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To what extent do TP53 mutations affect the success of targeted therapy in lung cancer treatment?

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Abstract. This dissertation investigates the extent to which TP53 mutations influence the efficacy of targeted therapies (EGFR-TKIs, ALK-TKIs, and ROS1-TKIs) in the treatment of Non-Small Cell Lung Cancer (NSCLC), which accounts for 85% of all lung cancer cases. To address the core research question, the study adopts a systematic literature review approach, synthesizing data from peer-reviewed clinical studies, meta-analyses, and guidelines published by authoritative bodies such as the FDA and EMA. The research focuses on three main themes: the functional mechanisms of TP53 mutations in driving treatment resistance, the quantitative impact of these mutations on important efficacy parameters (Progression-Free Survival [PFS] and Objective Response Rate [ORR]) across different targeted therapies, and the clinical consequences of TP53 testing for personalized treatment stratification. Key findings show that TP53 mutations exert a moderate-to-strong negative effect on targeted therapy outcomes: reducing ORR by 25 47% and decreasing PFS by 35 63% throughout EGFR, ALK, and ROS1-TKIs. Mechanistically, mutations impair DNA repair, promote tumor angiogenesis, and inhibit apoptosis, whereas a significant exception is the combination of EGFR-TKIs with anti-angiogenic inhibitors, which reduces this effect in select EGFR-positive patients. The study concludes that TP53 mutations are important drivers of lower targeted therapy efficacy, and combining TP53 testing as a complementary biomarker might guide clinical decision-making. However, standardised mutation detection protocols and bigger prospective trials are needed to corroborate findings, particularly for ROS1-TKI therapy and subtype-specific analyses.

Keywords: TP53 mutations, targeted therapy, Non-Small Cell Lung Cancer (NSCLC), Tyrosine Kinase Inhibitors (TKIs), drug resistance

1. Introduction

Lung cancer is the leading cause of cancer of cancer-related deaths around the world, ranking the highest mortality rate among both young and elderly populations [1]. Lung cancer is often determined at a late stage which limits treatment options [2]. The World Health Organization (WHO) determined lung cancer into two categories: Non-Small Cell Lung Cancer (NSCLC) which accounts for 85% cases worldwide and Small Cell Lung Cancer (SCLC) [3]. In Non-Small Cell Lung Cancer (NSCLC) treatment, TP53 mutations have close relationship with the effectiveness of targeted therapy.

To provide further clarity on the research context, this section will firstly introduce the mechanism of action of targeted therapy and the function of the TP53 gene. The content will help understand the interaction between TP53 mutations and treatment efficacy.

Targeted therapy kills cancer cells by looking at their gene or protein structure and delivering a cancer treatment that isn't toxic to normal cells. This differs from chemotherapy, which is less precise as it attacks normal at the same time [4]. The primary targeted therapies for NSCLC are EGFR-TKIs, ALK-TKIs and ROS1-TKIs, designed to block signal from mutated genes EGFR, ALK or ROS1, respectively [5]. According to Song et al. [6] these treatments usually provide longer PFS and present fewer side effects than chemotherapy. But several patients demonstrate poor responses, which are implicated in other genetic changes, for instance, TP53 mutations [3]. TP53 is a tumour suppressor gene that encodes p53, a protein often described as the guardian of the genome [7]. Under normal circumstances, p53 inhibits cells from dividing when it detects damage to the DNA. It either prevents cell division until the damage is mended or triggers cell death. In this way, it inhibits cancer [4].

The main function of p53 is to control a central genetic program of cellular senescence that serves to prevent tumorigenesis. Research confirms that mutations of the TP53 gene are associated with poor outcomes from targeted therapy however, what the precise impact is (e.g. how much lower is the ORR or how much shorter is the PFS) remains unclear and inconsistent across studies [3]. Chen et al. [8] found TP53-mutated EGFR-TKI patients had a risk of disease progression 1.7 times that of wild-type patients, but few studies directly challenge TP53's predictive value.

2. Research review

2.1. Proprietary terms

• Biomarker: A measurable genetic or protein change in cancer cells that helps doctors predict treatment response [4].
• Progression-Free Survival (PFS): The length of time a patient's cancer stays under control without worsening after treatment starts [4].
• Objective Response Rate (ORR): The percentage of patients whose tumors shrink significantly after treatment [4].
• TP53 gene vs. p53 protein: TP53 is the gene that provides instructions to make the p53 protein, which carries out tumor-suppressing functions [3].

2.2. Overview of TP53 and targeted therapy in NSCLC

To accomplish the first aim, the function of the TP53 gene in lung cancer is outlined in this section. The TP53 gene is known as the "guardian of the genome" due to the p53 protein it produces that prevents cells from becoming cancerous [7]. When DNA inside cells is damaged, for instance, by smoking or radiation, p53 stops cell division so the damage can be repaired. If the damage is too acute, p53 causes the cell to die [5]. This stops injured cells from growing and forming tumor.

2.3. TP53 mutations in NSCLC

The TP53 mutation results in a malfunctioning or even absent p53 protein [2]. The absence of functional p53 which would otherwise control damaged cells, no longer keeps the DNA of damaged cells in check. As a result, these cells continue dividing, accumulating more and more mutations and becoming more aggressive

[1]. TP53 mutations occur frequently in NSCLC, as approximately 40% of lung adenocarcinoma and 51% of lung squamous cell carcinoma are caused by this mutation [2]. The loss of control results in cancers becoming more difficult to treat as targeted therapies rely on slowing or stopping the growth of cancer cells. This is difficult to do when the cells have become more genetically unstable owing to TP53 mutations [3].

The next sections will discuss how TP53 mutations affect chemical therapy response to the three major targeted therapies.

2.4. How can TP53 mutations affect the way NSCLC patients respond to treatment?

According to EGFR, ALK, and ROS1-targeted therapies, TP53 mutations constantly associated with a decrease in treatment success rate, even though some differences are exist in different articles [3]. The key gap is quantifying the extent of this reduced efficacy for each therapy type to answer the core research question.

This section begins with EGFR-TKIs, the most widely used targeted therapy for NSCLC, to analyze the specific impact of TP53 mutations on treatment outcomes.

2.4.1. EGFR-TKI therapy

EGFR-TKIs are one of the main targeted treatments for NSCLC, prescribed to patients whose tumors have EGFR mutations [9]. They work by blocking signals from the EGFR protein that drive cancer cell growth [9].

TP53 mutations have consistently shown to reduce the effectiveness of the drug EGFR-TKI. Chen et al. [8] also stated that TP53 mutations resulted in a 1.7-fold increased risk of disease progression and hastened the development of drug resistance. An association was found between mutations in exons 6 and 7 with poor outcomes [1].

This indicates that mutations on TP53 significantly reduce the response to EGFR-TKI therapy and increase the risk of rapid disease progression. One limitation of the studies is that some adopted retrospective designs and this may result in bias due to unmeasured patient factors. However, similarity among cohorts makes it even more reliable due to consistency.

Moving on from EGFR-TKIs, the impact of TP53 mutations on ALK-TKIs—another key targeted therapy for NSCLC—is next explored to determine whether the negative effect is consistent across different treatment modalities.

2.4.2.ALK-TKIstherapy

ALK-TKIs target the abnormal ALK protein produced by ALK gene rearrangements, a mutation found in around 5% of NSCLC cases [4]. They are particularly used in younger, non-smoking patients with adenocarcinoma [9].

TP53 mutations reduce efficacy of ALK-TKI. According to the study that was conducted by Song et al. involving 64 ALK-positive patients, it was noted that TP53-mutated patients had a 47% lower ORR in comparison to those with wild-type TP53 (38% vs 72% respectively). Furthermore, the median PFS was 63% shorter as well (4.2 vs 11.5 months). Significantly, non-disruptive TP53 mutations (where some p53 function is retained) only reduced PFS by 35% [3].

This shows TP53 mutations have a significant adverse effect on ALK-TKI therapy, though they behave differently according to mutation type.

The primary limitation of the included studies was the sample size whereby results may not be generalizable to broader patients [6].

Having analyzed the impact on EGFR-TKIs and ALK-TKIs, the analysis now turns to ROS1-TKIs, the third major targeted therapy for NSCLC, to complete the picture of TP53 mutations' influence across all key treatment options.

2.4.3. ROS1-TKI therapy

ROS1-TKIs target ROS1 gene rearrangements, found in 1-2% of NSCLC cases, mostly in adenocarcinoma patients without other key mutations [4]. They work similarly to ALK-TKIs by blocking abnormal growth signals [9].

As the third major targeted therapy for NSCLC, ROS1-TKI therapy has fewer studies on how TP53 mutations affect it compared to EGFR and ALK therapies [3]. However, existing limited evidence still shows a consistent trend: TP53 mutations may reduce the effectiveness of ROS1-TKIs.

Moes-Sosnowska et al. [3] found that TP53 mutations reduce responsiveness to ROS1-targeted therapies—this raises the question: to what extent does this combination reverse the negative impact of TP53 mutations on EGFR-TKI success? This followed by the findings from EGFR and ALK studies, suggesting a common negative impact of TP53 mutations across major NSCLC targeted therapy groups.

A notable exception is when EGFR-TKIs are combined with angiogenesis inhibitors: some studies report positive outcomes in TP53-mutated patients, though the mechanisms and clinical significance of this phenomenon remain poorly understood.

TP53 mutations play a significant role in drug resistances (both the primary and acquired) in cancer. They do this by increasing genomic instability, blocking the Tyrosine Kinase Inhibitor/VEGF (TKI) pathway, or disrupting cell cycle arrest [1]. For patients, this means TP53 mutations directly weaken ROS1-TKIs' core function — leading to wide variability in treatment response: 2–40% of patients respond to EGFR-TKIs, 2–39% to ALK-TKIs, and at least 25% (ORR, objective response rate: the share of patients whose tumors shrink) to ROS1-TKIs [3, 6].

Because different TP53 mutations affect p53 protein function and response differently, this helps doctors select the best treatment plan [2]. In addition, TP53 mutations can reduce the effectiveness of targeted therapy.

After examining how TP53 mutations affect response to each targeted therapy, the next section will explore the potential of TP53 as a predictive biomarker for treatment stratification, a key clinical application of the research findings.

2.5. TP53 as a predictive biomarker for treatment stratification

TP53 shows that it as a predictive biomarker for guiding NSCLC treatment decisions, although its clinical response was limited [3]—a key reason for this limitation is the lack of clear data on the extent to which TP53 mutations predict reduced targeted therapy success. Most existing research focuses on EGFR/ALK therapies, so more studies are needed to confirm TP53's role in ROS1-TKI responses [3]

Notably, TP53 mutations are linked to worse outcomes across major targeted therapies:

For EGFR-TKIs: TP53 mutations reduce effectiveness [1]

For ALK-TKIs: TP53 mutations lower response rates [6].

For ROS1-TKIs: Early data suggests TP53 mutations may also weaken treatment benefits [3]

In clinical practice, doctors often use EGFR/ALK status (not TP53) to choose initial targeted therapies [6]. This is because TP53 mutations are common (up to 70% of NSCLC cases) and their effects on treatment vary widely [1]. For example:

TP53 mutations may reduce ROS1-TKI response rates [3], but combining ROS1-TKIs with other drugs (e.g., anti-angiogenic inhibitors) could improve outcomes in some TP53-mutated patients. Until more consistent data is available, TP53 is not yet a standard biomarker for ROS1-TKI treatment choices.

While the potential of TP53 as a biomarker is promising, it is important to acknowledge the limitations in current evidence that hinder its clinical application. The following section will outline these key limitations to provide a balanced view of the research landscape.

2.6. What are the limitations in current evidence

Current evidence on TP53's role in targeted cancer therapies is constrained by four key limitations. First,the precision of treatment outcome prediction is compromised by insufficient functional classification of TP53 mutation subtypes. This gap prevents TP53's causal contribution to the variability of response to therapy from being quantified, as subtype effects cannot be systematically linked to clinical endpoints [3].

Secondly, the dependence on small and non-representative cohorts of patients (e.g., a 47% objective response rate from a small sample) undermines the external validity of findings [6]: the effects associated with TP53 cannot be assumed to be true in other cohorts. This reduces confidence in the conclusion that TP53 would have a similar effect on agents such as EGFR-TKIs [3].

Another major mechanistic gap is the incomplete explanation of the molecular pathways mediating TP53-linked therapeutic resistance. TP53 mutations are associated with reduced efficacy (e.g., in 40% of ROS1-TKI-treated patients) [1], but the driving signalling cascades have not been defined. It restricts the creation of targeted strategies to tackle treatment failure [2].

In the end, the usage of non-standardized protocols by the authors of the various relevant studies which detect and report TP53 mutation (for instance the inconsistencies in annotating variants etc.) produces heterogeneity between the various studies [3]. 30% of the relevant studies are not comparable due to the lack of comparable data of variants which prohibits the synthesis meta-analysis of the findings from those studies and prevents arriving any definite conclusions about the clinical impact of TP53 on targeted therapy [1].

With a clear understanding of the current research findings, biomarker potential, and limitations, the Discussion/Development section will delve deeper into key themes such as combination therapy efficacy, the magnitude of TP53's impact, and implications for clinical practice and future research.

3. Discussion

The study by Chen et al. [8] further quantified this impact, showing that TP53 mutations increase the risk for disease progression by 1.7-fold in first-line EGFR-TKI treatment, with a magnitude comparable to other established negative prognostic factors, such as EGFR T790M secondary mutations (a typical driver of acquired resistance to the treatments) [1]. The reliability of these conclusions is illustrated by their consistency through significant (180 patients) and moderate (120 patients; Chen et al. [8], supplementary analysis) cohorts. TP53 mutations are more than minor confounders; rather they are impactful modifiers of EGFR-TKI efficacy.

The impact of TP53 mutations on ALK-TKI therapy was similarly bad but with slightly greater variability [6]. According to the report by Song et al. [6] the TP53-mutant patients had a 47% lower ORR (38% vs.72% in wild-type) and a 63% shorter median PFS (4.2 vs.11.5 months). This is a more severe reduction of PFS than observed in EGFR-TKI studies [6]. Nonetheless, Park and colleagues reported that, among patients with non-disruptive TP53 mutations, the aforementioned impact was substantially reduced. Within this population, median PFS was reported as reduced by 35% (6.8 vs.10.5 months). Due to this subtype-specific variation, TP53's impact on ALK-TKI therapy is "contextualized by mutation type" – that is, in mutations with less severe consequences, a meaningful barrier to effective treatment is still observed [3].

Seem a negative impact associated with ROS1-TKI therapy which is consistent with EGFR and ALK [3]. However, the evidence is not sufficient to precisely quantify the impact. Moes-Sosnowska et al. [3] combined data from a total of five small cohorts (n = 89). The authors noted that patients with TP53 mutation had a lower odds ratio response by 25% to 30%. Likewise, median PFS was reduced by 40% relative to wild-type patients [3]. The reliability of these estimates is affected by the small sample size, with none of the cohorts including more than 30 patients. Nonetheless, the estimates for TP53 mutations are in line with the findings for EGFR and ALK. This suggests a conserved negative effect of TP53 mutations across the three classes of targeted therapy, although with lower certainty in the ROS1 case [3].

Chen et al. [8] had a small number of patients in that group and their patients also benefitted in terms of PFS. Nonetheless, this effect for which treatment is protective is limited to EGFR-mutant NSCLC and not ALK or ROS1 cases (no studies have reported a similar effect in these subtypes). It is thus a limited exception rather than a reversal of TP53's detrimental influence overall [1]. In summary, the pre-clinical evidence shows that TP53 mutation has a moderate-to-strong, deleterious impact on the efficacy of lung cancer targeted therapy, resulting in 25%–47% lower ORR and 35%–63% shorter PFS across EGFR, ALK, and ROS1-TKIs [3, 6]. Only the rarest EGFR-specific combination therapy managed to ameliorate this effect. ALK-TKI therapy (especially for disruptive mutations) shows a greater impact. The data on ROS1-TKI is limited but follows the same trend. The EGFR-TKI therapy is the most well-validated. This summary indicates that TP53 mutations are not simply associated with poor outcomes but rather a driver of reduced efficacy with targeted therapies and should influence clinical decision making [2].

Despite the clear overall trend of TP53 mutations reducing targeted therapy efficacy, several areas of uncertainty remain—particularly regarding combination therapy and the reliability of current evidence. The following sections will explore these uncertainties to provide a comprehensive and balanced analysis.

3.1. Areas of uncertainty

For TP53-mutant cancer patients, some small-scale clinical observations suggest that combining Epidermal Growth Factor Receptor Tyrosine Kinase inhibitors (EGFR-TKIs)with anti-angiogenic inhibitors may improve outcomes an observation that contrasts with established findings, where TP53 mutations typically reduce responses to single-agent targeted therapies [3]. Two main questions are raised here: "What molecular mechanisms might lead to this combination therapy response?" and more importantly, "To what degree do TP53 mutations affect the effectiveness of EGFR-TKI in this particular situation?"

One hypothesized mechanism is that TP53 mutations upregulate the hypoxia-inducible factor 1 (HIF1) pathway, which promotes tumor angiogenesis a process targeted by anti-angiogenic inhibitors [6]. Combination therapy may lessen the main tumor-promoting effect of TP53 mutations by blocking this pathway; thus, EGFR-TKIs are able to increase the anticancer activity [3]. Nevertheless, large amounts of data still show that this mechanism is still unconfirmed by them.

Notably, this effect is not universal: some TP53-mutant patients still respond poorly to combination therapy. Co-mutations (e.g., in MET or KRAS) or tumor microenvironment features may affect this interaction [1], however current data do not explain which patients benefit most. Without large-scale prospective studies stratifying patients by TP53 mutation subtypes and co-mutation status, the clinical value of this combination in TP53-mutant populations is unknown [2].

To consider these uncertainties, it is essential to evaluate the reliability of the current research base, as limitations in study design and execution can further obscure the understanding of TP53's impact. The next section assesses the strengths and weaknesses of existing evidence.

3.2. Reliability of current research

When assessing how reliable existing evidence is for answering the core question of this study—To what extent do TP53 mutations reduce targeted therapy success?—the research base includes both strengths that increase credibility and limitations that hold back decisive conclusions.

On the positive side, some research increase dependability: many are published in high-authority, peer-reviewed journals (e.g., Cancer Cell, a major academic publishing [1]), and others use large sample sizes (like

Yu et al. [2]) to provide quantifiable results(e.g., a 40%reduction in progression-free survival for EGFR-TKIs). These factors make their conclusions about TP53 s influence more trustworthy.

However, the data is weakened by significant restrictions. First, results from small or unrepresentative samples (Song et al. [6], 4.7% ORR reduction for ALK-TKIs) might not be representative of results in bigger, more varied patient groups [3].

Second, TP53 s apparent effect may be distorted by missing data (e.g., patients stopping treatment early) because it seems to be stronger or weaker than it actually is [2]. Thirdly, inconsistent procedures (e.g., unconfirmed TP53 mutation detection) lead to contradicting results (like the unconfirmed 40%PFS reduction for ROS1-TKIs).

These shortcomings mean that it is not yet possible to reliably measure how much TP53 reduces therapy success. Large, well-designed prospective studies are needed to corroborate TP53's true effect [3] — a crucial step for answering the core research question of this study.

One of the most pressing uncertainties tied to research reliability is the clinical value of combination therapy for TP53-mutant patients, which warrants deeper exploration given its potential to mitigate treatment resistance.

3.3. Questions about the uncertain clinical value of combination therapy inTP53-mutant patients

Here is the question: Does TP53-mutated NSCLC patients respond to combination therapy (e.g., EGFR-TKIs+anti-angiogenic inhibitors) fairly better than those of TP53 therapy? Although some data points to this therapy may prolong Progression-Free Survival (PFS).

Very few samples (fewer than 100 patients) are used in the majority of research to support combination therapy; therefore, the extent to which the results can be trusted is limited. Other variables (e.g., genes such as MET or KRAS) that might have an impact on outcomes are also not taken into consideration by these studies. This means that the reported PFS benefit (2 to 5 months) might not be the result of TP53 mutation targeting; rather, it might be a result of patient selection that is biased or the results of the anti-angiogenic medication by itself—not the combination—rather than the result.

Right now, there are no large, well-designed studies that confirm combination therapy especially reverses TP53-linked treatment resistance. Until these studies are done, the benefit of this therapy for TP53-mutant patients remains unconfirmed.

Another key factor undermining research reliability is inconsistent mutation detection and reporting methods, which create heterogeneity across studies and hinder meaningful comparisons. The following section will address this critical issue.

3.4. Inconsistent mutation detection and reporting methods

Existing evidence routinely shows that TP53 mutations weaken the outcomes of targeted therapies (such as EGFR-TKIs, ALK-TKIs, and ROS1-TKIs) by shortening Progression-Free Survival (PFS) and lowering Objective Response Rates (ORR) [3], translating these findings into clinical practice and addressing remaining uncertainties are key to improving patient care. For lung cancer patients with driver mutations such EGFR, ALK, or ROS1, integrating TP53 testing into initial diagnostic workflows might serve as a guidance tool for personalized treatment decisions [1].

Specifically, for EGFR-mutant patients who also carry TP53 mutations who face a higher risk of early drug resistance doctors could prioritize combination therapies (such as EGFR-TKIs plus anti-angiogenic inhibitors) over single-agent treatment, as recommended in the 2025 edition of the China Anti-Cancer Association (CACA) Lung Cancer Diagnosis and Treatment Guidelines, which notes that this combination can extend survival by 6 months for patients with concurrent EGFR and TP53 mutations. for ALK-mutant patients with TP53 mutants, who generally have worse outcomes (e.g., a 2.9-month shorter survival compared to those without TP53 mutations [3]), TP53 testing can encourage more aggressive treatment approaches or closer monitoring(such as frequent imaging to detect tumor progression early). Importantly, TP53 testing should not replace established driver gene tests (e.g., EGFR or ALK detection) but rather act as a complementary tool, given that the impact of different TP53 mutation subtypes (e.g., disruptive vs. non-disruptive) on treatment responses remains incompletely understood [3].

To properly answer the main research question of this paper and specify the actual extent to which TP53 mutations affect targeted therapy success, future research must overcome three important gaps [1]. First, the underlying mechanisms of TP53-driven drug resistance need to be elucidated in greater detail: for example, do TP53 mutations activate alternative bypass pathways (such as the PI3K/AKT pathway) that allow tumors to grow despite targeted therapy, or do different mutation types (e.g., missense vs. nonsense mutations in the DNA-binding domain) lead to resistance through different mechanisms?

Research should second examine the ways in which TP53 mutations affect the tumor microenvironment—such as encouraging inflammation or creating a protective niche—that promotes tumor survival—and whether TP53-mutant patients can benefit from targeting these changes (e.g., with immunotherapies).

Third, it is necessary to standardize TP53 testing and reporting; existing researches use different methods (e.g., targeted next-generation sequencing panels vs. sublobular sequencing) and lack uniform criteria for classifying mutations, which leads to conflicting results and hinders cross-study comparisons [3]. Establishing agreed-upon standards for which regions of the TP53 gene to test, how to report mutation locations and types, and how to define clinically relevant subtypes (e.g., disruptive mutations) would greatly enhance the reliability of research findings. Additionally, building a centralized database of TP53-mutant lung cancer cases—linking mutation status, treatment regimens, and outcomes—would enable researchers to identify patterns across large cohorts, turning preliminary observations into precise tools for clinical decision-making [6]; Collectively, these clinical uses and future study areas will not only solve the problems in the main question of this study but also promote personalized treatment for lung cancer patients with TP53 mutations. This section describes how TP53 testing—focusing on why these changes matter—for addressing the research question posed in this paper—is done in a way that is both practical and accessible. First, TP53 testing procedures need to be fitted to patients' clinical needs. For advanced NSCLC patients (e.g., those with no standard treatment options), comprehensive testing (such as whole-exome sequencing or large-panel NGS) ensures that all TP53 mutations, including rare ones, are detected [3].

For patients requiring continuous observation (e.g., to track tumor changes during treatment), liquid biopsy (testing blood for tumor DNA) is a useful tool: the 2023 NSCLC Liquid Biopsy Guidelines [3] list TP53 as a key target for this dynamic monitoring, which helps track mutation status in real time. These customized approaches enable the acquisition of more complete, up-to-date TP53 data critical for quantifying its actual impact on therapy success.

Second, to guarantee dependable TP53 results, labs require straightforward quality checks. For example, in every test run, labs ought to include control samples—known TP53-mutant or normal tissue. In order to avoid erroneous results that might skew current knowledge of TP53's effect, this guarantees detection accuracy (sensitivity/specificity of at least 99%) [1]. Although official bodies (such as the College of American Pathologists) set formal standards, this fundamental step is easy to apply and immediately lessens the contradictory outcomes that have supported the findings of this study.

The reason for the changes is that better TP53 testing provides exact knowledge of which TP53 mutations are present and how they change over time. In turn, this paper estimates the amount by which TP53 lowers the success of therapy by directly addressing the uncertainty in its main research question, thereby increasing the reliability of the data. For instance, to verify whether a particular TP53 mutation (e.g., R175H) is associated with a 30% versus 50% reduction in treatment response—transforming imprecise observations into accurate, actionable results for patients and physicians—consistent and accurate testing represents the final step in this process.

In addition to inconsistent testing methods, retrospective study designs—another prevalent issue in current research—introduce biases that further complicate the understanding of TP53's true impact. The next section explores this bias and potential mitigation strategies.

3.5. Bias in retrospective study designs

Most studies on TP53 and targeted therapy use a retrospective design which means they look back at old medical records instead of collecting new data. While this is usual, it introduces biases that make it impossible to believe judgments about how much TP53 mutations affect therapy success.

First, TP53 tests need to be chosen to fit each patient's condition. For advanced NSCLC patients (who have limited treatment options), using comprehensive tests (like large-panel genetic sequencing) ensures that all TP53 mutations are found seven rare ones [3].

For patients having to follow tumor changes over time, liquid biopsy (testing blood for tumor DNA) works effectively: the 2023 NSCLC Liquid Biopsy Guidelines list TP53 as a primary target for this real-time monitoring. Matching tests to needs leads to the collection of complete, up-to-date TP53 data TP53 data critical for knowing how it affects therapy [3].

Secondly, to guarantee TP53 results are trustworthy, labs require basic checks. For instance, control samples (pieces of tissue with known TP53 mutations or no mutations) should be included in every test run. Since this guarantees the accuracy of the tests (approximately 99% of the time), false results that would distort current understanding of TP53's effect can be prevented [1]. Although professional groups—such as the College of American Pathologists—set formal guidelines, this straightforward step is simple and eliminates the contradictory results that have confounded this study.

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After exploring the key uncertainties, research limitations, and potential improvements in data reliability, the broader implications of the findings for clinical practice are discussed, and concrete directions for future research to address remaining gaps are outlined.

3.6. Implications for clinical practice and future research

The review findings have major clinical implications. Testing for TP53 mutations may help identify patients who are high risk and unlikely to benefit from targeted therapy. In this regard, the CACA Guidelines recommend EGFR-TKIs + anti-angiogenic inhibitors rather than a single agent for EGFR-positive patients who have TP53 mutations. TP53 mutations may indicate the need for alternative monitoring or immunotherapy in ALK-positive patients due to the ineffectiveness of TKIs [6]. It is important that TP53 testing should be used in addition to the existing biomarker tests, namely for EGFR, ALK and ROS1 which remain the main focus for treatment selection [3].

To further understanding of TP53-mediated resistance, future mechanistic studies should focus on three key areas [1]. Initially, the investigation concentrates on the interaction of TP53 mutations with the driver signaling pathways (EGFR, ALK, ROS1) that drive resistance. For example, will TP53 mutations upregulate bypass pathways e.g., PI3K-AKT that make TKIs ineffective or do they accelerate the accumulation of secondary driver mutations? Therefore, it can be reasoned that clarifying these interactions will provide insights into potential targets for overcoming resistance. The second is to explore whether the TP53 mutation subtype plays a role in response to therapy. Do non-disruptive mutations retain enough p53 function to sensitise tumours to TKIs, or do all TP53 mutations confer resistance regardless of function? This strongly suggests that subtype-specific analyses are essential for optimizing personalized treatment strategies [3]. In addition, explaining the relationship between TP53 mutations and Tumor Microenvironmental (TME) changes. TP53 mutations would cause global changes in TME, e.g., increase immune cell infiltration or stroma remodeling, to promote resistance. It may therefore be likely that targeting these TME changes could overcome TP53-mediated treatment failure. So targeting TME changes could overcome TP53-mediated failure. The response to these questions may reveal potential for novel combinations such as p53 activators add TKIs, immune checkpoint inhibitors add TKIs for TP53 mutant tumors.

To make sure that conflicting evidence gets resolved, the field must have standard protocols for TP53 mutation detection and reporting [3]. To begin, minimum requirements must be established for detection technologies: all studies must use NGS panels targeting the complete coding region of TP53 (exons 2–11) and with a sensitivity of at least 1% (to be able to detect subclonal mutations). Another essential requirement is to mandate the reporting of any TP53 variants that comply with HGVS. All variants should be described using their genomic position, e.g., c.524G > A and amino acid change, e.g., p.R175H. Also, they should be classified into functional subtypes (disruptive versus non-disruptive) using agreed criteria, e.g., IARC TP53 Database [1].

To begin with, creation of a central registry of TP53-mutated NSCLC cases with clinical outcome data would allow data sharing among researchers across studies, evaluation of subtype-specific effect, and discovery of rare, but clinically relevant variants [6]. Standardization would make TP53 a precise tool for personalized therapy instead of a vague prognostic marker [3].

To turn these clinical and research implications into accessible steps, the following sections will discuss specific solutions to address current research limitations, including prospective validation and policy support for TP53 testing.

3.7. Discussion on implementing solutions to address research limitations

First, clinical guidelines ought to include TP53 testing. The current guidelines frequently fail TP53 [1] and instead concentrate on testing for driver mutations, such as EGFR or ALK. Adding TP53 testing to recommendations can guarantee that physicians use it consistently (e.g., recommending it for patients with advanced NSCLC or those who are resistant to targeted therapy). Because of this, more trustworthy data must be consistently gathered in order to gauge how much TP53 lowers treatment success—the main question of this study. For instance, a more precise comparison between TP53-mutant and non-mutant groups would be possible if every advanced NSCLC patient receives TP53 testing.

Secondly, insurance payment methods ought to reward TP53 testing that is helpful. Insurance might only pay for testing if it results in better outcomes (for example, longer survival from targeted therapy); this is in contrast to paying for tests regardless of their value. While keeping costs reasonable, this value-based model would promote standardized, high-quality testing [3]. According to the findings of this study, there are fewer low-quality tests (and inconsistent results) that have confounded current understanding of TP53's influence.

These policy changes are important because TP53 testing is only useful if patients can access it. If testing is rare or inconsistent, the data needed to answer the main question of this paper will never be obtained: how much do TP53 mutations lower therapy success? That information may be used to help patients avoid costly therapies that are less likely to be used by them by creating testing standard and inexpensive, which will help us create a clearer picture of TP53 s role.

One of the most critical solutions to address research limitations is prospective validation, standardized data collection. The next section will outline a framework for this validation.

3.8. Prospective validation

Establishing a multinational specialized database for TP53 gene mutations in non-small cell lung cancer. Collaborating with organizations such as the International Association for the Study of Lung Cancer (IASLC) and the European Lung Cancer Congress (ELCC) to integrate Real-World Data (RWD) from Asia, Europe, and the Americas. This database should include patient baseline characteristics (age, smoking history, pathological subtype), treatment regimens (types and doses of tyrosine kinase inhibitors/TKIs and combination therapies), follow-up data (progression-free survival/PFS, overall survival/OS, duration of resistance), and biospecimen information (tissue/blood biobank). For example, the database structure of the NCI-MATCH trial conducted by the U.S. National Cancer Institute (NCI) can serve as a reference. This database has a dedicated 'TP53 Mutation Subtype' module that allows researchers to filter data and perform subgroup analyses based on mutation type and co-mutation status.

Meta-analysis based on real-world data. Using Mendelian randomization or instrumental variable methods to control for confounding factors (such as comorbidities and treatment regimens) and to verify the causal relationship between TP53 mutations and response to targeted therapy. For example, in patient populations treated with EGFR-TKIs, a meta-analysis can clarify whether 'TP53 mutations in exons approximately 90% are independent negative prognostic factors', thereby addressing the issue of insufficient statistical power in individual small-sample studies.

3.9. Medical insurance and policy support for TP53 mutation testing

First, clinical guidelines ought to include TP53 testing. The current guidelines frequently fail TP53 [1] and instead concentrate on testing for driver mutations, such as EGFR or ALK. Adding TP53 testing to recommendations can guarantee that physicians use it consistently (e.g., recommending it for patients with advanced NSCLC or those who are resistant to targeted therapy). Because of this, more trustworthy data must be consistently gathered in order to gauge how much TP53 lowers treatment success—the main question of this study. For instance, a more precise comparison between TP53-mutant and non-mutant groups would be possible if every advanced NSCLC patient receives TP53 testing.

Secondly, insurance payment methods ought to reward TP53 testing that is helpful. Insurance might only pay for testing if it results in better outcomes (for example, longer survival from targeted therapy); this is in contrast to paying for tests regardless of their value. While keeping costs reasonable, this value-based model would promote standardized, high-quality testing [3]. According to the findings of this study, there are fewer low-quality tests (and inconsistent results) that have confounded current understanding of TP53's influence.

These policy changes are important because TP53 testing is only useful if patients can access it. If testing is rare or inconsistent, the data needed to answer the main question of this paper will never be obtained: how much do TP53 mutations lower therapy success? That information may be used to help patients avoid costly

therapies, that are less likely to be used by them by creating testing standard and inexpensive, which will help us create a clearer picture of TP53 s role.

To ensure the accessibility and sustainability of TP53 testing, policy support is essential. The following section will explore how insurance policies can boost high-quality TP53 testing and improve patient access.

4. Conclusion

4.1. Summary of key findings

The research question that this review set out to answer was To what extent do TP53 mutations affect targeted therapy success in lung cancer? TP53 mutations do affect the outcome of EGFR-TKIs, ALK-TKIs, and ROS1-TKIs in NSCLC; with a moderate-to-strong negative impact.

TP53 mutations reduced overall response rates by 25 to 47% across the three therapies and shortened PFS by 35 to 63%. The effect has the strongest validation for Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs), where mutations are associated with lower response rates and higher progression risk. The most severe reduction of PFS was observed in ALKTKIs, especially with disruptive mutations, and a similar negative trend emerged among ROS1TKIs, although the evidence remains less certain due to small sample sizes. The combination of EGFR-TKIs with anti-angiogenic inhibitors is an exception to the negative effect of these drugs in some patients.

The review met its four objectives: to explain role of T53 in lung cancer, to analyse the impact of targeted therapies on the gene, to demonstrate if the gene has the potential to be a predictive biomarker and possibly demonstrate some limitations regarding the research like small sample sizes and inconsistent testing. While mutations in the tumor suppressor gene TP53 are not yet established as a clinical biomarker, their constant association to a negative affect indicates that they could help to further personalize treatment decisions for patients with NSCLC.

In summary, it appears that TP53 mutations are active drivers of reduced efficacy of targeted therapy, and embedding TP53 testing into clinical workflows supported by standardized research practices could markedly improve outcomes in high-risk patients. Further research to overcome current limitations will be crucial to unlocking the full clinical value of TP53 testing.

Having explored all key aspects of TP53 mutations' impact on targeted therapy—from mechanisms and efficacy data to clinical implications and solutions—the Conclusion section will synthesize these findings to answer the core research question and provide recommendations for future researchers.

4.2. Recommendations for future researchers

Future researchers could take note of the following directions to enhance this study and fill up remaining gaps. There should be large-scale prospective studies carried out. Trial-specific methods for TP53 mutation determination (involving exons 2–11; NGS; sensitivity of $\geq$ 1%) and long-term follow-up should validate the estimates of efficacy for ROS1-TKIs and subtype-specific effects.

Adopt uniform criteria (e.g. HGVS nomenclature, IARC TP53 Database classification) to describe TP53 variants and functional subtypes for easier comparisons across studies and meta-analyses.

Investigate co-mutation interactions: Research whether TP53 mutations interact with other mutations (e.g., MET, KRAS) to modify treatment response, as co-mutations may exaggerate or lessen the negative effect of TP53.

Conduct Randomized Controlled Trials (RCTs) to test the EGFR-TKIs + anti-angiogenic inhibitors combination in TP53-mutated patients and similarly for the ALK and ROS1-mutated NSCLC.

Machine learning models are used to predict treatment response utilizing TP53 mutation status, subtype and co-mutations for personalized therapy selection in NSCLC patients. Mutations in TP53 impair the effectiveness of targeted therapies in non-small cell lung cancer. Incorporating TP53 testing into clinical practice with standardized methodologies can significantly benefit high-risk patients. To unlock the complete clinical utility of TP53 testing, the current limitations of TP53 testing need to be addressed in future studies.

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