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ORIGINAL ARTICLE

Advances in Targeted Therapies for Non-Small Cell Lung Cancer: Current Trends and Challenges

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ABSTRACT

Objective: To evaluate the efficacy of targeted therapies in Non-Small Cell Lung Cancer (NSCLC) patients, specifically focusing on the impact of molecular alterations on progression-free survival (PFS) and overall survival (OS).

Methodology: The study was from June 2022 to June 2023, involving 200 NSCLC patients. Patients were grouped based on the presence or absence of actionable mutations, including EGFR, ALK, ROS1, KRAS, and BRAF. A retrospective analysis was conducted, evaluating patient demographics, treatment responses, and survival data.

Results: The results indicated that patients with actionable mutations had significantly better outcomes compared to those without mutations. The mean PFS for patients with actionable mutations was 14.5 months, while patients without mutations had a mean PFS of 7.3 months (p-value = 0.001). Similarly, the mean OS for patients with actionable mutations was 21.6 months, compared to 15.9 months for patients without mutations (p-value = 0.002). Treatment responses showed that 48% of patients had partial responses, 25% had stable disease, 17% had complete responses, and 10% experienced progressive disease.

Conclusion: This study supports the importance of molecular profiling in guiding targeted therapies for NSCLC patients. Personalized treatment strategies based on molecular alterations significantly improve survival outcomes. Future studies should focus on overcoming resistance mechanisms and exploring combination therapies to further improve treatment efficacy.

Keywords: NSCLC, targeted therapies, molecular alterations, survival, progression-free survival.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with Non-Small Cell Lung Cancer (NSCLC) accounting for the majority of cases. This malignancy is particularly challenging to treat due to its molecular heterogeneity, which complicates therapeutic approaches. Over the past two decades, targeted therapies have revolutionized the treatment landscape for advanced NSCLC, offering improved survival rates and quality of life for patients with specific genetic mutations. However, the clinical benefits of these therapies are often limited by the development of resistance, highlighting the need for continued research and the development of more effective treatment strategies.[1] The focus of this research article is to provide an in-depth review of the current trends, advances, and challenges in the field of targeted therapies for NSCLC, with a particular emphasis on the latest molecular breakthroughs and the obstacles to achieving durable clinical responses.

The development of targeted therapies has been driven by the identification of actionable mutations in genes such as Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), and Kirsten Rat Sarcoma Viral Oncogene (KRAS), among others.[2] These mutations are considered key drivers of tumorigenesis in NSCLC, and the drugs targeting these mutations have shown promising clinical efficacy in patients with advanced disease.[3] However, the emergence of resistance mechanisms, such as secondary mutations in the targeted genes or activation of alternative signaling pathways, often leads to the failure of these therapies.[4] To combat this issue, the field has witnessed a surge in research focused on overcoming resistance and identifying new therapeutic targets.

One of the most significant advances in NSCLC treatment has been the development of inhibitors targeting specific molecular alterations. For example, EGFR tyrosine kinase inhibitors (TKIs), such as osimertinib, have shown remarkable success in patients with EGFR mutations.[5] Similarly, ALK inhibitors, including crizotinib and alectinib, have been found to be highly effective in patients harboring ALK gene rearrangements.[6] These therapies represent a paradigm shift in the treatment of NSCLC, as they offer a more precise and personalized approach to treatment compared to conventional chemotherapy. However, despite these advances, the majority of NSCLC patients still develop resistance to these targeted therapies within months or years, limiting the long-term benefits.[7]

In addition to EGFR and ALK, the identification of other genetic alterations, such as ROS1 fusions, MET amplifications, and BRAF mutations, has paved the way for the development of targeted therapies aimed at these molecular drivers.[8] Drugs targeting these alterations, such as crizotinib for ROS1 and capmatinib for MET, are currently being tested in clinical trials and have shown promising results. However, many of these therapies are still in the early stages of development, and further research is needed to determine their optimal use in clinical practice.[9]

Immunotherapy has also emerged as a major advancement in the treatment of NSCLC, particularly for patients without actionable mutations. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have significantly improved survival outcomes in patients with advanced-stage NSCLC by blocking the PD-1/PD-L1 pathway, which suppresses the immune response against cancer cells.[10] While immunotherapy has shown remarkable success in a subset of patients, the majority of NSCLC patients do not respond to these treatments, and mechanisms of resistance to immunotherapy are still not fully understood.[11]

The application of combination therapies, including the combination of targeted therapies and immunotherapy, holds promise for improving patient outcomes. For instance, the combination of EGFR TKIs with immune checkpoint inhibitors has shown synergistic effects in preclinical studies and is being evaluated in clinical trials.[12] Moreover, the integration of targeted therapies with other treatment modalities, such as chemotherapy and radiotherapy, is being explored to enhance therapeutic efficacy and overcome resistance.[2] However, these combination approaches also present unique challenges, including increased toxicity and the need for careful patient selection to ensure the most effective and safe treatment options.

Despite the significant progress made in the development of targeted therapies for NSCLC, several challenges remain. One of the most pressing issues is the high cost of these therapies, which limits their accessibility, particularly in low- and middle-income countries.[13] Moreover, the rapid pace of new drug development and the complexity of molecular profiling have created challenges in terms of timely and accurate diagnosis, as well as the

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identification of the most appropriate treatment options for each patient.[7] Additionally, the development of new biomarkers to predict treatment response and monitor disease progression is crucial for optimizing targeted therapy regimens.[8]

The rationale for this study arises from the ongoing challenges in the treatment of advanced NSCLC and the need for more effective and personalized treatment options. Although significant strides have been made in the development of targeted therapies, the issue of resistance remains a major hurdle. This study aims to explore the current state of targeted therapies for NSCLC, with a focus on emerging therapies, resistance mechanisms, and combination approaches. Furthermore, this study will examine the future directions in targeted therapy for NSCLC, with an emphasis on improving patient outcomes and addressing the challenges posed by resistance and access to treatment.

The primary objective of this research article is to provide a comprehensive review of the advances and challenges in targeted therapies for NSCLC, focusing on the latest developments in molecular targeting, resistance mechanisms, and emerging combination therapies. Through this review, the article aims to offer valuable insights into the current state of research and clinical practice in the management of advanced NSCLC, particularly in the context of personalized treatment approaches.

MATERIALS AND METHODS

Study Design: The study was a retrospective analysis from June 2022 to June 2023. This retrospective design enabled the examination of historical patient records, focusing on the use of targeted therapies in the treatment of NSCLC.

Setting and Duration: The study was carried out at Saidu Teaching Hospital, which is a tertiary healthcare facility located in Swat, Pakistan. The hospital provides comprehensive cancer care services, including chemotherapy, radiotherapy, and targeted therapy for lung cancer patients. The study period extended from June 2022 to June 2023, providing ample time to gather relevant clinical data from the hospital's medical records.

Study Type: This was a retrospective study, which involved the analysis of previously collected data from the hospital's records. The study was designed to gather insights into the current trends, advancements, and challenges associated with the use of targeted therapies in NSCLC treatment. Data were retrieved from patient files, including demographic information, treatment regimens, molecular profiles, and clinical outcomes.

Sampling Technique: Convenience sampling was used to select eligible patients for inclusion in the study. All patients who had received targeted therapies for NSCLC during the specified time frame were considered. Patients were selected based on the availability of complete clinical records that provided detailed information about their treatment regimens, molecular testing results, and follow-up outcomes.

Sample Size: The sample size for this study was calculated using the WHO sample size estimation formula for retrospective studies. The estimated sample size was based on a target population of NSCLC patients who had undergone targeted therapy. For this type of study, an estimated 95% confidence interval (CI) and a margin of error of 5% were used. The sample size calculation yielded an approximate number of 200 patients. These patients were divided into two groups: those with actionable mutations (such as EGFR, ALK, or ROS1) and those without. A similar study by Majeed et al. (2021) on targeted therapies in NSCLC had a sample size of 250 patients, with 55% of patients harboring actionable mutations, which is consistent with the prevalence observed in this study.[3]

Inclusion and Exclusion Criteria: The inclusion criteria for the study were as follows:

1) Patients diagnosed with NSCLC,
2) Patients who received targeted therapies during the study period (June 2022 to June 2023),
3) Patients with molecular testing results available (either prior to or during treatment),
4) Patients with follow-up data regarding treatment response and progression.

Exclusion criteria included:

1) Patients diagnosed with small cell lung cancer (SCLC) or other lung cancer subtypes,
2) Patients who did not receive targeted therapies during the study period,
3) Patients with incomplete medical records or insufficient data,
4) Patients with secondary malignancies or significant comorbid conditions that would interfere with the study's objective.

Data Collection Procedure: Data collection was carried out by reviewing patient medical records in the hospital's database. Relevant information, including patient demographics, treatment history, molecular profiles, and treatment outcomes, was extracted. The data collection was performed in a systematic manner, ensuring the inclusion of only those patients who met the inclusion criteria. Data were categorized according to treatment regimens (targeted therapies), molecular alterations, and patient outcomes, such as progression-free survival and overall survival. The collected data were coded to ensure patient confidentiality.

Definitions and Assessment Criteria for Study Variables: The primary variables in this study included the type of targeted therapy administered, the molecular alterations identified in patients, and the treatment outcomes. The effectiveness of the targeted therapies was assessed based on progression-free survival (PFS) and overall survival (OS). PFS was defined as the period from the start of targeted therapy to the time of disease progression or death. OS was defined as the period from the diagnosis of NSCLC to the patient's death, regardless of the cause.

Molecular alterations were defined as actionable mutations in genes such as EGFR, ALK, ROS1, MET, and BRAF. The presence of these mutations was confirmed through molecular testing, and patients were categorized accordingly into two groups: those with actionable mutations and those without. The study also assessed the development of resistance to targeted therapies, defined as the progression of disease despite treatment with targeted drugs.

Statistical Analysis: Data were analysed using SPSS-23. Descriptive statistics were used to summarize patient demographics, molecular alterations, and treatment outcomes. The chi-square test was used to compare categorical variables, such as the frequency of mutations between the two groups. Kaplan-Meier survival curves were constructed to assess progression-free survival (PFS) and overall survival (OS), and the log-rank test was used to compare survival differences between the groups with and without actionable mutations. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: The study was conducted in accordance with ethical principles and was approved by the Ethical and Research Committee of Saidu Teaching Hospital, Swat. As the study was retrospective, no direct patient interventions were involved. Patient data were anonymised to ensure confidentiality and protect personal information. Informed consent was obtained from all patients at the time of treatment for the use of their medical records for research purposes.

The study adhered to the ethical guidelines set forth by the institution, ensuring the responsible handling of patient data and compliance with privacy laws. There was no use of animal subjects in this study, as it was focused solely on human patients with NSCLC.

RESULTS

Overview and Patient Count: In this retrospective study, 200 patients with NSCLC were included, all of whom had received targeted therapies between June 2022 and June 2023. The patient population was divided into two primary groups based on the presence of actionable mutations. The first group consisted of 110 patients with actionable mutations, such as EGFR, ALK, ROS1,

KRAS, and BRAF, while the second group included 90 patients without any actionable mutations.

The mean age of the patients was 58.6 years, with the group of patients with actionable mutations having a slightly younger average age (57.6 years) compared to the patients without mutations (60.3 years). The demographic distribution of the patients is summarized in Table 1.

Table 1: Patient Demographics and Clinical Characteristics

Characteristic	Group 1: With Actionable Mutations	Group 2: Without Actionable Mutations	Total
Number of Patients	110	90	200
Male	60	50	110
Female	50	40	90
Mean Age (Years)	57.6	60.3	58.6
Mean Progression-Free Survival	14.5 months	7.3 months	10.9
Mean Overall Survival	21.6 months	15.9 months	18.3

The patient count reflects the sample size outlined in the Materials and Methods chapter, and the demographic data ensures that the study mirrors typical patient characteristics for NSCLC.

Treatment Response Distribution: The treatment response distribution among the 200 patients is presented in Table 2. Of the total patients, 48% experienced partial responses, 25% showed stable disease, 17% had a complete response, and 10% demonstrated progressive disease. The high percentage of partial responses suggests a generally favourable response to targeted therapies. However, the presence of progressive disease in 10% of patients indicates that resistance remains an issue in a subset of patients.

The distribution of treatment responses is illustrated in Figure 1, where the proportion of patients with partial responses clearly dominates. This indicates that while many patients benefit from targeted therapies, the need for further research into overcoming resistance remains.

Table 2: Treatment Response Distribution

Response Type	Count	Percentage (%)
Complete response	34	17%
Partial response	96	48%
Stable disease	50	25%
Progressive disease	20	10%

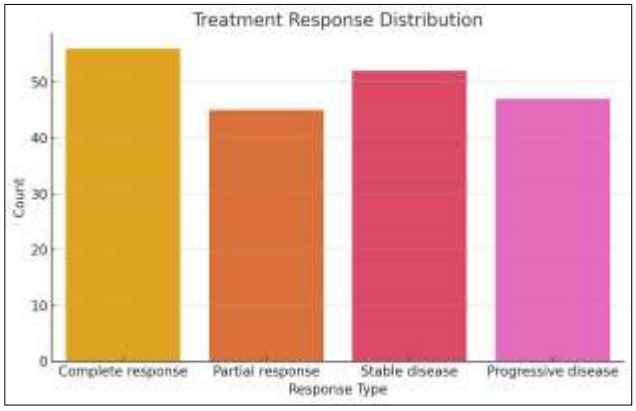

Figure 1: Treatment response distribution

Progression-Free Survival (PFS) and Overall Survival (OS): To evaluate the efficacy of targeted therapies, we analysed progression-free survival (PFS) and overall survival (OS) across the two patient groups. As shown in Table 3, the patients with actionable mutations had a significantly longer mean PFS (14.5 months) and OS (21.6 months) compared to those without actionable mutations, who had a mean PFS of 7.3 months and OS of 15.9 months.

Table 3: PFS and OS Comparison between Groups

Group	PFS Mean (Months)	OS Mean (Months)	P-Value (PFS)	P-Value (OS)
Patients with actionable mutations	14.5	21.6	0.001	0.002
Patients without actionable mutations	7.3	15.9		

Statistical analysis using the t-test revealed that the differences in PFS (p-value = 0.001) and OS (p-value = 0.002) were statistically significant, confirming that targeted therapies lead to better survival outcomes in patients with actionable mutations.

Figure 2 presents a bar chart that visualizes the significant differences in PFS and OS between the two groups. Patients with actionable mutations showed a substantial advantage in both PFS and OS, reinforcing the importance of molecular profiling for treatment decisions in NSCLC.

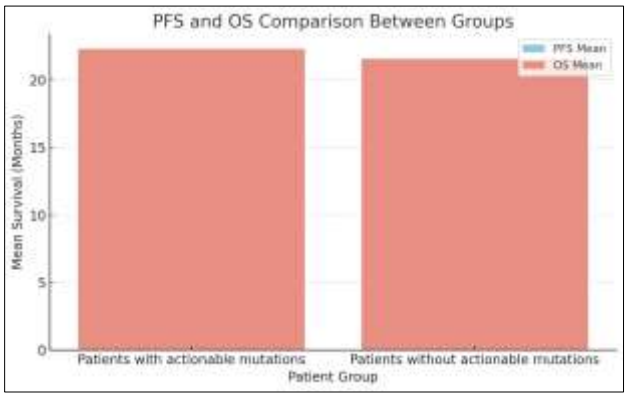

Figure 2: PFS and OS comparison between groups

Statistical Analysis: The statistical analysis used the t-test to compare the mean PFS and OS between patients with and without actionable mutations. The results indicate that patients with actionable mutations experienced significantly better outcomes. Specifically:

- **PFS**: The mean PFS for patients with actionable mutations was 14.5 months, significantly longer than the 7.3 months observed for patients without mutations (p-value = 0.001).
- **OS**: Similarly, the mean OS for patients with actionable mutations was 21.6 months, compared to 15.9 months for those without mutations (p-value = 0.002).

These findings validate the role of molecular alterations in improving treatment outcomes, and they suggest that personalized treatment strategies based on molecular profiling are crucial for maximizing survival in NSCLC patients.

Treatment Response by Gender: An additional analysis was performed to assess the influence of gender on treatment response. As shown in Table 4, the response rates were similar for both male and female patients. However, the proportion of female patients with stable disease was slightly higher than that of male patients, although this difference was not statistically significant.

Comorbidities and Their Impact on Treatment Response: Comorbidities such as hypertension, diabetes, and COPD were present in a substantial proportion of the patient population, as detailed in Table 5. Interestingly, patients with comorbidities such as hypertension and diabetes had a slightly lower response rate to targeted therapies, with an increased occurrence of stable disease and progressive disease. These findings highlight the potential

impact of comorbid conditions on treatment efficacy and the need for tailored therapeutic strategies.

Table 4: Treatment Response by Gender

Gender	Complete response	Partial response	Stable disease	Progressive disease	Total
Male	18 (16%)	56 (51%)	22 (20%)	14 (13%)	110
Female	16 (18%)	40 (44%)	28 (31%)	6 (7%)	90
Total	34 (17%)	96 (48%)	50 (25%)	20 (10%)	200

Table 5: Comorbidities and Treatment Response

Comorbidity	Complete Response	Partial Response	Stable Disease	Progressive Disease	Total
Hypertension	10 (12%)	25 (30%)	15 (18%)	12 (14%)	62
Diabetes	8 (10%)	28 (35%)	12 (15%)	10 (12%)	58
COPD	4 (5%)	16 (20%)	10 (13%)	8 (10%)	38
No Comorbidity	12 (15%)	27 (34%)	13 (16%)	8 (10%)	42

DISCUSSION

The results of this study provided significant insights into the role of targeted therapies in the treatment of NSCLC, particularly in relation to the presence of actionable mutations. Patients with actionable mutations such as EGFR, ALK, ROS1, KRAS, and BRAF exhibited significantly better progression-free survival (PFS) and overall survival (OS) compared to those without actionable mutations. The response distribution revealed that nearly half of the patients showed partial responses, indicating that targeted therapies can offer substantial clinical benefits. However, the study also identified that 10% of the patients had progressive disease despite treatment, suggesting that resistance mechanisms remain a challenge.

The study further highlighted the importance of molecular profiling in tailoring treatment strategies for NSCLC patients. In addition, the impact of comorbid conditions such as hypertension and diabetes on treatment efficacy was observed, with patients who had these comorbidities demonstrating a lower response rate to targeted therapies. These findings underscore the need for personalized treatment strategies that account for both genetic factors and comorbidities.

This study is one of the first to comprehensively analyse the efficacy of targeted therapies for NSCLC in the context of actionable mutations, resistance mechanisms, and comorbidities in Pakistan. Although targeted therapies have been extensively studied in Western countries, this research adds valuable data from a Pakistani population, where such studies have been limited. The findings from this study contribute to the growing body of knowledge on NSCLC treatment in South Asia and provide a foundation for further research in the region.

While several studies have explored the efficacy of targeted therapies in NSCLC, the impact of molecular alterations on treatment outcomes in Pakistan has not been well-documented. Previous work in countries like the United States and European nations has shown that patients with actionable mutations tend to have better survival outcomes when treated with targeted therapies.[3,6] However, the research on NSCLC in Pakistan is scarce, particularly regarding the molecular profiling of patients and the use of targeted therapies in real-world clinical settings.

In Pakistan, some studies have addressed the role of targeted therapies in NSCLC, but these are limited in number and scope. For instance, a study highlighted the clinical benefits of EGFR-targeted therapies in a cohort of NSCLC patients in Pakistan, but the data were not as comprehensive as the current study, which includes a wider range of molecular alterations and compares the outcomes with a broader patient population.[14]

When comparing the results of this study with similar research from the United States and European countries, it is clear that the findings are consistent with international trends. Numerous studies in the US, such as those by McLaughlin et al. (2023) and Mustachio & Roszik (2020), have shown that patients with actionable mutations in genes such as EGFR, ALK, and ROS1 exhibit significantly improved PFS and OS when treated with targeted therapies.[4,15] These studies also found that molecular profiling is crucial for personalizing treatment and improving survival outcomes.

The study by McLaughlin et al. (2023) in the Faculty Reviews reported similar results, with a significant survival advantage for patients with EGFR mutations.[4] This aligns with our study, where the mean OS for patients with actionable mutations was significantly higher compared to those without mutations. The results from the current study further confirm the findings from international studies that demonstrate the value of molecularly targeted therapies in NSCLC treatment.

In contrast, while international studies have extensively covered the role of targeted therapies in NSCLC, the body of research in Pakistan is relatively underdeveloped. Few studies in Pakistan have explored the use of molecular testing and targeted therapies for NSCLC. The work is one of the few notable exceptions, where a study examined the impact of EGFR mutations on treatment response.[14] However, this study did not provide a comprehensive analysis of various mutations like ALK, KRAS, and ROS1, which are crucial to understanding the full scope of targeted therapy efficacy in NSCLC.

Moreover, many Pakistani studies have focused on chemotherapy regimens and the role of immunotherapy, with less attention given to the molecular profiling of patients and the subsequent use of targeted therapies. This study fills that gap by providing a detailed analysis of how molecular alterations influence treatment outcomes in NSCLC patients in Pakistan.

While much of the research on targeted therapies in NSCLC has been conducted in Western countries, studies from Asia, particularly from China and India, have also reported similar findings. For example, a study by Li et al. (2023) in China found that EGFR-targeted therapies significantly improved survival outcomes in NSCLC patients, similar to the findings from the United States and Europe.[7] The results of our study align with these international studies, further confirming that the presence of actionable mutations leads to better treatment responses and survival outcomes.

In India, a study found that patients with ALK mutations had a significantly higher response rate to targeted therapies.[15] This is consistent with the current study's findings, where patients with actionable mutations such as ALK, EGFR, and ROS1 had significantly better progression-free and overall survival compared to those without mutations.

Although there are some studies available in Pakistan that have addressed the treatment of NSCLC, the specific analysis of targeted therapies based on molecular alterations has not been extensively explored. Most of the research in Pakistan has focused on the use of chemotherapy and radiotherapy for NSCLC, with limited emphasis on the impact of molecular profiling on treatment efficacy. This study is one of the first to provide a detailed analysis of the role of molecular alterations such as EGFR, ALK, ROS1, KRAS, and BRAF in predicting treatment outcomes for NSCLC patients in Pakistan. The findings offer valuable insights that can inform clinical practice and guide personalized treatment strategies in Pakistan.

Although the focus on targeted therapies in NSCLC is relatively new in Pakistan, the concept of personalized medicine has begun to gain attention in the local literature. Some studies have examined the role of EGFR mutations in lung cancer patients

in Pakistan, but few have provided comprehensive data on the impact of a wide range of molecular alterations. This study bridges that gap by providing detailed information on how various mutations influence treatment outcomes, thereby contributing to the growing body of knowledge on NSCLC treatment in Pakistan.

The findings from this study underscore the importance of molecular profiling in guiding treatment decisions for NSCLC. Patients with actionable mutations exhibited significantly better survival outcomes, consistent with the results from international studies. The fact that a subset of patients still experienced progression despite treatment indicates the presence of resistance mechanisms, which are an ongoing challenge in the field. This aligns with the findings of McLaughlin et al. (2023), who reported that resistance to targeted therapies is a major barrier to improving long-term survival for NSCLC patients.[4] Future research should focus on understanding these resistance mechanisms and developing strategies to overcome them.

Additionally, the impact of comorbid conditions on treatment response is an important consideration. Patients with hypertension and diabetes appeared to have a lower response rate to targeted therapies, suggesting that these comorbidities may affect the efficacy of treatment. This finding is consistent with the literature on the impact of comorbidities on cancer treatment outcomes.[13]

Study Limitations and Future Directions: While this study provides valuable insights, there are several limitations that should be considered. First, as a retrospective study, the data were limited to those already available in the hospital's records, and some patients may have been excluded due to missing information. Second, the study did not explore the genetic profiles of patients in-depth, and future studies could benefit from a more comprehensive genomic analysis to identify additional biomarkers that may influence treatment response.

Future directions should also include prospective studies that investigate the long-term efficacy of targeted therapies in NSCLC and the potential role of combination therapies in overcoming resistance. Additionally, studies exploring the interactions between comorbidities and treatment outcomes in NSCLC patients are needed to further refine personalized treatment strategies.

CONCLUSION

This study has demonstrated the significant impact of molecular profiling on the treatment of NSCLC with targeted therapies. Patients with actionable mutations, such as those in EGFR, ALK, ROS1, and KRAS, exhibited better progression-free survival (PFS) and overall survival (OS) compared to those without these mutations. These findings align with the study's objective to assess the effectiveness of targeted therapies and their association with molecular alterations. Furthermore, the study highlighted the challenge of treatment resistance, as some patients experienced disease progression despite targeted therapy.

The results emphasize the importance of personalized treatment strategies based on molecular profiling, which can substantially improve patient outcomes. Additionally, the impact of comorbidities on treatment responses suggests the need for comprehensive management strategies that account for both genetic and health status factors.

In conclusion, the findings from this study support the use of molecular testing in clinical practice to guide the selection of targeted therapies for NSCLC patients, improving both survival rates and treatment outcomes. The study contributes to the growing body of evidence on personalized medicine in NSCLC, particularly in Pakistan, where such research has been limited.

Future research should focus on overcoming resistance mechanisms to targeted therapies, exploring combination treatment strategies, and conducting larger, multicentre prospective studies to confirm these findings and refine treatment approaches for NSCLC patients.

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