Concurrent TP53 mutations predict a poor prognosis of EGFR-mutant NSCLCs treated with TKIs: An updated systematic review and meta-analysis

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Abstract. The prognostic value of tumor protein P53 (TP53) mutation for tyrosine kinase inhibitor (TKI) treatment in EGFR-mutant non-small-cell lung cancer (NSCLC) remains controversial. Therefore, the present meta-analysis was performed to investigate the potential association between the prognosis of TKI treatment for patients with advanced EGFR mutation-positive NSCLC and the presence or absence of concurrent TP53 mutations. In the present study, 24 eligible studies from the PubMed, Embase and Cochrane databases were identified by screening prior to inclusion. Data were extracted by two independent investigators and analyzed using STATA 14.0 software. Pooled odds ratios (ORs) with 95% confidence interval (CIs) were used to determine the association between objective response rates (ORRs) and TP53 mutations. In addition, differences in the incidence of TP53 mutations between patients with exon 21 L858R mutations and exon 19 deletions of EGFR were evaluated using this method. Pooled hazard ratios (HRs) with 95% CIs were used to calculate the prognostic value of TP53 mutations for progression-free survival (PFS) and overall survival (OS). No significant difference in the incidence of TP53 mutations was detected between the patients with exon 21 L858R mutation and those with exon 19 deletion (OR=0.91; 95% CI=0.65-1.27; P=0.568). However, the pooled results revealed that TP53 mutations were significantly associated with shorter PFS (HR=1.51; 95% CI=1.33-1.71; P<0.001) and OS (HR=1.64; 95% CI=1.33-2.02; P<0.001). By contrast, TP mutations were not associated with the ORR of EGFR-TKI treatment (OR=0.91; 95% CI=0.69-1.21; P=0.529). In conclusion, a worse prognosis for TKI treatment was observed in patients with EGFR-mutant NSCLCs and concurrent TP53 mutations, suggesting that TP53 mutations is associated with primary resistance to EGFR-TKIs.

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Abbreviations: TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; NGS, next-generation sequencing; ctDNA, circulating tumor DNA

Key words: EGFR, TKIs, NSCLC, TP53

Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide, with 40-50% of patients already at advanced stages (IIIB or IV) when first diagnosed, which precludes surgical resection (1). Non-small cell lung cancer (NSCLC) is the most common histological phenotype of lung cancer, accounting for 80-85% of all patients with lung cancer. EGFR is one of the most frequently observed drivers of NSCLC, with ~50% of Asian and 11.9-33.0% of non-Asian patients harboring activating EGFR mutations (2). Over the past decade, molecular-targeted therapy has greatly improved the prognosis of patients with NSCLC carrying EGFR mutations (3-5). In particular, tyrosine kinase inhibitors (TKIs) that can target activated EGFR, particularly those cases caused by exon 19 deletion and/or exon 21 L858R point mutations, are recommended as the standard therapeutic option for the management of NSCLCs positive for EGFR mutations according to the clinical guidelines of the National Comprehensive Cancer Network (6).

Although EGFR-TKIs exert strong efficacy in NSCLCs with EGFR mutations, 20-30% of EGFR-mutant NSCLCs eventually develop resistance to this treatment, while highly variable outcomes are observed in EGFR-TKI responders (7). In particular, certain responders may benefit for years, whilst others suffer from disease progression and recurrence within weeks. Therefore, the presence of non-responders and the heterogeneous prognosis of responders demonstrate that EGFR-TKI monotherapy is not always the optimal treatment strategy for EGFR-mutant NSCLCs. Further studies focusing on the genomic landscape of NSCLC are necessary to identify additional mechanisms of TKI resistance. However, there is evidence to suggest that multiple concurrent genetic alterations resulting in inhibitory PTEN mutations, increased programed death-ligand 1 expression, MET alterations, Bcl-2-like protein gene polymorphisms and/or PI3K/AKT pathway activation, are associated with primary resistance to EGFR-TKI treatment (8,9).

The p53 protein is a tumor suppressor that is encoded by the tumor protein p53 (TP53) gene and is a master regulator of cellular processes, including DNA damage response, DNA repair, cell-cycle arrest, cell senescence and apoptosis, which suppresses tumorigenesis (10). Under physiological conditions, wild-type p53 protein is a stress-responsive transcription factor with a sequence-specific DNA-binding domain, two N-terminal transactivation domains and an oligomerization domain required for transcriptional activity (11). When DNA damage occurs, the DNA damage response is triggered by the activation of ataxia-telangiectasia mutated (ATM) or Rad3-related protein (ATR) kinases. The activated ATM and/or ATR kinases then phosphorylate wild-type p53 protein via checkpoint kinase (CHK)1 and CHK2, respectively. Phosphorylated p53 recognizes specific promoter sites and halts the cell cycle at the G_1 phase via the transcriptional activation of cyclin-dependent kinase inhibitor 1A (11). This inhibits the process of cell division when DNA damage occurs, thereby preventing the proliferation of genetically unstable cells and transformation to a potentially cancerous phenotype (10). TP53 has been recognized as one of most frequently mutated genes in various types of human cancer. In particular, ~73% of the somatic TP53 alterations detected in all types of malignancies are missense mutations (12). TP53 missense mutations can disrupt the biological function of the p53 DNA-binding domain by blocking its ability to transcriptionally activate downstream target genes (12). In patients with NSCLC, co-existing TP53 mutations have been detected in 55-65% of EGFR mutation-positive cases; they are particularly prevalent in individuals who smoke and highly associated with the histological type of squamous cell carcinoma (13-16). Deleterious mutant p53 proteins acquire oncogenic properties that promote the proliferation, invasion, survival and metastasis of cancer cells (17). Consequently, alterations to the TP53 genetic structure are proposed to serve a key role in the clinical and molecular heterogeneity of oncogene-driven lung cancer subgroups, due to their effects on drug resistance and genomic instability (18).

Although previous studies have reported that mutant TP53 can be used to predict inferior clinical outcomes with trends of lower objective response rates (ORRs) and shorter progression-free survival (PFS) and overall survival (OS) after initial treatment with TKIs, ambiguities remain in the epidemiological data. Almost all previous studies on this subject are cohort studies with a small number of included cases. Although the cohort studies may have low heterogeneity with regard to the included cases, the relatively small number of cases in these studies limits their results and conclusions, which are therefore inconsistent. For example, Yu *et al* (19) found that TP53 mutations were not significantly associated with PFS, despite predicting a shorter OS in patients treated with gefitinib. By contrast, Tsui *et al* (20) reported that TP53 mutations were significantly associated with a shorter OS but did not alter the PFS following EGFR-TKI treatment.

Therefore, the present meta-analysis was performed to investigate the potential association between the prognosis of TKI treatment for patients with advanced EGFR mutation-positive NSCLCs and the presence or absence of concurrent TP53 mutations.

Materials and methods

Search strategy. All relevant articles published on dates prior to and including January 30, 2022 were searched for in the PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (www.embase.com) and Cochrane databases (www.cochrane.org) using a combination of 'lung cancer' and 'EGFR' and 'TP53' with associated terms (Tables SI-III). The present meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology checklist (21). The abstracts of the identified articles were screened before assessment of the corresponding full texts of the eligible articles using the inclusion/exclusion criteria.

Inclusion and exclusion criteria. Potentially eligible studies were required to meet the following criteria: i) All included patients were pathologically diagnosed with advanced NSCLC and surgery was no longer an option; ii) EGFR mutation was confirmed by gene sequencing methods; iii) patients were treated with EGFR-TKIs regardless of the line of treatment; iv) the status of the TP53 gene was analyzed by gene sequencing methods; and v) at least one set of survival and associated prognostic data was presented in the study. The mandatory types of survival or prognostic data were the PFS or OS for the TP53 mutant group vs. the TP53 wild-type group presented as hazard ratios (HRs) with associated 95% confidence intervals (CIs) or Kaplan-Meier (KM) curves, or ORRs in the TP53 mutant and wild-type TP53 groups.

Studies were excluded if they met the following criteria: i) Non-original research studies, such as reviews, editorials or expert opinions; ii) insufficient data for the extraction or calculation of ORRs or HRs with 95% CIs; iii) the status of the TP53 gene was not analyzed using a gene sequencing method; iv) EGFR-TKIs were used for postoperative adjuvant therapy; v) duplicate publications; vi) not published in the English language; and vii) studies with low quality.

Study selection and data abstraction. Two independent investigators (BLa and NZ) reviewed the titles, abstracts and full-texts of all potential studies. A third investigator (BLe) was responsible for resolving any disagreements between the first two investigators. Information was extracted from each eligible paper, including the name of the first author, publication year, country, type of study, EGFR-TKI used, histological type, EGFR mutation profile, line of TKI treatment, methods of TP53 detection, detected exons of TP53, samples extracted for TP53 detection, clinical outcomes and the number of patients with EGFR and/or TP53 mutations. Since exon 21 L858R mutation and exon 19 deletion are the most frequent genotypes of EGFR mutations, the number of patients concurrently harboring at least one of these mutations along with mutant TP53 was also recorded from each paper to investigate the incidence of TP53 mutations among these two genotypes with mutant EGFR genes. ORR data was extracted from the number of patients exhibiting a complete response (CR) and partial response (PR) in the TP53 mutation and wild-type TP53 groups, respectively. PFS and OS data were measured as HRs with 95% CIs for the TP53 mutant group vs. the wild-type TP53 groups. In addition, HRs estimated using multivariate models were selected if PFS or OS were both analyzed using univariate and

multivariate models. If the HR with 95% CI was not reported in the original article, the KM curves were digitized using Engauge Digitizer 4.1 software (http://markummitchell.github.io/engauge-digitizer/) prior to recalculation of the HR using the approach previously described by Guyot *et al* (22). To ensure consistency in the collected results, each recalculated HR was evaluated twice independently (BLa and NZ).

Quality appraisal. Quality appraisal was conducted using the Newcastle-Ottawa Scale (NOS) and performed by two independent investigators (BLa and NZ). The NOS evaluates the quality of each included study from the perspectives of 'selection', 'comparability' and 'outcome' to provide a maximum total score of 9 points (23). Based on the final score, the quality of each included study was classified as follows: High quality (score ≥7); medium quality (7> score ≥5)'; and low quality (score <5). Low quality indicates potential bias and confounding in the study. Since the inclusion of such studies in the analysis may affect the accuracy of the results, studies categorized as low quality were excluded.

Statistical analysis. The primary outcomes assessed for the present meta-analysis were ORR, PFS and OS. ORR was defined as the percentage of patients who exhibited CR or PR. PFS was defined as the period from the initiation of EGFR-TKI treatment until disease progression, recurrence or mortality. OS was defined as the period from the initiation of EGFR-TKI treatment to mortality. Pooled HRs with 95% CIs were used to assess the association between TP53 status and survival outcomes (PFS and OS). The pooled odds ratios (ORs) with 95% CIs were used for comparing the ORR between TP53 mutation-positive and -negative groups, in addition to the frequency of TP53 mutation between patients harboring EGFR exon 21 L858R mutation and/or EGFR exon 19 deletion.

Statistical heterogeneity among the included studies was measured using the χ^2-based Q-test, where a Q-test yielding P≤0.10 and/or an I^2-value of >50% was considered to indicate the existence of significant heterogeneity (24). A random-effects model was used to calculate the pooled OR or HR if significant heterogeneity was detected. Otherwise, a fixed-effects model was applied. Subgroups were stratified according to the type of study, histological type, genotype of mutant EGFR, line of TKI treatment, method of TP53 detection, detected exons of TP53 and type of samples used for TP53 detection. In the present study, all data synthesis was two-sided, where P≥0.05 or 95% CI crossing 1.00 was not considered to be statistically significant.

For the evaluation of publication bias, Begg's funnel plots and Egger's tests were performed. Egger's tests yielding P≤0.10 were considered to suggest potential publication bias. All data synthesis and analysis was performed using STATA 14.0 software (StataCorp LP).

Results

Study selection. In total, 941 relevant records were identified in the PubMed, Embase and the Cochrane library databases by January 30, 2022. Following screening of the titles and abstracts, 863 records were excluded and 78 full texts were reviewed. Finally, 24 studies involving a total of 2,227 patients with EGFR-mutant NSCLC met the inclusion criteria and were included in the present meta-analysis (Fig. 1).

Characteristics of the included studies. The characteristics of each included study are summarized in Table I. Of the included studies, six were conducted as prospective studies and 18 were retrospective in design. In total, 14 cohorts included patients who received EGFR-TKIs as the first-line treatment only, two cohorts included patients with at least one prior treatment, and nine cohorts analyzed patients receiving EGFR-TKIs as the first, second or further line of treatment.

Among the 2,227 patients who underwent TP53 gene sequencing, alterations in the TP53 gene were detected in 1,091 cases. For efficacy evaluation, 8 included studies provided ORR data, 20 studies reported PFS endpoints and 18 studies reported OS endpoints. The majority of the studies (17/24) used next-generation sequencing (NGS) as the sequencing method for detecting the status of the TP53 gene. The samples used for TP53 gene sequencing were tissue in 16 studies, both tissue and plasma in seven studies and plasma in one study.

Study quality. The results of quality appraisal as assessed using the NOS are shown in Table SIV. According to the final scores, 20 studies were classified as high quality, whilst the remaining four studies were classified as medium quality. Low quality indicates the presence of potential bias and confounding in the study. Therefore, no studies classified as low quality were included in the present analysis.

Associations between TP53 mutations and genotypes of mutant-EGFR. Exon 21 L858R mutation and exon 19 deletion are the most frequently found genotypes of EGFR mutations. Although more than eight studies included patients with the genotypes of EGFR Exon 21 L858R mutation and exon 19 deletion (Table II), only eight studies with nine cohorts included available data to calculate statistical significance of the incidence of TP53 mutations in these two genotypes. Among the 669 patients from the eight studies, the incidence of TP53 mutations in the exon 21 L858R mutation group was 53.82% (148/275), whilst the incidence of TP53 mutations in the exon 19 deletion group was 50.76% (200/394). No statistically significant difference in the incidence of TP53 mutations between these two groups was identified (OR=0.91; 95% CI=0.65-1.27; P=0.568; Fig. 2A). Q-test and I^2 analysis revealed no significant heterogeneity among the eight included studies (I^2=0%; P=0.803). Publication bias was not detected by Egger's test (P=0.386) or Begg's funnel plot (Fig. 3A).

Associations between concurrent TP53 mutations and ORR. The analysis of ORR was obtained from eight eligible studies with nine cohorts. The overall ORR to EGFR-TKI treatment was 62% (95% CI=51-73%) and 63% (95% CI=51-75%) in the mutant TP53 and wild-type TP53 groups, respectively. However, this difference in ORRs was not found to be statistically significant (OR=0.91; 95% CI=0.69-1.21; P=0.529; Fig. 2B). Statistically significant heterogeneity was not identified in this analysis (I^2=0%; P=0.508). Egger's test (P=0.265) and Begg's funnel plot (Fig. 3B) indicated the absence of publication bias. The results of specific subgroup analyses are shown in Table III, which reveal no significant associations

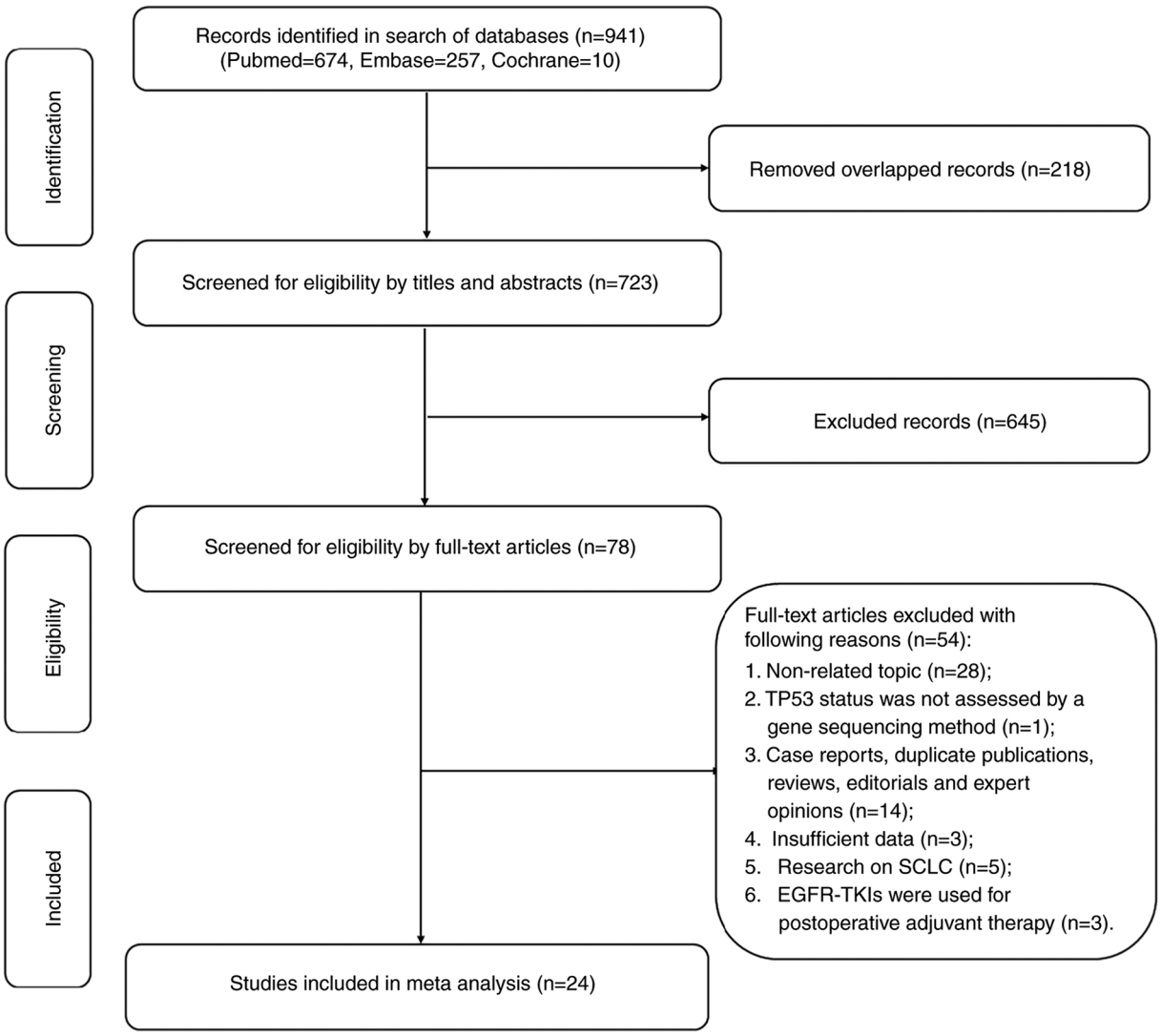

Figure 1. Flow diagram of the literature selection procedure.

between concurrent TP53 mutations and ORR among the subgroups.

Associations between concurrent TP53 mutations and PFS. The association between concurrent TP53 mutations and PFS was analyzed using the data from 20 eligible studies with 22 cohorts. No statistically significant heterogeneity was observed among these studies (I^2=15.0%; P=0.260). Patients with concurrent TP53 mutations showed a significantly shorter PFS (HR=1.51; 95% CI=1.33-1.71; P<0.001) following EGFR-TKI treatment (Fig. 2C). Among the included studies, publication bias was not detected by Egger's test (P=0.304) or Begg's funnel plot (Fig. 3C).

Subgroup analysis suggested that prospective (HR=1.32; 95% CI=1.02-1.72; P=0.036) and retrospective (HR=1.57; 95% CI=1.36-1.81; P<0.001) studies demonstrated that TP53 mutations were significantly associated with a shorter PFS. In terms of histological types, concurrent TP53 mutations predicted a shorter PFS in patients with lung adenocarcinoma (HR=1.54; 95% CI=1.34-1.77; P<0.001) and NSCLC (HR=1.36; 95% CI=1.02-1.81; P=0.036). With the respect to the line of TKI treatment, TP53 mutations were significantly associated with a higher risk of disease progression after first-line (HR=1.37; 95% CI=1.16-1.62; P<0.001), all lines (HR=1.63; 95% CI=1.33-1.99; P<0.001) and second line or further EGFR-TKI treatments (HR=2.21; 95% CI=1.33-3.67; P=0.002). Whenever mutations were detected in exons 5-8 (HR=1.35; 95% CI=1.03-1.77; P=0.031) or exons 2-11 (HR=1.64; 95% CI=1.26-2.12; P<0.001), PFS was significantly shorter in the TP53 mutant cohorts. However, the predictive value for PFS of TP53 mutations detected in both tissue and plasma specimens (HR=1.18; 95% CI=0.93-1.49; P=0.164) were not in concordance with TP53 mutations detected in tissue specimens alone (HR=1.66; 95% CI=1.42-1.92; P<0.001).

Association between concurrent TP53 mutations and OS. In total, 18 studies with 20 cohorts were included in the present analysis. Pooled results with a random-effects model demonstrated a significantly shorter OS in patients harboring concurrent TP53 mutations treated with EGFR-TKIs (HR=1.64; 95% CI=1.33-2.02; P<0.001; Fig. 2D). Significant heterogeneity was observed among the included studies (I^2=53.3%; P=0.003). Begg's funnel plot (Fig. 3D) and Egger's test (P=0.183) indicated no publication bias.

Table I. Basic characteristics of the included studies.

First author, year	Country	Type of study	Histological type	Patients included	Patients with EGFR mutations	Patients with TP53 mutations	TKIs	Line of TKI treatment	Outcomes	(Refs.)
CLCGP, 2013	Europe, Austria	Retrospective	NSCLC	1,225	80	27	Gefitinib, erlotinib	1st/≥2nd	OS	(43)
Molina-Vila, 2014	Spain	Retrospective	Adenocarcinoma	193	193	50	Gefitinib, erlotinib	1st/≥2nd	ORR, OS	(44)
Bria, 2015	Italy	Retrospective	Adenocarcinoma	18	18	6	Gefitinib	1st	PFS	(45)
Canale, 2017	Italy	Retrospective	Adenocarcinoma (98%)	123	123	37	Gefitinib, erlotinib, afatinib, dacomitinib	1st	PFS, OS	(46)
VanderLaan, 2017	USA	Retrospective	Adenocarcinoma	171	16	7	Gefitinib, erlotinib, afatinib	1st	PFS	(47)
Labbé, 2017	Canada	Retrospective	Adenocarcinoma (95%)	105	60	24	Gefitinib, erlotinib, afatinib	1st/≥2nd	ORR, PFS, OS	(32)
Tsui, 2018	UK	Prospective	NSCLC	50	30	12	Gefitinib	1st	ORR, PFS, OS	(20)
Aisner, 2018	USA	Prospective	Adenocarcinoma	904	60	34	Not reported	1st/≥2nd	OS	(48)
Aggarwal, 2018	USA	Retrospective	Adenocarcinoma	131	131	81	Not reported	1st	OS	(49)
Yu, 2018	USA	Retrospective	Adenocarcinoma	374	200	119	Erlotinib, dacomitinib, afatinib	1st/≥2nd	PFS, OS	(50)
Kim, 2019	Korea	Retrospective	Adenocarcinoma (98%)	307	157	101	Cohort 1: Gefitinib, erlotinib, afatinib; Cohort 2: osimertinib, olmutinib	Cohort 1: 1st; Cohort 2: ≥2nd	PFS, OS	(51)
Chang, 2019	China	Retrospective	Adenocarcinoma	33	33	10	Gefitinib, erlotinib, afatinib	1st	PFS, OS	(52)
Hou, 2019	China	Retrospective	Adenocarcinoma (96%)	163	71	43	Gefitinib, erlotinib, icotinib	1st/≥2nd	PFS, OS	(53)

Table I. Continued.

First author, year	Country	Type of study	Histological type	Patients included	Patients with EGFR mutations	Patients with TP53 mutations	TKIs	Line of TKI treatment	Outcomes	(Refs.)
Rachiglio, 2019	Italy	Retrospective	NSCLC	133	133	23	Gefitinib, erlotinib, afatinib	1st	PFS, OS	(54)
Canale, 2020	Italy	Retrospective	NSCLC	136	136	42	Gefitinib, erlotinib, afatinib	1st	ORR, PFS, OS	(41)
Cheng, 2020	China	Retrospective	Adenocarcinoma (99%)	179	76	53	Gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, avitinib	1st	PFS, OS	(55)
Li, 2021	China	Retrospective	Adenocarcinoma (96%)	195	195	134	Gefitinib, erlotinib	1st/≥2nd	ORR, PFS, OS	(56)
Steendam, 2020	The Netherlands	Prospective	NSCLC	41	41	23	Erlotinib, osimertinib	1st/≥2nd	PFS	(57)
Yang, 2021	China	Retrospective	Adenocarcinoma (97%)	62	50	37	Osimertinib	1st/≥2nd	PFS	(58)
Yu, 2021	China	Prospective	Adenocarcinoma	180	180	115	Gefitinib	1st	ORR, PFS, OS	(19)
Wang, 2021	China	Prospective	Adenocarcinoma	135	54	25	Gefitinib, icotinib, afatinib	1st	PFS	(42)
Tan, 2021	China	Retrospective	Adenocarcinoma (95%)	180	51	30	Gefitinib, erlotinib, icotinib, afatinib	1st	PFS	(40)
Wang, 2021	China	Prospective	Adenocarcinoma	106	62	26	Mefatinib	1st	ORR, PFS, OS	(59)
Roeper, 2022	Germany	Retrospective	Adenocarcinoma (99%)	77	77	32	Osimertinib	≥2nd	ORR, PFS, OS	(60)

TP53, tumor protein p53; TKI, tyrosine kinase inhibitor; CLCGP, Clinical Lung Cancer Genome Project; NSCLC, non-small-cell lung cancer; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

Table II. Details of gene alteration in the included studies.

First author, year	EGFR mutation profile	Methods of TP53 detection	Detected exons of TP53	Samples for TP53 detection	(Refs.)
CLCGP, 2013	Not reported	PCR	Exons 5-9	Tissue	(43)
Molina-Vila, 2014	Not reported	High-resolution melting	Exons 5-8	Tissue	(44)
Bria, 2015	Exon 19 deletion, exon 21 L858R mutation	Sanger sequencing	Exons 5-8	Tissue	(45)
Canale, 2017	Exon 18 point mutation, exon 19 deletion, exon 21 point mutation, exon 21 L858R mutation	Direct sequencing	Exons 5-8	Tissue	(46)
VanderLaan, 2017	Exon 18-21 mutations	NGS/JAX-Cancer Treatment Profile	Exons 5-8	Tissue	(47)
Labbé, 2017	Exon 19 deletion, exon 21 L858R mutation, exon 18 mutations, exon 19 insertion, exon 19 L747P mutation, multiple mutations	NGS or Sanger sequencing	Exons 3-8	Tissue	(32)
Tsui, 2018	Exon 21 L858R mutation, exon 19 deletion	Digital PCR	Exons 5-8	Plasma	(20)
Aisner, 2018	Exon 19 deletion, exon 19 insertion, exon 18 G719X mutation, exon 21 L861Q mutation	NGS	Exons 2-11	Tissue	(48)
Aggarwal, 2018	Exon 18-21 mutations	NGS	Exons 4-10	Tissue, plasma	(49)
Yu, 2018	Exon 19 deletion, exon 20 insertion, exon 21 p.L858R, exon 18 deletion, exon 19 insertion, exon 21 L861Q mutation, exon 19 L747P mutation, exon 18 E709X + exon 18 G719X mutation, exon 18 G719X + exon 20 S768I mutation, exon 18 G719X + exon 21 L861Q mutation	Illumina HiSeq400 platform	Exons 2-11	Tissue	(50)
Kim, 2019	Exon 21 L861Q mutation, exon 19 deletion, exon 21 L858R mutation, exon 18 G719A mutation, exon 21 L833V + exon 21 L858R mutation, exon 21 L833V + exon 21 H835L mutation	NGS	Exons 2-11	Tissue	(51)
Chang, 2019	Exon 18 mutation, exon 19 mutation, exon 21 mutation	NGS	Not reported	Tissue	(52)
Hou, 2019	Exon 19 deletion, exon 21 L858R mutation, uncommon mutations	NGS	Exons 1-10	Tissue	(53)
Rachiglio, 2019	Exon 19 deletion, exon 21 L858R mutation, exon 20 T790M mutation	NGS	Exons 2-11	Tissue	(54)
Canale, 2020	Exon 19 deletion, exon 21 L858R mutation, uncommon mutations	PCR/NGS	Exons 5-8	Tissue	(41)
Cheng, 2020	Exon 19 deletion, exon 21 L858R mutation, exon 20 insertion, exon 18 G719X mutation, exon 21 L861Q mutation	NGS	Not reported	Tissue, plasma	(55)
Li, 2021	Exon 19 deletion, exon 21 L858R mutation	NGS	Cohort 1: exons 4/7; Cohort 2: other exons	Tissue	(56)
Steendam, 2020	Exon 19 deletion, exon 19 deletion-insertion, exon 19 other mutation, exon 21 L858R mutation, exon 21 other mutation, exon 20 T790M	NGS	Exons 5-8	Tissue, plasma	(57)
Yang, 2021	Exon 20 insertion	NGS	Exons 1-10	Tissue, plasma	(58)
Yu, 2021	Exon 19 deletion, exon 21 L858R mutation	NGS	Not reported	Tissue, plasma	(19)

Table II. Continued.

First author, year	EGFR mutation profile	Methods of TP53 detection	Detected exons of TP53	Samples for TP53 detection	(Refs.)
Wang, 2021	Exon 19 deletion, exon 21 L858R mutation, uncommon mutations	ARMS-PCR/cSMART	Not reported	Tissue, plasma	(42)
Tan, 2021	Exon 19 deletion, exon 21 L858R mutation, uncommon mutations	NGS	Not reported	Tissue	(40)
Wang, 2021	Exon 19 deletion, exon 21 L858R mutation	NGS	Exons 5-8	Tissue, plasma	(59)
Roeper, 2022	Exon 19 deletion, exon 21 L858R mutation, exon 20 T790M	NGS	Not reported	Tissue	(60)

TP53, tumor protein p53; CLCGP, Clinical Lung Cancer Genome Project; NGS, next-generation sequencing; ARMS-PCR, amplification-refractory mutation system-PCR; cSMART, circulation single-molecule amplification and resequencing technology.

Subgroup analysis was subsequently performed. In retrospective studies, patients with TP53 mutants treated with EGFR-TKIs exhibited poorer overall survival outcomes (HR=1.71; 95% CI=1.36-2.15; P<0.001), as did those with adenocarcinoma (HR=1.63; 95% CI=1.25-2.11; P<0.001) and NSCLC (HR=1.68; 95% CI=1.18-2.38; P=0.004). TP53 mutations were also associated with a shorter OS regardless of the TKI treatment line, namely first line (HR=1.43; 95% CI=1.06-1.94; P=0.020), all lines (HR=1.63; 95% CI=1.25-2.12; P<0.001) and second line or further (HR=3.89; 95% CI, 1.15-13.19; P=0.029). Furthermore, OS was only shorter in the TP53 mutant cohort if mutations were detected in exons 2-11 (HR=2.44; 95% CI=1.45-4.11; P<0.001).

Discussion

According to a previous study, the frequency of concurrent TP53 and EGFR mutations in NSCLC is within the range of 55-65% (14). In the present study, concurrent TP53 mutations were observed in 49% of cases (1,091/2,227), which was similar to the previously reported frequency (14). Elucidating the role of concurrent TP53 mutations in EGFR-TKI resistance may be beneficial for the precise identification of populations who are most likely to benefit from TKI treatment. Evidence from previous pre-clinical studies suggests that the TP53 gene status influences the response to EGFR-TKIs. For example, wild-type TP53 was shown to increase gefitinib sensitivity by facilitating apoptosis in EGFR-mutant NSCLC cell lines, while the sensitivity to TKIs was suppressed in TP53 mutant NSCLC cell lines (25,26). In addition, numerous clinical studies have demonstrated that EGFR-mutant NSCLCs with coexisting TP53 mutations treated with TKIs exhibit a trend towards lower ORR, shorter PFS and OS compared with those in NSCLCs with wild-type TP53. However, the results from previous studies have exhibited inconsistencies.

According to a previous meta-analysis, which included a fewer number of studies, patients with NSCLCs harboring concurrent TP53 mutations have a significantly worse prognosis than those without TP53 mutations when treated with EGFR-TKIs (27). The present study was performed with the inclusion of updated data and more recent studies to provide a more thorough analysis. In the present meta-analysis, the association between concurrent TP53 mutations and the clinical outcomes of patients with EGFR-mutant NSCLC treated with TKIs was investigated. Concurrent TP53 mutations were found to be associated with shorter PFS and OS but not with the ORR, suggesting that concurrent TP53 mutations are associated with primary resistance to TKI therapy. There are limited reports on the incidence of TP53 mutations in patients with the two classical genotypes of EGFR gene alterations, namely exon 21 L858R mutation and exon 19 deletion. The combined analysis of these reports in the present meta-analysis identified no significant difference in the incidence of TP53 mutations between patients with exon 21 L858R mutation and exon 19 deletion.

It should be noted that there is no evidence conclusively showing that TP53 mutations are directly involved in the mechanism of resistance to EGFR-TKIs. Mutations in the TP53 gene can lead to p53 protein losing its function in the maintenance of genomic stability, which has been previously

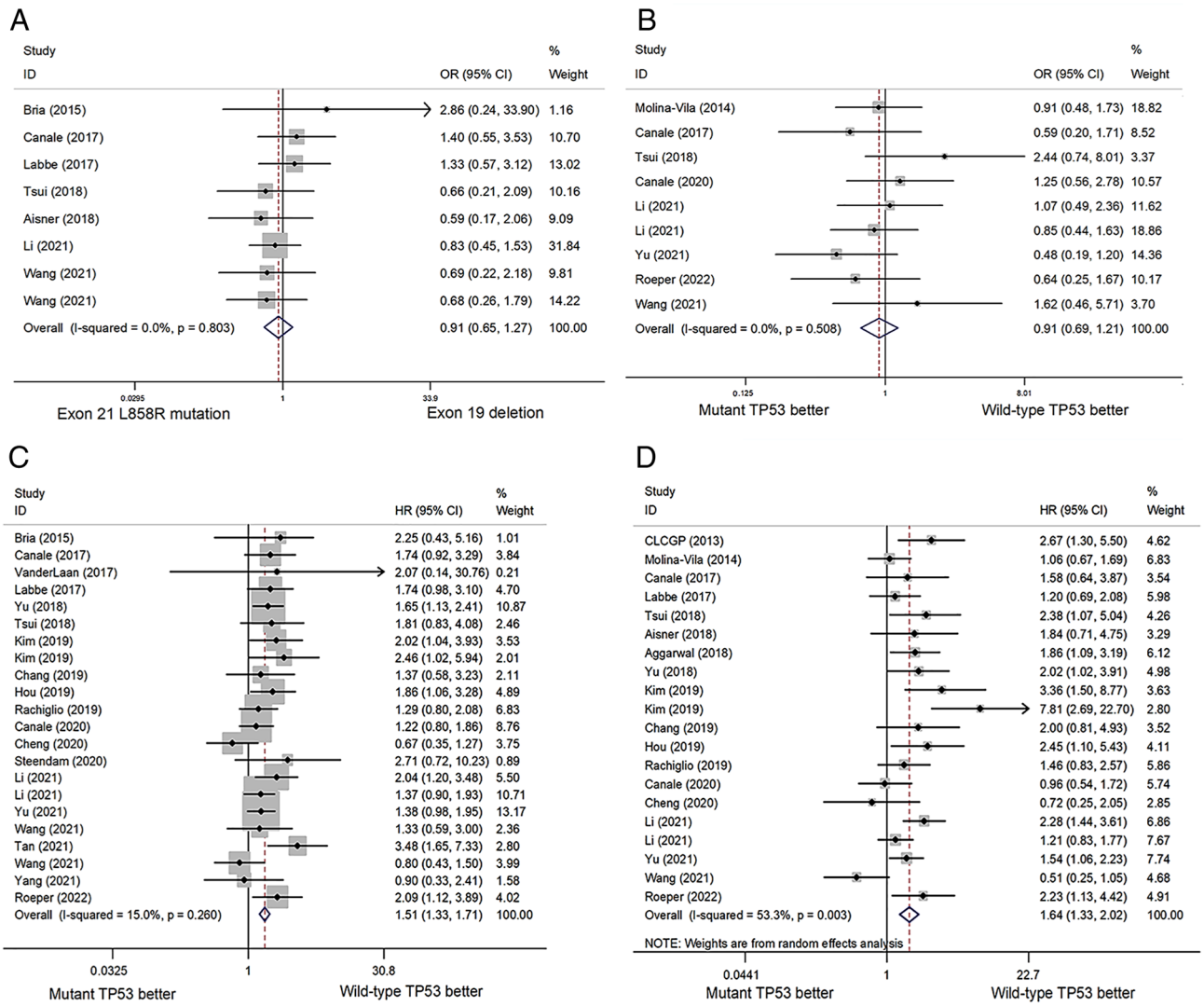

Figure 2. Forest plots for studies on TP53 mutations. (A) Difference in the incidence of TP53 mutations between patients with exon 21 L858R mutation and those with exon 19 deletion. Pooled effects of TP53 mutations on the (B) objective response rate, (C) progression-free survival and (D) overall survival of patients who have undergone EGFR-tyrosine kinase inhibitor treatment. TP53, tumor protein p53.

reported to be associated with a higher tumor mutational burden in cancers (28). The development of drug resistance in cancers is closely associated with genetic alterations. Genomic instability and higher frequencies of gene mutations facilitate the occurrence of resistance-associated mutations at earlier stages of molecular-targeted therapy. Cancer cells carrying resistance-associated mutations proliferate more readily to form sub-clones, leading to clinical progression, recurrence and metastasis (29). This may explain the shorter PFS and OS following EGFR-TKI treatment in the TP53 mutant group in the present meta-analysis, although the ORRs for TP53 mutant and TP53 wild-type patient groups were similar.

The DNA-binding domain encoded by exons 5-8 is the main functional domain of the p53 protein. The binding of p53 to specific DNA response elements promotes the expression of genes that guard against malignant cell transformation and cancer progression (30,31). Previous reports have revealed that the frequency of mutations occurring in exons 5-8 is higher compared with that in other coding regions of the TP53 gene (19,32). Mutations occurring in exons 5-8 of the TP53 gene may result in functional deficiency and counterintuitive tumorigenic properties of the p53 protein (33). In the present meta-analysis, the association between TP53 mutations and the response to TKI therapy varied among the subgroups stratified according to mutant exons. According to the subgroup analysis, mutations occurring in exons 5-8 predicted a poorer prognosis, including shorter PFS and OS, following EGFR-TKI treatment, which is consistent with the aforementioned studies. In terms of influence on the function of p53 protein and the degree of disturbance of the protein structure, TP53 gene alterations can be classified into disruptive and non-disruptive mutations (34). However, due to the lack of studies on this topic, the impact of disruptive/non-disruptive mutations on the clinical outcomes could not be assessed in the present study.

With the development of gene sequencing technology, NGS has become the most frequently used method for detecting and analyzing the tumor genotypes of NSCLC in clinical practice (35). Although the consistency of NGS and other methods for TP53 sequencing requires further validation, the predictive value of NGS-detected TP53 mutations was consistent with

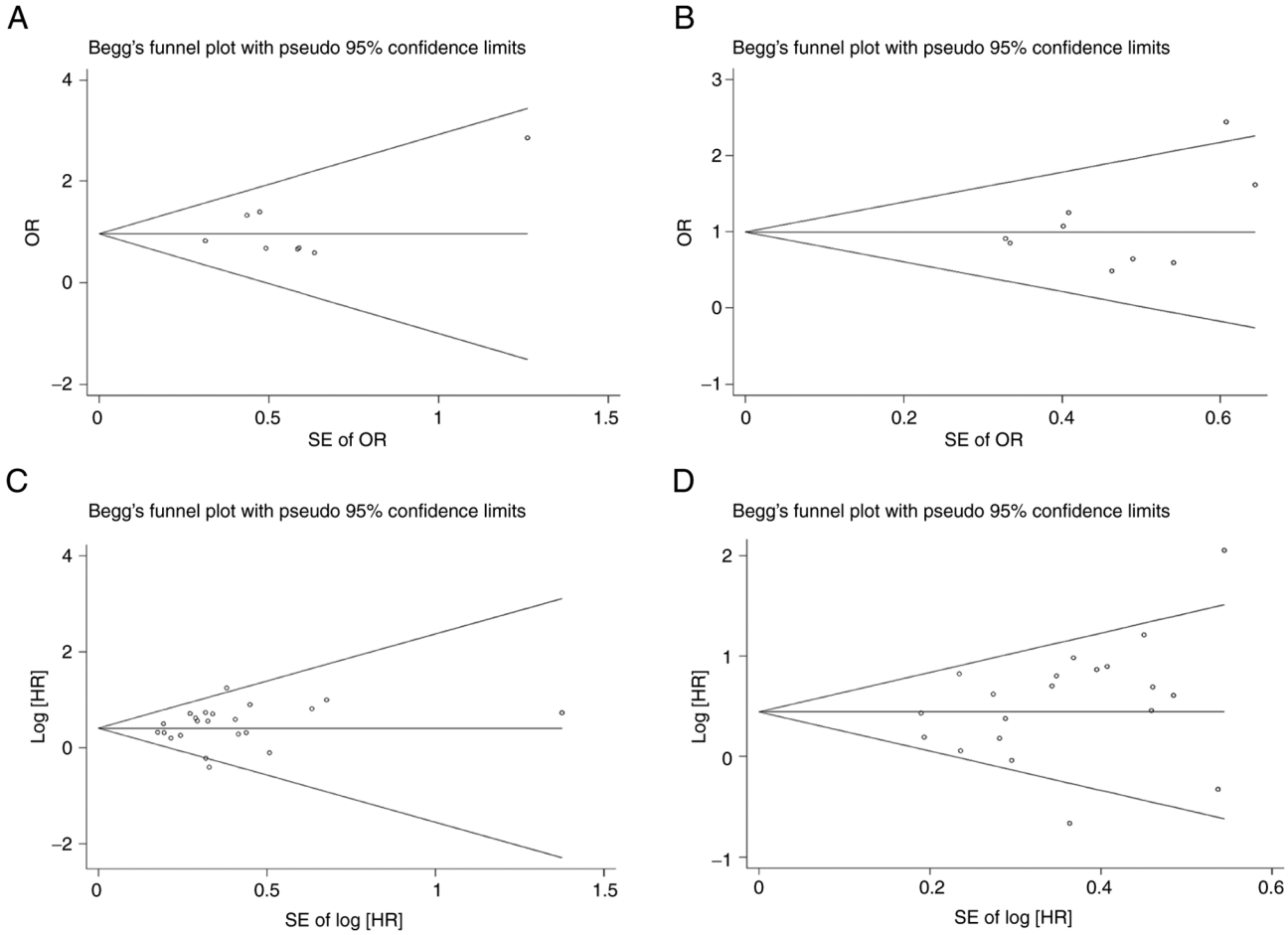

Figure 3. Begg's funnel plots for studies on TP53 mutations. Begg's funnel plots for studies on the associations between (A) TP53 mutations and genotypes of mutant-EGFR, (B) TP53 mutations and objective response rate, (C) TP53 mutations and progression-free survival and (D) TP53 mutations and overall survival. TP53, tumor protein 953; OR, odds ration; HR, hazard ratio; SE, standard error.

TP53 mutations detected using other methods according to the current subgroup analysis. Likewise, the liquid biopsy of circulating tumor DNA (ctDNA) has become widely used for the identification of the real-time molecular characteristics of advanced and metastatic NSCLC. TP53 mutations detected in ctDNA by liquid biopsy appeared to have associations with PFS and OS, whilst TP53 mutations in tissue specimens were predictors of shorter PFS and OS in the present study. This discrepancy may be due to the relatively small number of eligible studies focusing on liquid biopsy. TKI treatment is recommended as the first line of treatment for advanced and metastatic NSCLCs with sensitive EGFR mutations according to various clinical guidelines (36). Based on the results of the subgroup analysis in the present study, TP53 mutations predict a decreased responsiveness of patients receiving EGFR-TKI therapy regardless of the line of therapy.

It must be emphasized that the present study has a number of limitations that must be addressed. The predictive values of concurrent TP53 mutations on the efficacy of specific EGFR-TKIs, including gefitinib, erlotinib, afatinib and osimertinib, remain unclear. Similarly, there is insufficient evidence to verify whether the effects of concurrent TP53 mutations on TKI efficacy are consistent among populations with different genotypes of mutant EGFR. However, it has been documented that various EGFR mutation genotypes may lead to heterogeneous responsiveness to TKIs (37-39). Yu *et al* (19) reported that patients harboring EGFR exon 19 deletion and TP53 mutations treated with gefitinib had a longer PFS and OS compared with those with EGFR L585R mutation and TP53 mutations (19). In addition, a retrospective study by Tan *et al* (40) demonstrated that the co-existence of uncommon EGFR mutations and TP53 mutations is associated with a shorter PFS. By contrast, Canale *et al* (41) observed significantly shorter PFS and OS times in the subgroup of TKI-treated patients with EGFR exon 19 deletion compared with those without this deletion, whilst Wang *et al* (42) identified no significant difference in PFS between patients with EGFR exon 19 deletion and EGFR L585R mutations. Such evidence is not sufficient to completely clarify the intrinsic association between TP53 mutations and *EGFR*-TKI efficacy. Finally, the present study was not prospectively registered in an appropriate registry, such as the National Institute for Health Research's PROSPERO database.

Collectively, the present study suggests that concurrent TP53 mutations are associated with the primary resistance of NSCLC to EGFR-TKIs and predict poorer clinical outcomes with shorter PFS and OS following EGFR-TKI treatment.

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Not applicable.

Table III. Subgroup analysis of ORR, PFS and OS.

	ORR				PFS				OS			
Subgroup	Cohorts (n)	Pooled OR (95%CI)	I^2 (%)	P-value	Cohorts (n)	Pooled HR (95%CI)	I^2 (%)	P-value	Cohorts (n)	Pooled HR (95%CI)	I^2 (%)	P-value
Line of TKI treatment												
1st	5	0.97 (0.63-1.50)	37.7	0.895	13	1.37 (1.16-1.62)	29.2	<0.001	10	1.43 (1.06-1.94)	50.8	0.020
≥2nd	-	-	-		2	2.21 (1.33-3.67)	0.0	0.002	2	3.89 (1.15-13.19)	73.4	0.029
1st/≥2nd	3	0.92 (0.62-1.37)	0.0	0.695	7	1.63 (1.33-1.99)	0	<0.001	8	1.63 (1.25-2.12)	41.4	<0.001
Samples for TP53 detection												
Tissue	6	0.89 (0.65-1.23)	0.0	0.490	15	1.66 (1.42-1.92)	0	<0.001	15	1.76 (1.39-2.23)	49.0	<0.001
Tissue/plasma	3	0.99 (0.55-1.78)	61.5	0.962	7	1.18 (0.93-1.49)	26.9	0.164	5	1.28 (0.78-2.10)	67.4	0.337
Methods of TP53 sequencing												
NGS	5	0.82 (0.56-1.19)	0.0	0.070	14	1.49 (1.27-1.73)	41.7	<0.001	13	1.73(1.30-2.29)	60.3	<0.001
Other	4	1.05 (0.69-1.60)	12.6	0.806	8	1.55 (1.25-1.92)	0	<0.001	7	1.48 (1.09-2.00)	36.3	0.012
Detected exons of TP53												
Exons 5-8	5	1.10 (074-1.64)	0.0	0.638	7	1.35 (1.03-1.77)	0	0.031	5	1.10 (0.7-1.72)	55.6	0.665
Exons 2-11	-	-	-		4	1.64 (1.26-2.12)	0	<0.001	5	2.44 (1.4-4.11)	53.1	0.001
Exons 1-10	-	-	-		2	1.56 (0.95-2.55)	35.4	0.077	-	-	-	
Type of study												
Prospective	3	0.99 (0.55-1.78)	61.5	0.962	5	1.32 (1.02-1.72)	5.7	0.036	4	1.35 (0.73-2.48)	78.7	0.340
Retrospective	6	0.89 (0.65-1.23)	0.0	0.633	17	1.57 (1.36-1.81)	16.6	<0.001	16	1.71(1.36-2.15)	49.8	<0.001
Histological type												
NSCLC	2	1.54 (0.79-2.98)	0.0	0.205	4	1.36 (1.02-1.81)	0.0	0.036	5	1.68 (1.18-2.38)	36.5	0.004
Adenocarcinoma	7	0.81 (0.60-1.11)	0.0	0.286	18	1.54 (1.34-1.77)	23.6	<0.001	15	1.63 (1.25-2.11)	59.0	<0.001

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; OR, odds ratio; HR, hazard ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor; TP53, tumor protein p53; NSCLC, non-small-cell lung cancer.

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Availability of data and materials

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

Authors' contributions

BL and KD were responsible for the conception and design of the study. BL, NZ and BLL collected data. BL, BLL and NZ performed the data analysis and interpretation. All authors were responsible for writing the manuscript. All authors read and approved the final manuscript. BL and NZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2022. CA Cancer J Clin 72: 7-33, 2022.
2. Melosky B, Kambartel K, Häntschel M, Bennetts M, Nickens DJ, Brinkmann J, Kayser A, Moran M and Cappuzzo F: Worldwide prevalence of epidermal growth factor receptor mutations in non-small cell lung cancer: A meta-analysis. Mol Diagn Ther 26: 7-18, 2022.
3. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, *et al*: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11: 121-128, 2010.
4. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, *et al*: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13: 239-246, 2012.
5. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, *et al*: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378: 113-125, 2018.
6. National Comprehensive Cancer Network (NCCN): non-small cell lung cancer. NCCN guidelines version 1, 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450. Accessed April 2, 2022.
7. Hirsch FR, Suda K, Wiens J and Bunn PA Jr: New and emerging targeted treatments in advanced non-small-cell lung cancer. Lancet 388: 1012-1024, 2016.
8. Jin Y, Shi X, Zhao J, He Q, Chen M, Yan J, Ou Q, Wu X, Shao YW and Yu X: Mechanisms of primary resistance to EGFR targeted therapy in advanced lung adenocarcinomas. Lung Cancer 124: 110-116, 2018.
9. Guo Y, Song J, Wang Y, Huang L, Sun L, Zhao J, Zhang S, Jing W, Ma J and Han C: Concurrent genetic alterations and other biomarkers predict treatment efficacy of EGFR-TKIs in EGFR-mutant non-small cell lung cancer: A review. Front Oncol 10: 610923, 2020.
10. Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, Morrione A, Giordano A and Cenciarelli C: p53 signaling in cancer progression and therapy. Cancer Cell Int 21: 703, 2021.
11. Gomes AS, Ramos H, Inga A, Sousa E and Saraiva L: Structural and drug targeting insights on mutant p53. Cancers (Basel) 13: 3344, 2021.
12. Vaddavalli PL and Schumacher B: The p53 network: Cellular and systemic DNA damage responses in cancer and aging. Trends Genet 38: 598-612, 2022.
13. Kumari S, Sharma V, Tiwari R, Maurya JP, Subudhi BB and Senapati D: Therapeutic potential of p53 reactivation in prostate cancer: Strategies and opportunities. Eur J Pharmacol 919: 174807, 2022.
14. Hong S, Gao F, Fu S, Wang Y, Fang W, Huang Y and Zhang L: Concomitant genetic alterations with response to treatment and epidermal growth factor receptor tyrosine kinase inhibitors in patients with EGFR-mutant advanced non-small cell lung cancer. JAMA Oncol 4: 739-742, 2018.
15. Deben C, Deschoolmeester V, Lardon F, Rolfo C and Pauwels P: TP53 and MDM2 genetic alterations in non-small cell lung cancer: Evaluating their prognostic and predictive value. Crit Rev Oncol Hematol 99: 63-73, 2016.
16. Mogi A and Kuwano H: TP53 mutations in nonsmall cell lung cancer. J Biomed Biotechnol 2011: 583929, 2011.
17. Muller PAJ and Vousden KH: p53 mutations in cancer. Nat Cell Biol 15: 2-8, 2013.
18. Skoulidis F and Heymach JV: Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer 19: 495-509, 2019.
19. Yu R, Bai H, Li T, Gao B, Han J, Chang G, Zhang P, Fei K, He X and Wang J: TP53 mutations in circulating tumor DNA in advanced epidermal growth factor receptor-mutant lung adenocarcinoma patients treated with gefitinib. Transl Oncol 14: 101163, 2021.
20. Tsui DWY, Murtaza M, Wong ASC, Rueda OM, Smith CG, Chandrananda D, Soo RA, Lim HL, Goh BC, Caldas C, *et al*: Dynamics of multiple resistance mechanisms in plasma DNA during EGFR-targeted therapies in non-small cell lung cancer. EMBO Mol Med 10: e7945, 2018.
21. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB: Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 283: 2008-2012, 2000.
22. Guyot P, Ades AE, Ouwens MJ and Welton NJ: Enhanced secondary analysis of survival data: Reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 12: 9, 2012.
23. Wells G, Shea BJ and O'Connell J: The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2014.
24. Fletcher J: What is heterogeneity and is it important? BMJ 334: 94-96, 2007.
25. Chang GC, Hsu SL, Tsai JR, Liang FP, Lin SY, Sheu GT and Chen CY: Molecular mechanisms of ZD1839-induced G1-cell cycle arrest and apoptosis in human lung adenocarcinoma A549 cells. Biochem Pharmacol 68: 1453-1464, 2004.
26. Rho JK, Choi YJ, Ryoo BY, Na II, Yang SH, Kim CH and Lee JC: p53 enhances gefitinib-induced growth inhibition and apoptosis by regulation of Fas in non-small cell lung cancer. Cancer Res 67: 1163-1169, 2007.
27. Qin K, Hou H, Liang Y and Zhang X: Prognostic value of TP53 concurrent mutations for EGFR-TKIs and ALK-TKIs based targeted therapy in advanced non-small cell lung cancer: A meta-analysis. BMC Cancer 20: 328, 2020.
28. Ulivi P, Urbini M, Petracci E, Canale M, Dubini A, Bartolini D, Calistri D, Cravero P, Fonzi E, Martinelli G, *et al*: Wide next-generation sequencing characterization of young adults non-small-cell lung cancer patients. Cancers (Basel) 14: 2352, 2022.
29. Park S, Shim JH, Lee B, Cho I, Park WY, Kim Y, Lee SH, Choi Y, Han J, Ahn JS, *et al*: Paired genomic analysis of squamous cell carcinoma transformed from EGFR-mutated lung adenocarcinoma. Lung Cancer 134: 7-15, 2019.
30. Riley T, Sontag E, Chen P and Levine A: Transcriptional control of human p53-regulated genes. Nat Rev Mol Cell Biol 9: 402-412, 2008.
31. Levine AJ: The many faces of p53: Something for everyone. J Mol Cell Biol 11: 524-530, 2019.

32. Labbé C, Cabanero M, Korpanty GJ, Tomasini P, Doherty MK, Mascaux C, Jao K, Pitcher B, Wang R, Pintilie M, *et al*: Prognostic and predictive effects of TP53 co-mutation in patients with EGFR-mutated non-small cell lung cancer (NSCLC). Lung Cancer 111: 23-29, 2017.
33. Petitjean A, Mathe E, Kato S, Ishioka C, Tavtigian SV, Hainaut P and Olivier M: Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: Lessons from recent developments in the IARC TP53 database. Hum Mutat 28: 622-629, 2007.
34. Poeta ML, Manola J, Goldwasser MA, Forastiere A, Benoit N, Califano JA, Ridge JA, Goodwin J, Kenady D, Saunders J, *et al*: TP53 mutations and survival in squamous-cell carcinoma of the head and neck. N Engl J Med 357: 2552-2561, 2007.
35. De Maglio G, Pasello G, Dono M, Fiorentino M, Follador A, Sciortino M, Malapelle U and Tiseo M: The storm of NGS in NSCLC diagnostic-therapeutic pathway: How to sun the real clinical practice. Crit Rev Oncol Hematol 169: 103561, 2022.
36. Hayashi H, Nadal E, Gray JE, Ardizzoni A, Caria N, Puri T and Grohe C: Overall treatment strategy for patients with metastatic NSCLC with activating EGFR mutations. Clin Lung Cancer 23: e69-e82, 2022.
37. Zhang Y, Sheng J, Kang S, Fang W, Yan Y, Hu Z, Hong S, Wu X, Qin T, Liang W and Zhang L: Patients with exon 19 deletion were associated with longer progression-free survival compared to those with L858R mutation after first-line EGFR-TKIs for advanced non-small cell lung cancer: A meta-analysis. PLoS One 9: e107161, 2014.
38. Hong W, Wu Q, Zhang J and Zhou Y: Prognostic value of EGFR 19-del and 21-L858R mutations in patients with non-small cell lung cancer. Oncol Lett 18: 3887-3895, 2019.
39. Naidoo J, Sima CS, Rodriguez K, Busby N, Nafa K, Ladanyi M, Riely GJ, Kris MG, Arcila ME and Yu HA: Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer 121: 3212-3220, 2015.
40. Tan J, Hu C, Deng P, Wan R, Cao L, Li M, Yang H, Gu Q, An J and Jiang J: The predictive values of advanced non-small cell lung cancer patients harboring uncommon EGFR mutations-the mutation patterns, use of different generations of EGFR-TKIs, and concurrent genetic alterations. Front Oncol 11: 646577, 2021.
41. Canale M, Petracci E, Delmonte A, Bronte G, Chiadini E, Ludovini V, Dubini A, Papi M, Baglivo S, De Luigi N, *et al*: Concomitant TP53 mutation confers worse prognosis in EGFR-mutated non-small cell lung cancer patients treated with TKIs. J Clin Med 9: 1047, 2020.
42. Wang X, Liu Y, Meng Z, Wu Y, Wang S, Jin G, Qin Y, Wang F, Wang J, Zhou H, *et al*: Plasma EGFR mutation abundance affects clinical response to first-line EGFR-TKIs in patients with advanced non-small cell lung cancer. Ann Transl Med 9: 635, 2021.
43. Clinical Lung Cancer Genome Project (CLCGP); Network Genomic Medicine (NGM): A genomics-based classification of human lung tumors. Sci Transl Med 5: 209ra153, 2013.
44. Molina-Vila MA, Bertran-Alamillo J, Gascó A, Mayo-de-las-Casas C, Sánchez-Ronco M, Pujantell-Pastor L, Bonanno L, Favaretto AG, Cardona AF, Vergnenègre A, *et al*: Nondisruptive p53 mutations are associated with shorter survival in patients with advanced non-small cell lung cancer. Clin Cancer Res 20: 4647-4659, 2014.
45. Bria E, Pilotto S, Amato E, Fassan M, Novello S, Peretti U, Vavalà T, Kinspergher S, Righi L, Santo A, *et al*: Molecular heterogeneity assessment by next-generation sequencing and response to gefitinib of EGFR mutant advanced lung adenocarcinoma. Oncotarget 6: 12783-12795, 2015.
46. Canale M, Petracci E, Delmonte A, Chiadini E, Dazzi C, Papi M, Capelli L, Casanova C, De Luigi N, Mariotti M, *et al*: Impact of TP53 mutations on outcome in EGFR-mutated patients treated with first-line tyrosine kinase inhibitors. Clin Cancer Res 23: 2195-2202, 2017.
47. VanderLaan PA, Rangachari D, Mockus SM, Spotlow V, Reddi HV, Malcolm J, Huberman MS, Joseph LJ, Kobayashi SS and Costa DB: Mutations in TP53, PIK3CA, PTEN and other genes in EGFR mutated lung cancers: Correlation with clinical outcomes. Lung Cancer 106: 17-21, 2017.
48. Aisner DL, Sholl LM, Berry LD, Rossi MR, Chen H, Fujimoto J, Moreira AL, Ramalingam SS, Villaruz LC, Otterson GA, *et al*: The impact of smoking and TP53 mutations in lung adenocarcinoma patients with targetable mutations-the lung cancer mutation consortium (LCMC2). Clin Cancer Res 24: 1038-1047, 2018.
49. Aggarwal C, Davis CW, Mick R, Thompson JC, Ahmed S, Jeffries S, Bagley S, Gabriel P, Evans TL, Bauml JM, *et al*: Influence of TP53 mutation on survival in patients with advanced EGFR-mutant non-small-cell lung cancer. JCO Precis Oncol 2018: PO.18.00107, 2018.
50. Yu HA, Suzawa K, Jordan E, Zehir A, Ni A, Kim R, Kris MG, Hellmann MD, Li BT, Somwar R, *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 24: 3108-3118, 2018.
51. Kim Y, Lee B, Shim JH, Lee SH, Park WY, Choi YL, Sun JM, Ahn JS, Ahn MJ and Park K: Concurrent genetic alterations predict the progression to target therapy in EGFR-mutated advanced NSCLC. J Thorac Oncol 14: 193-202, 2019.
52. Chang SC, Lai YC, Chang CY, Huang LK, Chen SJ, Tan KT, Yu PN and Lai JI: Concomitant genetic alterations are associated with worse clinical outcome in EGFR mutant NSCLC patients treated with tyrosine kinase inhibitors. Transl Oncol 12: 1425-1431, 2019.
53. Hou H, Qin K, Liang Y, Zhang C, Liu D, Jiang H, Liu K, Zhu J, Lv H, Li T and Zhang X: Concurrent TP53 mutations predict poor outcomes of EGFR-TKI treatments in Chinese patients with advanced NSCLC. Cancer Manag Res 11: 5665-5675, 2019.
54. Rachiglio AM, Fenizia F, Piccirillo MC, Galetta D, Crinò L, Vincenzi B, Barletta E, Pinto C, Ferraù F, Lambiase M, *et al*: The presence of concomitant mutations affects the activity of EGFR tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer (NSCLC) patients. Cancers (Basel) 11: 341, 2019.
55. Cheng Y, Ma L, Liu Y, Zhu J, Xin Y, Liu X, Wang Y, Zhang T, Yang C, Wang S, *et al*: Comprehensive characterization and clinical impact of concomitant genomic alterations in EGFR-mutant NSCLCs treated with EGFR kinase inhibitors. Lung Cancer 145: 63-70, 2020.
56. Li XM, Li WF, Lin JT, Yan HH, Tu HY, Chen HJ, Wang BC, Wang Z, Zhou Q, Zhang XC, *et al*: Predictive and prognostic potential of TP53 in patients with advanced non-small-cell lung cancer treated with EGFR-TKI: Analysis of a phase III randomized clinical trial (CTONG 0901). Clin Lung Cancer 22: 100-109. e3, 2021.
57. Steendam CMJ, Veerman GDM, Pruis MA, Atmodimedjo P, Paats MS, van der Leest C, von der Thüsen JH, Yick DCY, Oomen-de Hoop E, Koolen SLW, *et al*: Plasma predictive features in treating EGFR-mutated non-small cell lung cancer. Cancers (Basel) 12: 3179, 2020.
58. Yang GJ, Li J, Xu HY, Sun Y, Liu L, Li HS, Yang L, Zhang Y, Li GH and Wang Y: Osimertinib for Chinese advanced non-small cell lung cancer patients harboring diverse EGFR exon 20 insertion mutations. Lung Cancer 152: 39-48, 2021.
59. Wang P, Li Y, Lv D, Yang L, Ding L, Zhou J, Hong W, Chen Y, Zhang D, He S, *et al*: Mefatinib as first-line treatment of patients with advanced EGFR-mutant non-small-cell lung cancer: A phase Ib/II efficacy and biomarker study. Signal Transduct Target Ther 6: 374, 2021.
60. Roeper J, Christopoulos P, Falk M, Heukamp LC, Tiemann M, Stenzinger A, Thomas M and Griesinger F: TP53 co-mutations as an independent prognostic factor in 2nd and further line therapy-EGFR mutated non-small cell lung cancer IV patients treated with osimertinib. Transl Lung Cancer Res 11: 4-13, 2022.