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Baseline genetic abnormalities and effectiveness of osimertinib treatment in patients with chemotherapy-naïve EGFR-mutated NSCLC based on performance status

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Abstract

Background/Aim For patients treated with osimertinib as first-line therapy, there have been no studies comparing both progression-free survival (PFS) and overall survival (OS) according to performance status (PS). Furthermore, no studies have examined differences in baseline genetic abnormalities between patients with poor and good PS. Therefore, we aimed to investigate differences in baseline genetic abnormalities and treatment effects between patients with poor and good PS who received osimertinib as the primary treatment.

Patients and methods This is a secondary analysis of the ELUCIDATOR study, which is a multi-center prospective observational study in Japan that assessed mechanisms underlying resistance to osimertinib as first-line treatment for advanced non-small cell lung cancer with epidermal growth factor receptor mutations.

Results There were 153 and 25 patients in the good and poor PS groups, respectively. Multivariate analysis revealed no significant between-group differences in PFS (hazards ratio [HR]: 0.98, 95% confidence interval [CI]: 0.52–1.72, $p=0.946$). Multivariate analysis of OS revealed that poor PS was a poor prognostic factor (HR: 2.67, 95% CI: 1.43–4.73, $p=0.003$). Regarding baseline genetic abnormalities, there was a significant increase in APC-positive cases (20.0% vs. 2.2%, $p=0.009$) and a trend toward more CTNNB1-positive cases in the poor PS group than in the good PS group (14.3% vs. 2.9%, $p=0.062$).

Conclusion There was no between-group difference in PFS, although OS was significantly inferior in the poor PS group. Additionally, there was a significant increase in APC-positive cases and a trend toward more CTNNB1-positive cases in the poor PS group.

Keywords EGFR mutations, Osimertinib, Overall survival, Performance status, Progression-free survival

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Introduction

The prevalence of epidermal growth factor receptor (EGFR) mutations in patients with non-small cell lung cancer (NSCLC) ranges from approximately 10–30% [1, 2]. Osimertinib is a third-generation, irreversible, oral EGFR tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI–sensitizing and EGFR p.Thr790Met (T790M) resistance mutations; further, it has shown efficacy in patients with NSCLC [3]. Among patients with treatment-naïve advanced EGFR-mutated NSCLC, osimertinib significantly prolonged overall survival (OS) compared with a first-generation EGFR-TKI [4, 5].

However, since existing phase III trials for third-generation EGFR-TKIs excluded patients with poor performance status (PS) and specific comorbidities, their results are not directly applicable to real-world settings. Several studies have indicated that osimertinib could be beneficial in patients with poor PS and EGFR T790M mutation-positive NSCLC following the progression of first- and second-generation EGFR-TKI treatments [6–8]. Moreover, several studies have evaluated the effectiveness of first-line osimertinib treatment in patients with poor PS [9–11], with inconsistent findings being reported. Additionally, no studies have compared both progression-free survival (PFS) and OS according to PS.

Co-occurring alterations in tumor suppressor genes (TSGs) affect outcomes among patients with EGFR-mutated NSCLC. These alterations, including mutations in tumor protein (TP) 53 and other TSGs, have been associated with worse outcomes in patients treated with EGFR-TKIs [12]. Furthermore, no studies have examined differences in baseline genetic abnormalities between patients with poor and good PS.

Therefore, this prospective study aimed to assess differences in baseline genetic abnormalities and treatment effects between patients with poor and good PS who received osimertinib as the primary treatment.

Table 1 Patient characteristics

*$P<0.05$	Good PS ($n=153$)	Poor PS ($n=25$)	*P*-value
Sex: Male – no. (%)	52 (34.0)	7 (28.0)	0.651
Age (range)	74 (36–91)	76 (55–86)	0.435
PS (0/1/2/3)	68/85/0/0	0/0/21/4	
Smoking: Yes – no. (%)	65 (42.5)	9 (36.0)	0.663
EGFR (L858R/Del-19)	76/77	7/18	0.053
Brain metastasis: Yes – no. (%)	40 (26.1)	8 (32.0)	0.627
Pleural effusion: Yes – no. (%)	63 (41.2)	9 (36.0)	0.667
Liver metastasis: Yes – no. (%)	13 (8.5)	4 (16.0)	0.266
Bone metastasis: Yes – no. (%)	42 (27.5)	13 (52.0)	0.019*

*$P<0.05$

PS, performance status; EGFR, epidermal growth factor receptor

Patients and methods

This study is a secondary analysis of the ELUCIDATOR study, which was a prospective observational study conducted at multiple centers of the National Hospital Organization Group in Japan. The ELUCIDATOR study evaluated resistance-related mutations and alternations of osimertinib as first-line chemotherapy for advanced NSCLC harboring EGFR-sensitizing mutations. The eligibility criteria included (i) a definitive diagnosis of non-squamous NSCLC confirmed through biopsy or cytology, (ii) the presence of EGFR mutations (exon 19 deletion or exon 21-point mutation L858R), (iii) osimertinib planned as first-line chemotherapy, and (iv) ability to provide blood specimens. Serial plasma samples were collected at baseline. Progressive disease was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1. In the present analysis, we used data regarding patient background, treatment efficacy, survival, baseline genetic abnormalities, and post-treatment. This study follows the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before the study was performed; in addition, and the National Hospital Organization Review Board for Clinical Trial approved this protocol before the start of the study. This prospective observational study was registered on December 10, 2018, in the Japanese Register of Clinical Trials (clinical Trial Number: jRCTs031180051).

Statistical analyses

Survival curves were estimated using the Kaplan–Meier method, with between-group comparisons using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model. Between-group differences in continuous and categorical variables were evaluated using the Wilcoxon rank-sum and Fisher's exact tests, respectively. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using the JMP statistical software program (14th version, SAS Institute Inc., Cary, NC) to compare clinical outcomes according to patient characteristics.

Results

There were 153 and 25 patients in the good (PS 0 and 1) and poor (PS 2 to 4) PS groups, respectively. There were no significant between-group differences in sex; age; smoking history; type of EGFR gene mutation; and proportion of patients with brain metastases, pleural effusion, or liver metastases. Bone metastases were more common in the poor PS group than in the good PS group (Table 1).

There was no significant difference in PFS between the good and poor PS groups (19.5, 95% confidence interval [CI] 17.2 to 23.3 months vs. 13.5, 95% CI 5.97 to NE months, hazards ratio [HR]: 1.09, 95% CI: 0.61–1.82,

p=0.758). The reasons for discontinuation of treatment were disease progression (n=11), treatment toxicity (n=4), and other reasons (n=3) in the poor PS group; and disease progression (n=74), treatment toxicity (n=26), and other reasons (n=6) in the good PS group. However, OS was significantly longer in the good PS group than in the poor PS group (40.9, 95% CI 32.3 to NE vs. 14.4, 95% CI 9.2 to NE months; HR: 2.51, 95% CI: 1.42–4.22, p<0.001) (Fig. 1). Multivariate analysis of PFS revealed that L858R was a poor prognostic factor (HR: 1.59, 95% confidence interval CI: 1.08–2.35, p=0.019); further, PFS tended to be shorter in patients with brain (HR: 1.48, 95% CI: 0.96–2.23, p=0.076), liver (HR: 1.88, 95% CI: 0.97–3.42, p=0.061), and bone metastases (HR: 1.45, 95% CI: 0.95–2.17, p=0.081); however, there was no significant between-group difference (HR: 0.98, 95% CI: 0.52–1.72, p=0.946) (Table 2). Multivariate analysis of OS revealed that poor PS was a poor prognostic factor (HR: 2.67, 95% CI: 1.43–4.73, p=0.003); further, OS tended to be shorter in patients with smoking history (HR: 1.75, 95% CI: 0.96–3.17, p=0.067) and L858R (HR:1.59, 95% CI: 0.98–2.57, p=0.060) (Table 3). During the observation period, 76 deaths were identified. Four deaths were treatment-related: 2 pulmonary embolisms, 1 drug-induced pneumonia, and 1 heart failure. The remaining deaths were tumor related.

The overall response rate was higher in the poor PS group than in the good PS group (76.0% vs. 53.6%, p=0.049), with the disease control rates being similar (88.0% vs. 82.4%, p=0.773).

Regarding genetic abnormalities before osimertinib treatment, there was a significant increase in APC-positive cases (20.0% vs. 2.2%, p=0.009) and a trend toward more CTNNB1-positive cases (14.3% vs. 2.9%, p=0.062) in the poor PS group than in the good PS group (Table 4).

Regarding post-treatment with osimertinib therapy, the proportions of patients who received post-treatment (28.0% vs. 40.5%), two or more post-treatments (16.0% vs. 27.5%), platinum-combination chemotherapy (20.0% vs. 31.4%), and immunotherapy (8.0% vs. 14.4%) were all lower in the poor PS group than in the good PS group (Table S1). Comparing the response to post-treatment in the poor PS and good PS groups, the response rate to platinum-combination chemotherapy was 29.17% vs. 0%, and the response rate to ICI was 31.82% vs. 0%.

Discussion

This is the first study to compare both PFS and OS among patients receiving osimertinib as first-line therapy between the good and poor PS groups. There was no significant between-group difference in PFS; however, OS was significantly inferior in the poor PS group. Notably, the response rate was rather favorable in the poor PS group. Additionally, this was the first study to examine

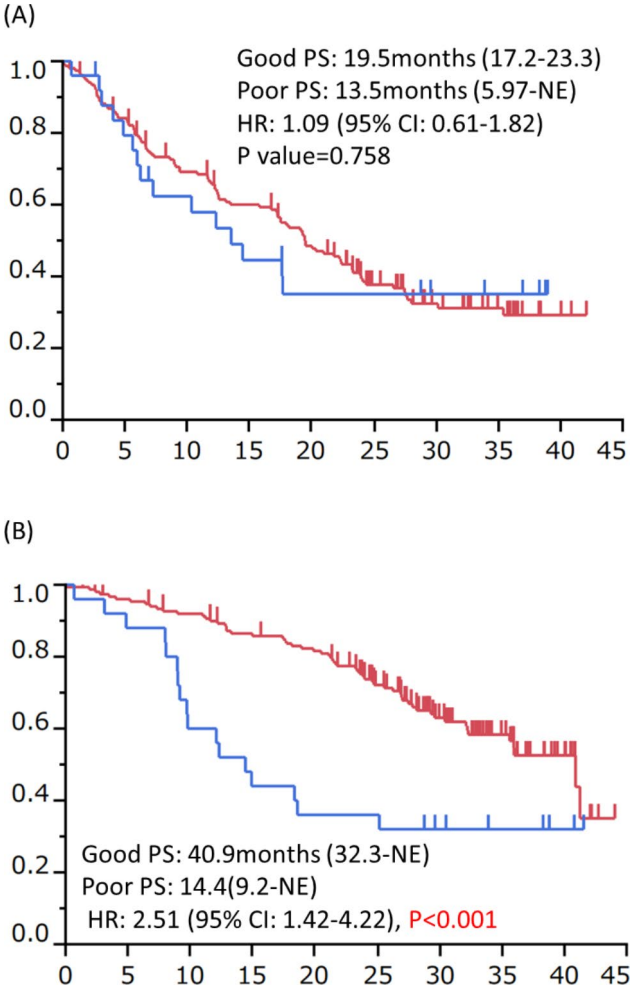

Fig. 1 Survival analysis of 178 patients with non-small cell lung carcinoma treated with osimertinib. (**a**) Progression-free survival curves of patients treated with osimertinib stratified according to the PS score. (**b**) Overall survival curves of patients treated with osimertinib stratified according to the PS score. PFS, progression-free survival; OS, overall survival; PS, performance status; HR, hazards ratio; CI, confidence interval

Table 2 Multivariate Cox proportional hazards model analysis of factors associated with progression-free survival

	HR	95% CI	*P*-value
Sex (Male)	1.20	0.71–2.03	0.498
Age (≥ 75)	1.19	0.81–1.77	0.375
PS (≥ 2)	0.98	0.52–1.72	0.946
Smoking (Yes)	1.12	0.67–1.83	0.671
EGFR (L858R)	1.59	1.08–2.35	0.019*
Brain metastasis	1.48	0.96–2.23	0.076**
Pleural effusion	1.29	0.87–1.91	0.198
Liver metastasis	1.88	0.97–3.42	0.061**
Bone metastasis	1.45	0.95–2.17	0.081**

*P<0.05, **P<0.10

HR, hazard ratio; CI, confidence interval; PS, performance status; EGFR, epidermal growth factor receptor

Table 3 Multivariate Cox proportional hazards model analysis of factors associated with overall survival

	HR	95% CI	*P*-value
Sex (Male)	1.31	0.72–2.40	0.382
Age (≥ 75)	1.42	0.89–2.27	0.138
PS (≥ 2)	2.67	1.43–4.73	0.003*
Smoking (Yes)	1.75	0.96–3.17	0.067**
EGFR (L858R)	1.59	0.98–2.57	0.060**
Brain metastasis	1.56	0.92–2.58	0.100
Pleural effusion	1.08	0.66–1.76	0.747
Liver metastasis	1.42	0.66–2.84	0.354
Bone metastasis	1.40	0.84–2.28	0.195

*$P<0.05$, **$P<0.10$

HR, hazard ratio; CI, confidence interval; PS, performance status; EGFR, epidermal growth factor receptor

Table 4 Genetic abnormality before osimertinib administration

	Good PS (*n* = 153)	Poor PS (*n* = 25)	*P*-value
TP53 (Yes/No)	56/87	11/13	0.653
EGFR amplification (Yes/No)	56/86	12/12	0.373
MET amplification (Yes/No)	21/122	4/20	0.762
ERBB2 amplification (Yes/No)	1/142	0/24	1.000
KIT (Yes/No)	2/141	0/24	1.000
MET (Yes/No)	7/136	2/22	0.619
PIK3CA (Yes/No)	6/137	2/22	0.323
CTNNB1 (Yes/No)	4/139	3/21	0.062**
APC (Yes/No)	3/139	4/20	0.009*
BRCA (Yes/No)	6/137	0/24	0.595
EGFR Compound mutation (Yes/No)	21/119	4/20	0.765

*$P<0.05$, **$P<0.10$

PS, performance status; TP, tumor protein; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; APC, adenomatous polyposis coli

differences in baseline genetic abnormalities before osimertinib treatment between patients with good and poor PS. Furthermore, there was a significant increase in APC-positive cases and a trend toward more CTNNB1-positive cases in the poor PS group.

A retrospective study of 61 patients (16 patients with poor PS) who received first-line osimertinib treatment reported that poor PS (2-4) negatively impacted PFS; however, OS was not verified [9]. Moreover, a prospective observational study on first-line osimertinib therapy in 16 patients with EGFR-mutated NSCLC who had poor PS reported that the overall objective response rate and median PFS were 56.3% and 10.5 months, respectively; further, the PS score improved in 8 of the 16 patients [10]. Furthermore, a multicenter retrospective study evaluated patients treated with osimertinib with a PS score of 2–4. In our study, we observed between-group differences in OS but not PFS. This suggests that osimertinib can be used to treat patients with poor PS and that differences in OS may have resulted from differences in post-treatment characteristics.

Among 36 patients with a PS score of 2, the median PFS, 1-year PFS, median OS, and 1-year OS were 14.5 months, 65.4%, 18.1 months, and 72.7%, respectively. Among 20 patients with a PS score of 3–4, the median PFS, 1-year PFS, median OS, and 1-year OS were 3.0 months, 27.1%, 5.0 months, and 46.1%, respectively [11]. In our study, the PFS and OS in the poor PS group were 13.5 and 14.4 months, respectively. The lack of significant between-group differences in our study could be attributed to the small sample size; however, this may have been influenced by the lower post-treatment rate in the poor PS group.

In patients with EGFR mutation-positive NSCLC, several genetic abnormalities have been shown to affect the efficacy of EGFR-TKIs. TP53 mutations, along with mutations in other TSGs such as RB1, NF1, ARID1A, BRCA1, and PTEN, have been shown to drive poor outcomes in patients with EGFR/TP53-mutated NSCLC [12]. Garon et al. identified baseline alterations co-occurring with activating EGFR in 69 genes, most commonly TP53 (43%), EGFR (other than activating EGFR; 25%), and PIK3CA (10%). Other genetic alterations included NF1 ($n=30$, 7.8%), APC ($n=27$, 7.0%), BRAF ($n=24$, 6.2%), CDK6 ($n=20$, 5.2%), and MET ($n=20$, 5.2%) [13]. In our study, there was a significant increase in APC-positive cases and a trend toward more CTNNB1-positive cases in the poor PS group. APC mutations, which result in increased intestinal epithelial cell proliferation and loss of differentiation, are crucially involved in the oncogenesis and progression of colon cancer [14, 15]. Furthermore, methylation of the APC gene promoter has been found to be higher in lung cancer tissues than in autologous controls, suggesting its importance in NSCLC carcinogenesis [16]. Moreover, APC mutations lead to the deregulation of the Wnt signaling pathway, promoting increased cell proliferation and decreased cell differentiation, which can contribute to tumor progression and metastasis. This disruption can create a more aggressive tumor phenotype, potentially diminishing the efficacy of EGFR-TKIs by fostering resistance mechanisms or by altering the tumor microenvironment [17–19]. However, there have been no previous reports regarding the role of APC in EGFR-mutated lung cancer. Aberrant activation of CTNNB1 contributes to carcinogenesis and tumor progression. Increased invasive potential of NSCLC cells in vitro has been reported with CTNNB1 co-mutation in EGFR-mutated lung cancer. This alteration is often detected at advanced stages and is involved in processes that begin late in tumor progression and dissemination [20, 21]. In addition, CTNNB1, encoding beta-catenin, is a key component of the Wnt signaling pathway. Mutations in CTNNB1 lead to the stabilization

and accumulation of beta-catenin in the cytoplasm and its subsequent translocation to the nucleus, where it activates target genes involved in cell proliferation and survival. This aberrant activation can enhance the invasive and metastatic potential of cancer cells, reducing the effectiveness of EGFR-TKIs by promoting pathways that circumvent EGFR inhibition [22–24]. Moreover, CTNNB1 mutations have been associated with poor recurrence-free postoperative survival in patients with EGFR-mutated lung adenocarcinomas [25]. Furthermore, mutations in PIK3CA and CTNNB1 are more common in advanced-stage tumors than in early-stage tumors, indicating their functional roles in malignant progression and metastasis; contrastingly, TP53, RB1, and NKX2–1 alterations appear to occur with comparable frequencies in early- and advanced-stage tumors [20, 26–29], which is consistent with our findings.

This study has several limitations. First, this study is a secondary analysis of a multicenter prospective observational study that was not designed for this study; therefore, it may have had insufficient statistical power. Second, the sample size of the poor PS group was small and did not allow sufficient comparison with the good PS group. Third, baseline genetic abnormalities were not tested in all cases due to an insufficient amount of ct-DNA.

Conclusion

We observed no significant between-group difference in PFS, although OS was significantly inferior in the poor PS group. Additionally, there was a significant increase in APC-positive cases and a trend toward more CTNNB1-positive cases in the poor PS group.

Abbreviations

EGFR	Epidermal growth factor receptor
NSCLC	Non-small cell lung cancer
OS	Overall survival
PS	Performance status
PFS	Progression-free survival
TSGs	Tumor suppressor genes
TP	Tumor protein
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03212-5.

Supplementary Material 1

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Author contributions

Yoshihiko Taniguchi, Akihiro Tamiya, Mitsuo Osuga, Shun-ichi Isa, Masahiko Ando and Yasuhiro Koh developed the study concept initiated the project. Yoshihiko Taniguchi, Akihiro Tamiya, Shun-ichi Isa, Masahiko Ando and Yasuhiro Koh coordinated protocol design. Masahiko Ando was responsible for the statistical analysis. Yoshihiko Taniguchi wrote the original draft. All authors have read and approved the final article.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

This prospective observational study was registered on December 10, 2018, in the Japanese Register of Clinical Trials (JRCT; Clinical Trial Number: jRCTs031180051). Written informed consent was obtained from all patients before the study began, and the National Hospital Organization Review Board for Clinical Trials approved this protocol prior to the start of the study.

Consent for publication

Not Applicable.

Competing interests

Taniguchi Y has received honoraria from Chugai Pharmaceutical, Ono Pharmaceutical, AstraZeneca, and MSD. Tamiya A has received honoraria from Eli Lilly, Ono Pharmaceutical, Chugai Pharmaceutical, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Amgen, Taiho Pharmaceutical, Kyowa Kirin, MSD, Takeda Pharmaceutical, Nihon-Kayaku, Novartis, Thermo Fischer, Amgen, Tsumura, Daiich-Sankyo and Merck BioFarma, and research funding from Daiichi-Sankyo, Beigene, and AstraZeneca. Harada D has received honoraria from Takeda Pharmaceutical, Eli Lilly, Chugai Pharmaceutical, AstraZeneca, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Towa Pharmaceutical, and Boehringer Ingelheim. Oki M has received Honoraria from AMCO, AstraZeneca, Canon Medical Systems, Chugai Pharmaceutical, Fujifilm Toyama Chemical, Kaneka Medix, Merit Medical Japan, Novartis Pharma, Olympus and Sanofi, and research funding from AbbVie, AstraZeneca, Chugai Pharmaceutical, Fujifilm Toyama Chemical, GlaxoSmithKline, Janssen Pharmaceutical, MSD, Ono Pharmaceutical, Parxel International, Pfizer, Sanofi. Mori M received honoraria from AstraZeneca, Boehringer Ingelheim, MSD, Eli Lilly, Novartis, Chugai Pharmaceutical, Taiho Pharmaceutical, Kyowa-kirin, Ono Pharmaceutical, Otsuka, Nihon-kayaku, Pfizer, Daiici-Sankyo, Takeda Pharmaceutical, and Shionogi and research funding from Chugai Pharmaceutical, Ono Pharmaceutical, MSD, and Delt-fly. Koh Y has received honoraria from Chugai Pharmaceutical, Guardant Health, Amgen, Takeda Pharmaceutical, and Tosoh Corporation and received consulting or advisory roles from Tosoh Corporation and research funding from Boehringer Ingelheim, AstraZeneca, Chugai Pharmaceutical, Tosoh Corporation, Daiichi Sankyo, Zeon Corporation, Amgen, and Takeda Pharmaceutical. The other co-authors received no honoraria or research funding.

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References

1. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7:78985–93. https://doi.org/10.18632/oncotarget.12587.
2. Greenhalgh J, Boland A, Bates V, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev. 2021;3:CD010383. https://doi.org/10.1002/14651858.CD010383.pub2.
3. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2016;376:629–40. https://doi.org/10.1016/j.lungcan.2018.10.027.
4. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2017;378:113–25. https://doi.org/10.1056/NEJMoa1713137.
5. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. N Engl J Med. 2020;382:41–50. https://doi.org/10.1056/NEJMoa1913662.
6. Kato Y, Hosomi Y, Watanabe K, et al. Impact of clinical features on the efficacy of osimertinib therapy in patients with T790M-positive non-small cell lung cancer and acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors. J Thorac Dis. 2019;11:2350–60. https://doi.org/10.21037/jtd.2019.06.03.
7. Nakashima K, Ozawa Y, Daga H, et al. Osimertinib for patients with poor performance status and EGFR T790M mutation-positive advanced non-small cell lung cancer: a phase II clinical trial. Invest New Drugs. 2020;38:1854–61. https://doi.org/10.1007/s10637-020-00943-0.
8. Tsubata Y, Watanabe K, Saito R, et al. Osimertinib in poor performance status patients with T790M-positive advanced non-small-cell lung cancer after progression of first- and second-generation EGFR-TKI treatments (NEJ032B). Int J Clin Oncol. 2022;27:112–20. https://doi.org/10.1007/s10147-021-02043-2.
9. Teranishi S, Sugimoto C, Nagaoka S, et al. Retrospective analysis of independent predictors of progression-free survival in patients with EGFR mutation-positive advanced non-small cell lung cancer receiving first-line osimertinib. Thorac Cancer. 2022;13:2741–50. https://doi.org/10.1111/1759-7714.14608.
10. Igawa S, Fukui T, Kasajima M, et al. First-line osimertinib for poor performance status patients with EGFR mutation-positive non-small cell lung cancer: a prospective observational study. Invest New Drugs. 2022;40:430–7. https://doi.org/10.1007/s10637-021-01195-2.
11. Takamizawa S, Okuma Y, Kato Y, Hakozaki T, Kitagawa S, Zenke Y. First-line osimertinib in EGFR mutation-positive non-small cell lung cancer patients with poor performance status. Future Oncol. 2022;18:291–300. https://doi.org/10.2217/fon-2021-0947.
12. Stockhammer P, Grant M, Wurtz A, et al. Co-occurring alterations in multiple tumor suppressor genes are associated with worse outcomes in patients with EGFR-mutant lung cancer. J Thorac Oncol. 2024;19:240–51. https://doi.org/10.1016/j.jtho.2023.10.001.
13. Garon EB, Reck M, Nishio K, et al. Ramucirumab plus Erlotinib versus placebo plus erlotinib in previously untreated EGFR-mutated metastatic non-small-cell lung cancer (RELAY): exploratory analysis of next-generation sequencing results. ESMO Open. 2023;8:101580. https://doi.org/10.1016/j.esmoop.2023.101580.
14. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990:61:759–767. https://doi.org/10.1016/0092-8674(90)90186-i
15. Szvicsek Z, Oszvald A, Szabo L, et al. Extracellular vesicle release from intestinal organoids is modulated by apc mutation and other colorectal cancer progression factors. Cell Mol Life Sci. 2019;76:2463–76. https://doi.org/10.1007/s00018-019-03052-1.
16. Hu B, Zhang H, Wei H, et al. Does adenomatous polyposis coli gene promoter 1A methylation increase non-small cell lung cancer risk? A meta-analysis. Thorac Cancer. 2017;8:410–6. https://doi.org/10.1111/1759-7714.12450.
17. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759–67. https://doi.org/10.1016/0092-8674(90)90186-I.
18. Kinzler KW, Vogelstein B, Herrup K, et al. Identification of a gene located at chromosome 5q21 that is mutated in colorectal cancers. Science. 1991;251:1366–70. https://doi.org/10.1126/science.1848370.
19. Esteller M, Fraga MF, Guo M, et al. DNA methylation patterns in hereditary human cancers mimic sporadic tumorigenesis. Hum Mol Genet. 2001;10:3001–7. https://doi.org/10.1093/hmg/10.26.3001.
20. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer. 2019;19:495–509. https://doi.org/10.1038/s41568-019-0179-8.
21. Pezzuto F, Hofman V, Bontoux C, et al. The significance of co-mutations in EGFR-mutated non-small cell lung cancer: optimizing the efficacy of targeted therapies? Lung Cancer. 2023;181:107249. https://doi.org/10.1016/j.lungcan.2023.107249.
22. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride and carboplatin/paclitaxel in advanced non–small-cell lung cancer. J Clin Oncol. 2008;23:5892–9. https://doi.org/10.1200/JCO.2005.02.7347.
23. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from never smokers and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA. 2005;101:13306–11. https://doi.org/10.1073/pnas.0405220101.
24. Dong ZY, Zhong WZ, Zhang XC, et al. Potential biomarker for checkpoint blockade immunotherapy and treatment strategy. J Thorac Oncol. 2019;14:519–27. https://doi.org/10.1016/j.jtho.2018.12.013.
25. Kim Y, Ahn B, Yoon S, et al. An oncogenic CTNNB1 mutation is predictive of post-operative recurrence-free survival in an EGFR-mutant lung adenocarcinoma. PLoS ONE. 2023;18:e0287256. https://doi.org/10.1371/journal.pone.0287256.
26. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015;5:850–9. https://doi.org/10.1158/2159-8290.CD-15-0285.
27. Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014;511:543–50. https://doi.org/10.1038/nature13385.
28. Yu HA, Suzawa K, Jordan E, et al. Concurrent alterations in EGFR-mutant lung cancers associated with resistance to EGFR kinase inhibitors and characterization of MTOR as a mediator of resistance. Clin Cancer Res. 2018;24:3108–18. https://doi.org/10.1158/1078-0432.CCR-17-2961.
29. Blakely CM, Watkins TBK, Wu W, et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. Nat Genet. 2017;49:1693–704. https://doi.org/10.1038/ng.3990.

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