases. In some cases, TAPOs have recurred, either at the same or at different sites on the lung. Noonan et al.[14] suggest that these lesions should be distinguished from pneumonia, disease progression, pulmonary edema, hemorrhage, radiation pneumonitis, and prior interstitial pneumonitis, which are differential diagnoses of ILD.

Thus, we tried to validate TAPOs in Korean patients who were treated with osimertinib and analyzed the radiologic findings and clinical implications of TAPOs.

Methods

Patients

In this retrospective study, 74 patients who participated in clinical trials (AURA, AURA3, and AURA 17) for T790M-positive NSCLC after failure to prior EGFR TKIs and who were treated with osimertinib from September 2013 to September 2015 at Samsung Medical Center were included.

Analysis of Transient Asymptomatic Pulmonary Opacities

We analyzed all the serial chest computed tomography (CT) scans during osimertinib taking period. These scans were repeated every 6 weeks according to the study protocol. When the event occurred, CT was repeated according to the physician's description. All the chest CT scans were reviewed by a chest radiologist (H.Y Lee, with 15 years of chest CT interpretation experience) independently without knowing any clinical information. TAPOs were classified according to radiologic pattern. The patterns of TAPO were classified as cryptogenic organizing pneumonia (COP), simple eosinophilic pneumonia (SEP), and nodular type.[15,16] The COP-like pattern is observed as multifocal areas of parenchymal opacification or nodules with subpleural or peribronchial distribution.[17] The radiographic manifestations of SEP consist of transient and migratory areas of consolidation that typically spontaneously within 1 month.[18,19] In SEP diagnosis, peripheral eosinophilia was defined as more than 450/uL). The correlation of TAPO with clinical outcomes such as tumor response, progression-free survival (PFS), and overall survival (OS) were analyzed.

Statistical Analysis

The purpose of this study was to investigate the difference of response, OS, and PFS according to the presence or absence of TAPOs. Tumor response was evaluated by Response Evaluation Criteria in Solid Tumor criteria. Median OS and PFS were calculated with the use of the SPSS statistics version 24 (IBM; Armonk, New York). Patients were divided into two groups according to the presence or absence of TAPOs, and compared using the Kaplan-Meier method.

Results

Clinical Characteristics

A total of 74 NSCLC patients were treated with osimertinib (5 at 40 mg per day, 61 at 80 mg per day, and 8 at 160 mg per day). Data cutoff was October 20, 2017, and the median follow-up period was 25 months (range, 3 to 49 months). Among the 74 patients, TAPOs were observed in 15 patients (20.3%) (Table 1). The median age at study enrollment was 59.0 years (range, 43 to 85 years) in the TAPO-positive group, and 58.0 years (range, 34 to 81 years) in the TAPO-negative group. Other patient characteristics including gender, smoking status, and ECOG performance status were comparable between the two groups. All enrolled patients had activating EGFR mutation, 41% (n = 30) with L858R, 55% (n = 41) with exon 19 deletion and all patients (100%) with T790M mutation in exon 20. Two patients were treated with osimertinib as first-line therapy (in the TAPO-negative group). Seventy-two patients had been previously treated with other EGFR TKIs before osimertinib treatment. Most patients received either gefitinib or erlotinib, and 9 patients received both gefitinib and afatinib.

Characteristics of TAPO

During the follow-up, TAPO occurred in 15 of 74 patients and 22 lesions were identified. The patient

Table 1. Clinical Characteristics of Patients

	Total	TAPO Positive n (%)	TAPO Negative n (%)
n (%)	74 (100)	15 (20.3)	59 (79.3)
Median age at study enroll	58.0 (34-85)	59.0 (43-85)	58.0 (34-81)
Sex, n			
Male	30	5 (33)	25 (42)
Female	44	10 (67)	34 (58)
Smoking history			
Yes	23	4 (M = 3, F = 1)	19 (M = 17, F = 2)
No	51	11 (M = 2, F = 9)	40 (M = 8, F = 32)
EGFR mutation, n			
Exon 19 deletion	41	6 (40)	35 (59)
L858R	30	7 (47)	23 (39)
Others	3	2 (13)	1 (2)
T790M	74	15 (100)	59 (100)
Prior EGFR TKI (%)			
Gefitinib only	36	12 (80)	24 (41)
Erlotinib only	26	1 (7)	25 (42)
Afatinib only	1	0	1 (2)
Gefitinib and Afatinib	9	2 (13)	7 (12)
Non-TKI user (1st line treatment)	2	0	2 (3)
AZD9291 dose, mg, n (%)			
40	5	0	5 (8.5)
80	61	13 (86.7)	48 (81.4)
160	8	2 (13.3)	6 (10.1)

TAPO, transient asymptomatic pulmonary opacity; TKI, tyrosine kinase inhibitor.

characteristics for TAPO are summarized in Table 2. Nine patients had only one lesion (60%) and five patients had two lesions (33.3%). One patient (Patient No. 1) developed three TAPOs during 144 weeks. The median time to TAPO development after osimertinib treatment was 24 weeks (range, 1 to 72 weeks). The earliest case (Patient No. 71) occurred within 1 week after osimertinib treatment, whereas the latest case (Patient No. 23) occurred even after 18 months. The median duration of TAPO was 6 weeks (range, 5 to 24 weeks). The timing of TAPO development pattern for each patient is described in Figure 1.

Table 2. Characteristics of TAPO Positive

	TAPO Positive n (%)
Total patients	15 patients (20.3%)
Number of TAPO development	Average 1.47 (1-3)
1	9 (60)
2	5 (33.3)
3	1 (6.7)
TAPO pattern	Total N = 15 patients (22 TAPOs)
COP	11 TAPOs (50)
SEP	10 TAPOs (45.5)
Nodular	1 TAPO (4.5)
Mixed (COP + SEP)	4 patients (26.7)
Time to development of TAPOs (wk)	24 weeks (1-72, median)
Period of TAPOs (wk)	6 weeks (5-24, median)

TAPO, transient asymptomatic pulmonary opacity; COP, cryptogenic organizing pneumonia; SEP, simple eosinophilic pneumonia.

According to the study protocol, patients with a history of ILD were excluded before study enrollment. Two patients had histories of pulmonary tuberculosis, three received lung or mediastinal radiation therapy, and none had history of aspiration pneumonia. Most patients were asymptomatic at the time of TAPO development except two patients with mild cough. None of the 15 patients who developed TAPOs had evidence of disease progression, neutrophilia, eosinophilia, C-reactive protein elevation, or fever. TAPO lesions were asymptomatic and localized, and spontaneously disappeared without any treatment. All the 15 patients with TAPO continued osimertinib treatment.

Radiological Patterns of TAPOs

During osimertinib use, a radiologist analyzed a total serial chest CT of 74 patients and excluded radiologic findings manifesting aspiration, bronchopneumonia/bronchiolitis. There were 11 cases (11 of 22, 50%) of TAPOs with COP, 10 cases (10 of 22, 45.5%) of TAPOs with SEP, and 1 case of TAPOs with nodular pattern (1 of 22, 4.5%). Four patients had both patterns of COP and SEP (Table 2).

Two representative cases of SEP and COP are shown in Figure 2. Patient No.41 received osimertinib and TAPOs occurred in right upper lobe (RUL) at 35 weeks (Fig. 2*A*). The SEP pattern of TAPOs was an ill-defined ground glass opacity (GGO) without any accompanying respiratory

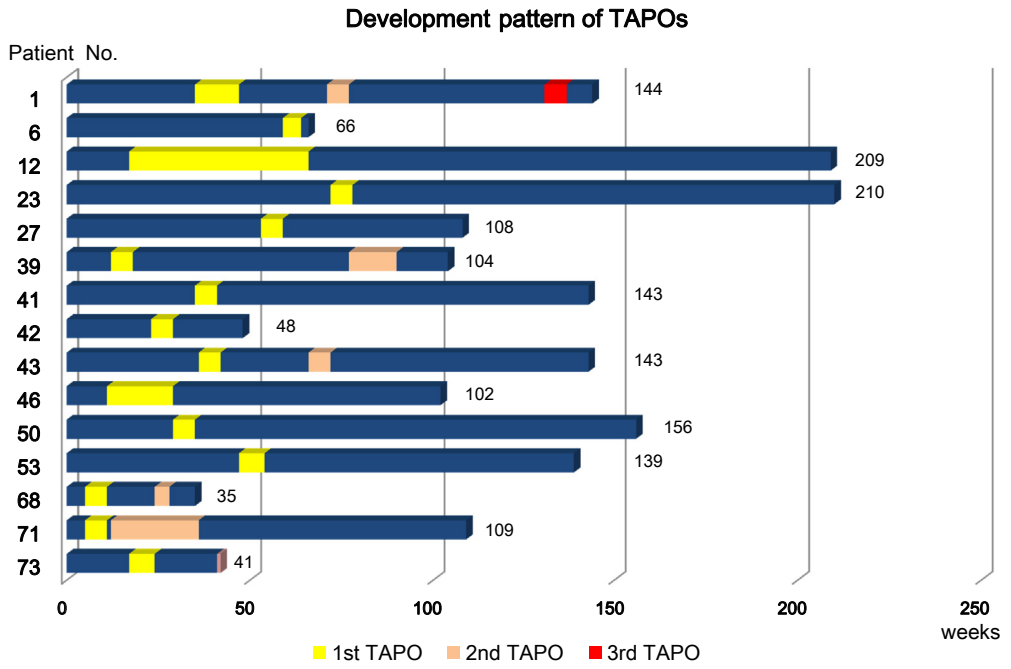

Figure 1. Development pattern of transient asymptomatic pulmonary opacities.

symptoms. During continuation of osimertinib treatment, follow-up chest CT was performed 6 weeks later, and then previous TAPOs disappeared spontaneously (Fig. 2*B*). In another case, patient no.73, a prominent GGO halo appeared in the RUL at 17 weeks after taking osimertinib (Fig. 2*C*). This patient was asymptomatic and the lesion disappeared 7 weeks later (Fig. 2*D*). These two cases show typical radiological patterns of SEP.

As for COP pattern, starry-shaped peribronchovascular consolidations appeared in the RUL in patient no.71 (Fig. 2*E*). This consolidation pattern gradual improved, and 24 weeks later disappeared (Fig. 2*F*, 2*G*, and 2*H*). In patient no. 68, a reversed halo sign (typical COP, bronchiolitis obliterans organizing pneumonia) appeared in the RUL while receiving osimertinib (Fig. 2*I*). Four weeks later, this consolidation disappeared. These two patients developing typical COP were also asymptomatic.

Of the 59 patients who were excluded according to the TAPO analysis (the TAPO-negative group), 21 patients developed new lung lesions while receiving AZD9291 use. Pneumonia was diagnosed in 10 patients, and 8 patients were found to have newly pulmonary metastases. One patient each had the following: atelectasis, nonspecific bronchiolitis, and bronchial secretion.

Response to Osimertinib Response According to the TAPOs

The duration of exposure to osimertinib was significantly longer in the TAPO-positive group than the TAPO-negative group (25.0 months versus 13.0 months, $p = 0.009$). However, the overall response rate to osimertinib was similar between two groups (66.7% [10 of 15] for the TAPO-positive versus 71.2% for the TAPO-negative group). The median PFS was 22 months for the TAPO-positive group and 15 months for the TAPO-negative group, respectively, which is not statistically significant ($p = 0.293$). The median OS was numerically longer in patients from the TAPO-positive group than the TAPO-negative group (37 months versus 24 months, $p = 0.059$). Forty percent of TAPO-positive patients are currently alive and eight of nine patients died of disease progression (Figs. 3 and 4).

Discussion

ILD is a rare, but serious adverse event related to EGFR TKIs. The incidence of all-grade ILD from EGFR TKI treatment ranged from 0% to 5.7%, and high-grade ILD ($\geq$ grade 3) was associated with increased mortality, requiring dose reduction and permanent discontinuation of treatment.[11] A meta-analysis reported the mortality rate related to ILD to be 13%.[11] Similar to other first- and second-generation EGFR TKIs, the incidence of ILD associated with osimertinib is 2% to 3%, even though most patient who developed ILD had their cases resolved with use of corticosteroid or discontinuation of drug.[13] Therefore, permanent discontinuation of osimertinib without rechallenge is usually recommended if patients develop ILD. Given

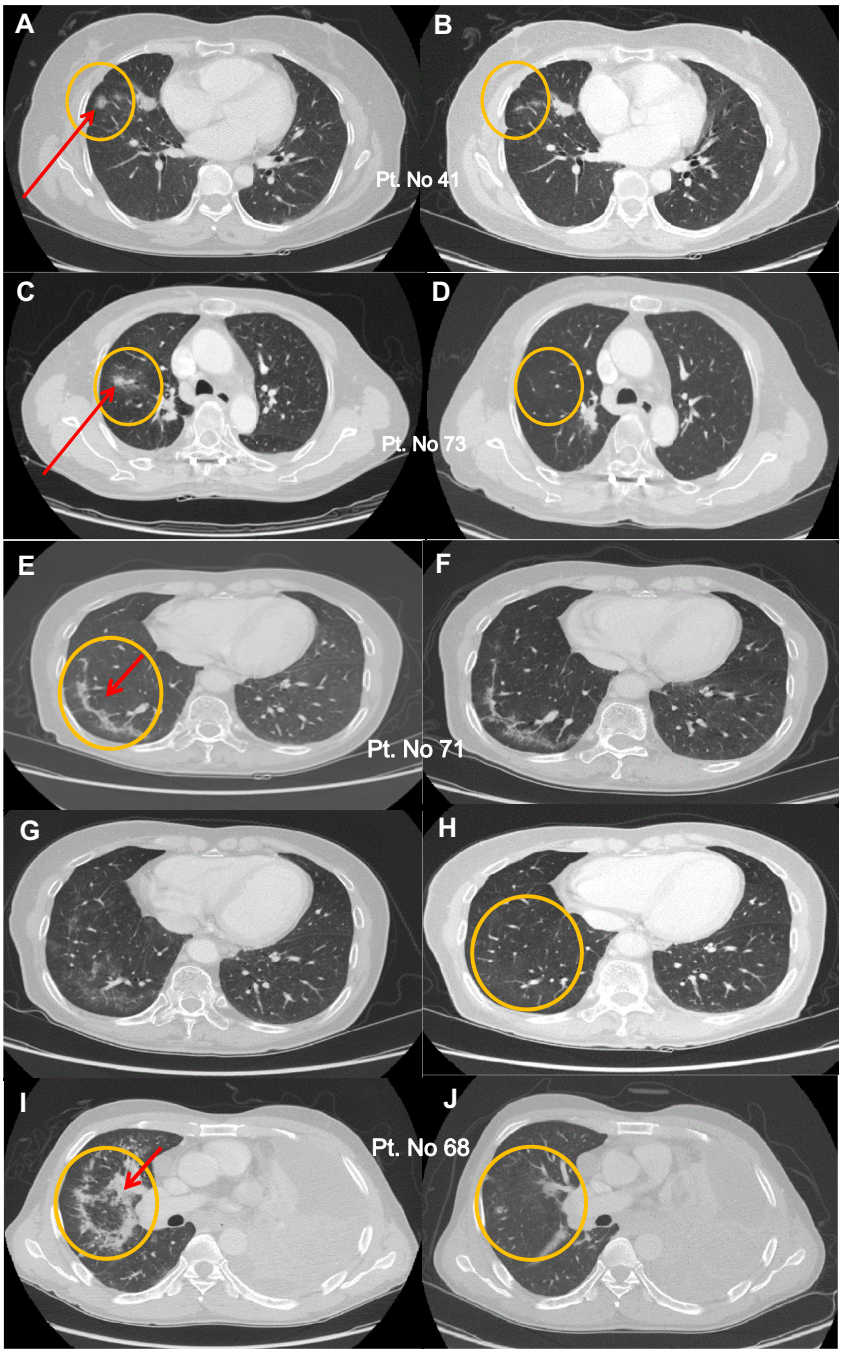

Figure 2. Transient asymptomatic pulmonary opacities pattern. (*A-D*) Simple eosinophilic pneumonia. (*A*) Ill-defined ground glass opacity (GGO) pattern appeared in right upper lobe during while receiving osimertinib. (*B*) Six weeks later, this GGO pattern disappeared. (*C*) Prominent GGO halo with ill-defined part solid lesion in right upper lobe while receiving osimertinib. (*D*) Seven weeks later, this GGO pattern disappeared. (*E-J*) Cryptogenic organizing pneumonia (COP). (*E-H*) Patient no. 71. (*E*) Starry shaped peribronchovascular consolidation (typical COP) appeared in right upper lobe while receiving osimertinib. (*F-H*) This consolidation pattern gradually improved and disappeared 24 weeks later. (*I*, *J*) Patient no. 68. (*I*) Reversed halo sign (typical COP, also known as bronchiolitis obliterans organizing pneumonia) appeared in right upper lobe while receiving osimertinib. (*J*) Four weeks later, this consolidation disappeared.

that osimertinib is the only approved drug with high efficacy for the treatment of patients with EGFR T790M mutation who failed prior EGFR TKIs, a careful approach is crucial to making the decision to stop osimertinib when radiological abnormalities suggesting ILD are observed. Otherwise, only chemotherapy remains as a further treatment option for these patients.

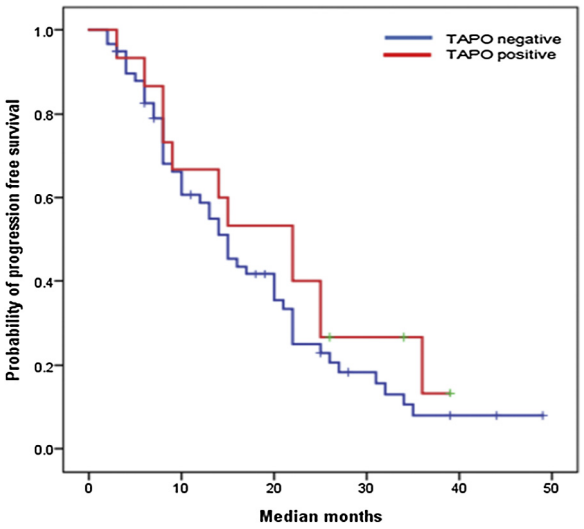

Figure 3. Progression-free survival according to status of transient asymptomatic pulmonary opacity (TAPO). Shown are Kaplan-Meier estimates of progression-free survival among patients with NSCLC who received AZD9291. In the subgroup of patients with TAPO (*red*), the median overall survival was 22.0 months. In the subgroup of patients without TAPO (*blue*), the median overall survival was 15.0 months (95% confidence intervals, p value = 0.293).

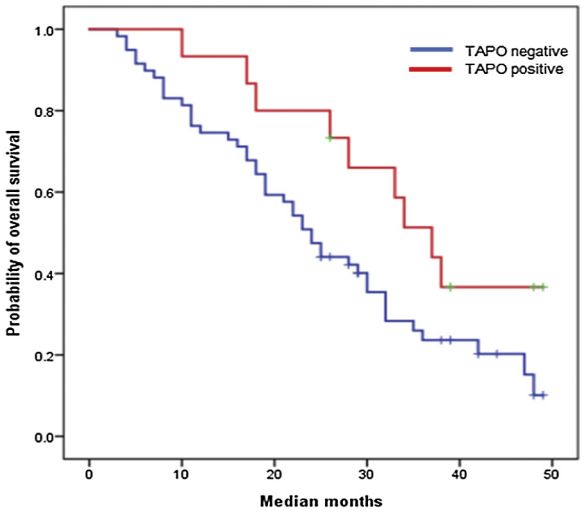

Figure 4. Overall survival according to status of transient asymptomatic pulmonary opacity (TAPO). Shown are Kaplan-Meier estimates of overall survival among patients with NSCLC who received AZD9291. In the subgroup of patients with TAPO (*red*), the median overall survival 35.16 was months. In the subgroup of patients without TAPO (*blue*), the median overall survival was 25.79 months (95% confidence intervals, p value = 0.059).

In this study, the incidence of TAPO was 20.3% in patients treated with osimertinib, which is common. We also found that TAPO can occur at any time during osimertinib treatment. Most patients who develop TAPOs are asymptomatic and radiological lesions are localized and disappear spontaneously without any intervention, which is consistent with previous reports.[14]

Through comprehensive analysis of serial chest CT scans for patients who participated in three prospective clinical trials and treated with osimertinib, we were able to classify TAPO into three distinct radiological patterns such as COP, SEP, and nodular type. Among them, COP and SEP were most frequently observed. We also found that the clinical outcomes including response rate to osimertinib, PFS, or OS were not significantly different between the TAPO-positive and TAPO-negative groups (Table 3). Given the asymptomatic radiological lesions related to TAPOs in this study, all the patients were able to receive osimertinib without discontinuation. Close monitoring is essential when a lesion suspicious for ILD appears on chest CT scan during osimertinib treatment. Furthermore, because the radiological patterns are different from ILD, close discussion with a radiologist is required to make the decision to discontinue osimertinib treatment.

In conclusion, TAPOs are frequently observed with osimertinib treatment and may be mistaken for isolated pulmonary progression or drug-induced ILD. Given the lack of serious clinical deterioration, it is reasonable to continue osimertinib with regular CT scan follow-up. For further clinical validation of TAPOs, long-term follow-up and large studies are warranted. Also, it may be interesting to compare whether patients treated with first- or second-generation EGFR TKIs also experience TAPOs.

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Table 3. Osimertinib (AZD9291) Response

	TAPO Positive	TAPO Negative
n (%)	15 (20.3)	59 (79.3)
Period of use AZD9291 (mo)	25 (5-48)	13 (1-49)
Best response, n (%)		
CR	0	1 (1.7)
PR	10 (66.7)	41 (69.5)
SD	4 (26.7)	13 (22.0)
PD	1 (6.6)	4 (6.8)
Overall response rate (%)	66.7 %	71.2 %
Progression -free survival (mo)	22 (6-39)	15 (1-49)
Overall survival (mo)	37 (10-48)	24 (3-49)
Alive, n (%)	6 (40)	14 (24)
Death, n (%)	9 (60)	45 (76)
Disease progression	8	38
Other cause	1	7

TAPO, transient asymptomatic pulmonary opacity; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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