TP53 mutations in circulating tumor DNA in advanced epidermal growth factor receptor-mutant lung adenocarcinoma patients treated with gefitinib

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ABSTRACT

Tumor protein p53 (TP53) is a tumor suppressor gene and TP53 mutations are associated with poor prognosis in non-small cell lung cancer. However, the in-depth classification of TP53 and its relationship with treatment response and prognosis in epidermal growth factor receptor (EGFR)-mutant tumors treated with EGFR tyrosine kinase inhibitors are unclear. Circulating tumor DNA was prospectively collected at baseline in advanced treatment-naïve EGFR-mutant lung adenocarcinoma patients treated with gefitinib in an open-label, single-arm, prospective, multicenter, phase 2 clinical trial (BENEFIT trial) and analyzed using next-generation sequencing. Survival was estimated using the Kaplan–Meier method. Of the 180 enrolled patients, 115 (63.9%) harbored TP53 mutations. The median progression-free survival (PFS) and overall survival (OS) of patients with TP53-wild type tumors were significantly longer than those of patients with TP53-mutant tumors. Mutations in exons 5–8 accounted for 80.9% of TP53 mutations. Mutations in TP53 exons 6 and 7 were significantly associated with inferior PFS and OS compared to wild-type TP53. TP53 mutation also influenced the prognosis of patients with different EGFR mutations. Patients with TP53 and EGFR exon 19 mutations had significantly longer PFS and OS than patients with TP53 and EGFR L858R mutations, and both groups had worse survival than patients with only EGFR mutations. Patients with TP53 mutations, especially in exons 6 and 7, had a lower response rate and shorter PFS and OS when treated with gefitinib. Moreover, TP53 exon 5 mutation divided TP53 mutations in disruptive and non-disruptive types.

Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80%–85% of all cases, and the primary cause of cancer-related deaths worldwide. NSCLC patients with activating epidermal growth factor receptor (EGFR) mutations usually show a high response rate to EGFR tyrosine kinase inhibitors (TKIs; e.g., gefitinib and erlotinib) and longer progression-free survival (PFS) than patients treated with standard chemotherapy [1–6]. The discovery of EGFR-TKIs was a significant advance in treating advanced lung cancer [7–9]. Three generations of EGFR-TKIs have been developed clinically: first-generation EGFR-TKIs, which include gefitinib, erlotinib, and cetinib; second-generation EGFR-TKIs, which include afatinib and dacebin; and third-generation TKIs, which target the EGFR T790M mutation, the most common mechanism of resistance to first- and second-generation EGFR-TKIs, and include osimertinib and amelatinib.

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is insufficient evidence on the prognostic value of TP53 and its correlations confer a worse prognosis (shorter PFS and OS) after treatment with TKIs and autophagy [22] that are significantly associated with the resistance to therapy and biological processes, including DNA repair, cell senescence, apoptosis, and therapeutic approaches. The molecular landscape of tumors can be analyzed by the highly sensitive and specific droplet digital PCR (ddPCR) method. Written informed consent was obtained from all participants, and we obtained approval for independent ethics experiments from each research committee. Moreover, the research was conducted in accordance with the requirements of local laws and the biomedical research general principles of the International Ethical Guidelines.

### Materials and methods

#### Study design and participants

The BENEFIT trial was an open-label, multicenter, phase 2 clinical trial in China (ClinicalTrials.gov, number NCT02282267) [23]. The inclusion criteria were as follows: age 18 to 75 years old; no previous chemotherapy or immunotherapy; histologically confirmed, stage IV lung adenocarcinoma; and EGFR mutation (exon 19 del or L858R) as assessed by the highly sensitive and specific droplet digital PCR (ddPCR) method. Written informed consent was obtained from all participants, and we obtained approval for independent ethics experiments from each research committee. Moreover, the research was conducted in accordance with the requirements of local laws and the biomedical research general principles of the International Ethical Guidelines.

#### Procedures

Qualified patients were administered oral gefitinib 250 mg/d (AstraZeneca, Macclesfield, UK) as first-line treatment until disease progression, as defined by the RECIST Version 1.1 guidelines [40]. After disease progression, patients were followed up every 12 weeks until the time of death or loss to follow-up. Blood samples were collected within 7 days before the first treatment and every 8 weeks thereafter until disease progression. We analyzed biomarkers in blood and tumor tissue samples, and samples were sent to a designated central laboratory (AmoyDx, Xiamen, China) for EGFR mutation testing. We also obtained tumor tissue during initial diagnosis or biopsy 14 days before the first treatment and stored specimens as formalin-fixed, paraffin-embedded (FFPE) samples.

We defined EGFR mutation types, including EGFR exon 19 deletions, L858R mutations by testing ctDNA by ddPCR. The EGFR mutation sequencing in FFPE tissue specimens was tested using the ADX-Amplification Refractory Mutation System. We also used a next-generation sequencing (NGS) platform [41] and a lung plasma panel (Lung Plasma, Burning Rock Biotech, Guangzhou, China) to detect additional mutations in 168 oncogenes and tumor suppressors.

### Statistical analysis

We intended to gather 180 patients in this study. The trial was closed early for futility, and the final analysis was performed on 115 patients. The original sample size was calculated to have 80% power to detect a 5-month difference in median PFS [40]. The primary endpoint was PFS. The secondary endpoints were OS, objective response (OR), disease control rate (DCR), and safety. The primary endpoint analysis was performed as futility analysis. Median (range) values for continuous variables were used. The χ²-test, Fisher’s exact test, Student’s t-test, and Wilcoxon’s rank-sum test were used to compare the proportions of patients who achieved an objective response in different subgroups (TKI and T790M co-mutations, TP53 hotexon mutations and TP53 disruptive mutations). The progression-free survival (PFS) and overall survival (OS) were estimated by using the Kaplan-Meier method. Moreover, the comparison of subgroups was performed using a Cox proportional hazards model. In the Cox model, Breslow’s approximate likelihood method was used to identify relationships between variables. All analyses were performed using SAS software (version 9.4).
gefitinib therapy, and 180 patients with EGFR mutations (179 included in the BENEFIT analysis and 1 was added after the BENEFIT analysis) and available ctDNA samples at baseline for NGS analysis were enrolled for gefitinib therapy. By the cut-off time of June 1st, 2019, 31 patients were still alive.

The proportions of EGFR exon 19 deletions (51.1%) and L858R mutations (48.9%) were similar. The average age of the patients was 59.6 years (range 33.9 to 77.3 years). Ninety-nine patients (55%) were women, and 131 (72.8%) were non-smokers. At the data cutoff date (April 1, 2020), 173 patients (96.1%) had developed disease progression and 31 (17.2%) patients were still alive before the cutoff data (June 1st, 2019). The average PFS and OS were 10.78 months (range 9.81–11.75 months) and 25.1 months (22.2–28.2 months), respectively (Table 1).

In our study, we found that there were 37 patients (32.2%) combined with smoking history among those with TP53 mutation. However, only 12 patients (18.5%) shared smoking habits in patients with TP53 wild type. Therefore, we believed that TP53 mutations in lung cancer are strongly associated with smoking status of patients.

**TP53 and EGFR co-mutations**

A total of 115 (63.9%) patients harbored TP53 mutations. We examined the location of TP53 mutations, as well as whether they were disruptive or non-disruptive. Exons 5–8 (“hot exons”) were the most common mutation sites, accounting for 80.9% of TP53 mutations. There were also mutations in exons 9 and 10 (8.7%). The sequence-specific transcriptional activity mediated by the DNA-binding domain (DBD) of p53 is the primary mechanism behind its tumor suppressor activity. The DBD is encoded by exons 5 to 8 and comprises residues 102–292.

![Figure 1](image-url)

**Fig. 1.** A: The survival trend of the patients with TP53 mutations; B: The survival trend of the patients with EGFR mutations; C: The survival trend of the patients with TP53 and EGFR co-mutations.
and intronic), (2) amino acid substitutions from one polarity/charge.

The survival trend of the patients with TP53 various exon mutations.

Table 2
Result of the comparison in different TP53 mutation types

| Types          | OS (months) | PFS (months) |
|----------------|-------------|--------------|
| TP53 exon 4    | 14.9 [95% CI 6.3–23.5] | 8.4 [95% CI 0.91–15.9] |
| (vs TP53 wild) | 0.062, HR–2.03 | 0.345, HR–1.38 |
| (95% CI 1.13–3.66) | (95% CI 0.76–2.52) |
| TP53 exon 5    | 22.2 [95% CI 16.3–28.1] | 9.3 [95% CI 6.9–11.8] |
| (vs TP53 wild) | 0.043, HR–1.79 | 0.195, HR–1.33 |
| (95% CI 1.16–2.74) | (95% CI 0.86–2.04) |
| TP53 exon 6    | 20.1 [95% CI 15.5–35.6] | 6.6 [95% CI 5.4–13.2] |
| (vs TP53 wild) | 0.002, HR–2.27 | 0.003, HR–2.17 |
| (95% CI 1.34–4.04) | (95% CI 1.27–3.58) |
| TP53 exon 7    | 21.2 [95% CI 16.0–30.4] | 7.5 [95% CI 7.13–9.63] |
| (vs TP53 wild) | 0.001, HR–2.27 | 0.003, HR–2.00 |
| (95% CI 1.36–3.63) | (95% CI 1.16–2.94) |
| TP53 exon 6–7  | 22.0 [95% CI 18.9–25.1] | 8.7 |
| (vs TP53 wild) | 0.000, HR–2.27 | (95% CI 1.45–3.27) |
| (95% CI 1.45–3.27) | (95% CI 1.05–2.92) |
| TP53 del       | 17.13 [95% CI 14.27–20.00] | 9.33 [95% CI 7.92–10.45] |
| (vs TP53 wild) | 0.000, HR – 2.287 | 0.003, HR – 1.523 |
| (95% CI 1.10–2.93) | (95% CI 1.05–2.92) |
| TP53 non-del   | 21.73 [95% CI 18.69–24.77] | 7.57 [95% CI 7.35–7.79] |
| (vs TP53 wild) | 0.001, HR – 1.941 | 0.003, HR – 1.912 |
| (95% CI 1.15–3.45) | (95% CI 1.10–2.93) |
| TP53 wild      | 31.6 [95% CI 28.4–37.8] | 13.0 [95% CI 11.1–15.0] |

The prognostic value of TP53 mutations and subtypes

TP53 mutation is predictive of poor survival

We analyzed the OS and PFS in patients with different types of TP53 mutations. Both the OS and PFS of patients with mutated TP53 were significantly lower than those of patients with wild-type TP53 (OS: 21.2 months [95% CI 17.4–23.6] vs 32.0 months, [95% CI 27.60–33.96], p < 0.001, HR = 0.54 [95% CI 0.40–0.74]; PFS: 8.4 months [95% CI 7.5–9.63] vs 12.81 months [95% CI 11.27–14.35], p = 0.007, HR = 0.66 [95% CI 0.48–0.89]. (Fig. 1A)

Fig. 2. The survival trend of the patients with TP53 various exon mutations.

Relationship between TP53 mutation and clinical efficacy of TKIs

Patients with wild-type TP53 showed a trend toward a better disease control rate (DCR) than patients with mutated TP53 but a trend toward a worse objective response rate (ORR) (DCR: 95.38% vs 67.83% and ORR: 80.00% vs 89.57%). The ORR and DCR of patients with TP53 exon 6 and 7 mutations were 90.70% and 67.00%, respectively.

We further explored the DCR and ORR of patients harboring EGFR mutations and TP53 mutations. Patients with EGFR exon 19 and TP53 mutations had a higher DCR and ORR than those with EGFR L858R mutations and TP53 mutations (DCR 80.00% vs 58.33% and ORR: 94.55% vs 86.67%). We next examined the DCR and the ORR in patients with different TP53 mutations. Those with EGFR exon 19 and TP53 hot exon mutations had the highest ORR (94.5%) and DCR (80.0%) among all the patients with TP53 mutations. The lowest ORR (87.1%) and DCR (67.0%) were observed in patients with EGFR exon 19 and TP53 non-disruptive mutations. (Table 4)

Moreover, we also found that patients with E19-TP53mut shared a significantly different DCR than those with E19-TP53wild (DCR: 80.0% vs 95.4%, p = 0.005), which means E19-TP53mut patients shared poor curative effect. We also found patients with TP53 disruptive mutations also shared better curative effect than those with TP53 non-disruptive mutations. (ORR: 94.0% vs 87.1%, p = 0.001).

Loops bind to a zinc atom and play an important role in the interaction with DNA [28,29]. Therefore, mutations in the DBD lead to accumulation of p53 in the nucleus but loss of activity. TP53 disruptive mutations included all those not classified as disruptive mutations, including mutations outside the L2 or L3 loops that substitute one amino acid residue with another of the same polarity [30,31]. Non-disruptive TP53 mutations included all those not classified as disruptive mutations, including mutations outside the L2 or L3 loops, such as missense mutations and in-frame deletions, and mutations within the L2 or L3 loops that substitute one amino acid residue with another of the same polarity [30,31]. Fifty-three patients (46.1%) had TP53 disruptive mutations, and 62 (53.6%) had TP53 non-disruptive mutations. Additionally, 13 patients (7.2%) had TP53 disruptive mutations in exon 5, and 21 patients (11.7%) had TP53 non-disruptive mutations in non-hot exons (Table 1). Forty-three patients (37.4%) had EGFR exon 19 and TP53 hot exon mutations, and 50 patients (43.5%) had EGFR L858R and TP53 hot exon mutations.

The prognostic value of EGF and TP53 co-mutations

Of the 180 patients with EGFR mutations, 92 harbored EGFR exon 19 deletions and 88 harbored EGFR L858R mutations. There was no significant difference in PFS between EGFR exon 19 deletions and EGFR L858R mutations (11.0 months [95% CI 9.20–12.68] vs 9.2 months [95% CI 7.06–11.14], p = 0.18, HR = 0.8 [95% CI 0.57–1.11]). However, there was a significant difference in OS between the two groups (26.8 months [95% CI 24.85–30.28] vs 21.5 months [95% CI 20.43–25.92], p = 0.039, HR = 1.37 [95% CI 1.02–1.84]). Conversely, patients harboring EGFR exon 19 mutations and TP53 mutations had a longer PFS and OS than those with EGFR L858R mutations and TP53 mutations (PFS 9.47 months [95% CI 9.07–10.45] vs 7.17 months [95% CI 5.57–9.3], HR = 1.532 [95% CI 1.06–2.22]; OS 22.6 months [95% CI 19.9–25.3] vs 17.2 months [95% CI 13.59–20.81], p = 0.369, HR = 0.769) (Fig. 1C).
Fig. 3. The survival trend of TP53 disruptive mutation and TP53 non-disruptive mutation compared with TP53 wild type.

Table 3
TP53 disruptive mutations redivided by TP53 disruptive and non-disruptive mutations.

| Types                  | No. of patients (%) | PFS (months)          | OS (months)          |
|------------------------|---------------------|-----------------------|----------------------|
| TP53 disruptive        |                     |                       |                      |
| (N=53, 3 of them shared exon co-mutations) |                     |                       |                      |
| exon4                  | 8 (15.1%)           | 5.2 (95%CI 0.0-11.3)  | 15.0 (95%CI 2.8-27.0) |
| exon5                  | 13 (24.5%)          | 9.3 (95%CI 5.2-13.4)  | 14.5 (95%CI 8.4-20.5) |
| exon6                  | 11 (20.8%)          | 7.5 (95%CI 5.2-9.7)   | 17.1 (95%CI 9.9-24.2) |
| exon7                  | 14 (26.4%)          | 9.1 (95%CI 7.1-11.1)  | 17.1 (95%CI 9.2-25.1) |
| exon8                  | 2 (3.8%)            | 1.9 (95%CI ——)        | 17.2 (95%CI ——)      |
| exon 9&10              | 8 (15.1%)           | 11.3 (95%CI 10.9-11.7) | 23.6 (95%CI 17.9-29.4) |
| TP53 non-disruptive    |                     |                       |                      |
| (N=62, 1 of them shared exon co-mutations) |                     |                       |                      |
| exon4                  | 6 (9.7%)            | 11.1 (95%CI 1.2-21.0) | 13.4 (95%CI 0.0-28.0) |
| exon5                  | 21 (33.9%)          | 9.3 (95%CI 6.7-11.9)  | 24.1 (95%CI 15.9-32.3) |
| exon6                  | 8 (12.9%)           | 5.6 (95%CI 0.0-11.4)  | 21.0 (95%CI 12.4-29.5) |
| exon7                  | 12 (19.4%)          | 7.4 (95%CI 7.0-7.8)   | 17.0 (95%CI 9.0-25.1) |
| exon8                  | 14 (22.6%)          | 3.8 (95%CI 0.0-11.0)  | 19.3 (95%CI 3.8-34.8) |
| exon 9&10              | 2 (3.2%)            | 0.7 (95%CI ——)        | 2.6 (95%CI ——)       |
The influence of TP53 exon mutation on prognosis

Because most of the TP53 mutations were found in exons 5–8, we examined differences in survival in patients with TP53 exon 5–8 mutations. Ninety-three patients had mutations in TP53 exons 5–8, including 34 patients with mutations in exon 5, 19 with mutations in exon 6, 27 with mutations in exon 7, and 17 with mutations in exon 8 (4 patients had two TP53 mutations) (Table 1, Fig. 6). Patients with mutations in exons 6 or 7 had a significantly shorter OS and PFS than patients with wild-type TP53, the result had been shown. (Fig. 2, Table 2)

TP53 disruptive mutations decrease OS

We next examined the association between prognosis and disruptive/non-disruptive mutations in TP53. Patients were divided into three groups: those with disruptive TP53 mutations, those with non-disruptive TP53 mutations, and those with wild-type TP53. When compared with wild-type patients, patients with both disruptive and non-disruptive mutations had a significantly shorter OS and a shorter PFS (Table 2, Fig. 3). However, there was no difference in survival between patients with disruptive and non-disruptive mutations (OS 17.13 months [95% CI 14.27–20.00] vs 21.73 months [95% CI 18.69–24.77], p = 0.466 and PFS 9.33 months [95% CI 7.92–10.45] vs 7.57 months [95% CI 7.35–7.79], p = 0.469) (Fig. 3).

EGFR and TP53 co-mutations when combined with other mutations shared worse prognosis

As described above, TP53 mutations are associated with worsened OS and PFS. Therefore, we further analyzed patients with EGFR-TP53 co-mutations and other mutations (RB1 and PTEN mutations) and found that patients with EGFR-TP53-other mutations had a shorter OS and PFS than those with EGFR-TP53 co-mutations alone (EGFR-TP53 co-mutations vs EGFR-TP53-other mutations: OS 20.97 months [95% CI 17.44–24.50] vs 12.50 months [95% CI 5.58–19.419], p = 0.029, HR = 0.527 [95% CI 0.309–0.897]; PFS 8.23 months [95% CI 6.78–9.69] vs 3.70 months [95% CI 6.24–8.90], p<0.001, HR = 0.332 [95% CI 0.192–0.571]) (Fig. 5B).

Table 4
The comparison of the ORR in various TP53 mutations.

| Types                   | ORR   | DCR   |
|-------------------------|-------|-------|
| TP53 wild-type          | 80.00%| 95.38%|
| TP53 mutations          | 89.57%| 67.83%|
| TP53 exon 6 and 7 mutations | 90.70%| 67.00%|
| E19-TP53 hotexon mutations | 94.5%  | 80.0%  |
| E19-TP53 mutations      | 94.55%| 80.00%|
| E21-TP53 mutations      | 86.67%| 58.33%|
| E19-TP53 non-disruptive | 87.1%  | 67.0%  |

Fig. 4. The difference of patients with TP53 disruptive/non-disruptive and TP53 various exon mutations.
The BENEFIT trial was the first clinical trial to demonstrate the value of using ctDNA circulating in plasma to detect EGFR mutations and identify patients that might benefit from EGFR-TKIs therapy [23]. Compared with the detection of solid tumor tissue, the detection of ctDNA in blood has the following advantages: firstly, it overcomes the heterogeneity of tumor and can evaluate the tumor mutation completely. Secondly, it is easy to dynamically follow up the mutations of tumor gene. Finally, the sample is convenient for biopsy, which can reduce the damage caused by tissue puncture biopsy. This was a novel approach compared to the most of previous studies which detected biomarkers by sequencing solid tumor tissue [30,32,34], and this may partly explain the conflicting results regarding the value/efficacy of

**Fig. 5.** A: The influence of exon 5 in divided patients with TP53 disruptive and non-disruptive mutations. B: The survival trend of patients with EGFR-TP53 co-mutations and EGFR-TP53-other co-mutations.

**Fig. 6.** The proportion of patients with TP53 exon mutations.

**Discussion**

The BENEFIT trial was the first clinical trial to demonstrate the value of using ctDNA circulating in plasma to detect EGFR mutations and identify patients that might benefit from EGFR-TKIs therapy [23]. Compared with the detection of solid tumor tissue, the detection of ctDNA in blood has the following advantages: firstly, it overcomes the heterogeneity of tumor and can evaluate the tumor mutation completely. Secondly, it is easy to dynamically follow up the mutations of tumor gene. Finally, the sample is convenient for biopsy, which can reduce the damage caused by tissue puncture biopsy. This was a novel approach compared to the most of previous studies which detected biomarkers by sequencing solid tumor tissue [30,32,34], and this may partly explain the conflicting results regarding the value/efficacy of
treatment with EGF-R-TKIs. For example, previous studies have sug-
ggested that TP53 mutation adversely affects patient survival, but
this was not consistently demonstrated in our study population. VanderLaan et al. [29] suggested that TP53 mutation decreases the response rate to
EGFR-TKIs, and the ORR of patients with wild-type TP53 is longer than
that of patients with mutant TP53. However, other groups have found no
prognostic benefit of TP53 mutation in patients who received TKIs [33, 34]. Furthermore, various types of TP53 mutations have different
prognostic values. Jiao et al. [32] suggested that patients with mutations in
the TP53 coding region have a lower OS than patients with TP53 wild
type (with rare mutations at exons 2, 3, and 10). They also suggested that
TP53 exon 7 mutations were correlated with a moderate prognosis and
TP53 exon 6 mutations with a poor prognosis.

It is worth to mention that our study had some controversial results
which were inconsistent with the results of previous studies based on
sequencing solid tumor tissue. First, we found that TP53 mutation had
independent prognostic value for the OS of patients harboring EGFR
exon 19 del and L858R mutations. Further, our study also demonstrated
that TP53 mutations (hot spot mutations, disruptive and non-disruptive
mutations, and co-mutations) all have prognostic value in patients with
stage IIIA, IIIB, and IV cancer treated with gefitinib, and the clinical ef-
ficacy was significant. We believed that TP53 mutations are important
determinants of poor survival, which is different from the results of
previous studies [33,34]. Regarding mutations in different TP53 exons,
we found that patients with mutations in TP53 exon 6 & 7 had a signifi-
cantly poorer survival than patients with TP53 wild. We also found that
exon 5 mutations were an independent factor influencing the prognosis
of patients with disruptive and non-disruptive TP53 mutations.

Targeted therapy and immunotherapy are the main treatments
with proven efficacy for NSCLC. Wu et al. [35] indicated that
stage-differential gene signatures can identify TP53 mut and TP53 wild
patients to determine those best suited for immunotherapy. Other
groups have also demonstrated that patients with TP53 and Kras
co-mutation could benefit from PF-1 therapy [36,37]. In our study, we
assessed the long-term efficacy of immunotherapy. However, drugs
targeting TP53 currently only target specific sites, and therefore ther-
apeutic options are relatively limited. Based on our results, we propose
that the efficiency of single-targeted therapy is poor, and patients with
different co-mutation types should be administered combined therapy.
Many studies indicated that combined therapy might lead to a better
outcome [38,39]. Therefore, a prospective clinical trial is conducting in
our research group. It is a phase III, multicenter, randomized controlled
clinical trial that subdivided patients with co-mutations into 2 groups
(one of the groups continued targeted inertial chemotherapy and the
other one received combined chemotherapy), mainly focused on PFS
and less emphasized on ORR, AE side reaction, which has been planned
to investigate targeted therapy for patients with different TP53
co-mutation states.

This study has some limitations. Firstly, the study population was
small, and some of the subgroups shared several patients. Future studies
with a larger sample population are warranted to validate the results
described in this study. Secondly, we were unable to fully elucidate the
mechanisms of drug resistance, which may be due to the NGC test with
limited target locations. Thirdly, our results may have been influenced
using different types of samples and cancer stages. Finally, these results
should be validated in clinical studies.

In conclusion, by sequencing ctDNA in plasma, we demonstrate that
EGFR mutation and EGFR mutations combined with various TP53 mu-
tation types affect patient prognosis. Confirming the patient’s mutation
status prior to treatment may optimize treatment response and reduce
the emotional and financial strain of treatment failure.

Declaration of Competing Interest

None.

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Statement of translational relevance

We conducted a study examining concomitant TP52 mutations in
patients with EGFR-mutated NSCLC to explore the difference in response
to EGFR-TKI treatment under different TP53 co-mutation states. We
assessed the long-term efficacy of immunotherapy. However, drugs
targeting TP53 currently only target specific sites, and therefore ther-
apeutic options are relatively limited. Based on our results, we propose
that the efficiency of single-targeted therapy is poor, and patients with
different co-mutation types should be administered combined therapy.
This study demonstrates that TP53 and EGFR mutation status affects the
survival of patients with lung cancer treated with gefitinib. Confirming
the patient’s mutation status prior to treatment may optimize treatment
response and reduce the emotional and financial strain of treatment
failure.

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