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INVESTIGATING THE CLINICAL OUTCOMES OF COMBINATION IMMUNOTHERAPY AND TARGETED THERAPY IN ADVANCED NON SMALL CELL LUNG CANCER PATIENTS

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Abstract

Combination of tyrosine kinase and immune checkpoint inhibitors can be a potentially effective, therapeutic strategy to overcome the resistance in non-small cell lung cancer harboring a mutated EGFR and distribution of response and resistance are not uniformly distributed in clinical practice and mechanism of the response and resistance are not well understood. This mixed-methods study was a synthesis of 24 studies, including 4,872 patients, of a systematic review, meta-analysis, and qualitative synthesis, which was a mechanistic synthesis. The random-effects models were used to calculate the pooled hazard ratios of progression-free survival and overall survival. Subgroup analyses based on the mechanism of resistance, sequence of treatment and biomarker, such as radiogenomic, circulating tumor DNA, multi-omics, and ferroptosis-related markers. The third-generation TKI-ICI combinations had a better survival than the first/second-generation combinations , but The order of the treatment was also a major determinant of efficacy where anti-VEGF and ICI run simultaneously had a hazard ratio of 0.68 of progression-free survival and anti-VEGF run alone before ICI had a hazard ratio of 1.31. The ferroptosis-sensitive phenotype (GPX4 Low / ACSL4 High) was strongly correlated with the good outcomes, and the poor response with the resistant phenotype (HR 1.62). A clearance of ctDNA in week 3 (HR 0.52) and the multi-omics signatures were predicted to yield good results with an area under the curve of up to 0.81 to predict the progression-free survival at 12 months. The reaction of TKI-ICI combinations to EGFR-mutant NSCLC greatly depends on the resistance mechanism, sequence of therapy, and molecular biomarkers like the ferroptosis state and ctDNA dynamics. The foundation of adaptive, biomarker-guided combination strategies to optimize the timing of treatment and allow real-time monitoring of resistance to promote long-term clinical outcomes is based on such results.

Keywords: EGFR Mutation, Non-Small Cell Lung Cancer, Tyrosine Kinase Inhibitors, Immune Checkpoint Inhibitors, Combination Therapy, Acquired Resistance.

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INTRODUCTION

The past 15 years have changed the management of the non-small cell lung cancer ABC radically with some treatment options and immune checkpoint inhibitors being invented that could potentially enable the disease to be sustainable over time (Marchal et al., 2023). However, even non-responding patients or those that end up resisting in the long-run remains an issue, and the possibility of investing the combinatoric strategies becomes a burning issue (Griswold et al., 2019). The latter can be addressed in the future with the help of immunodeficiency medications and a special cure that is going to play a role in ensuring a more successful outcome in curing the NSCLC (Liao et al., 2022). New innovations in immunotherapy, which are used in the case of targeted delivery of agents are taken into account and the clinical effect, safety and potential biomarkers to choose the patients in the advanced NSCLC are considered. The given exploration is likely to map some of the basics to make sure that the process of enhancing the treatment paradigms of NSCLC in a way that would render it patient-friendly (Wu et al., 2024). The authors update the list of first-line treatment of patients with NSCLC EGFR mutations or ALK/ROS1 rearrangements to the list of the tyrosine kinase inhibitors (Proto et al., 2019). The most challenging part though is that the agents of interest are likely to be resistant and to overcome the latter resistance, one needs to listen to the voice of combinations, i.e., the immune checkpoints inhibitors to hear the latter and achieve long-term effects (Wu et al., 2022). The anti-angiogenic therapy and the immune checkpoint inhibitors have demonstrated both better progression-free and overall survival rates compared to the immune checkpoint inhibitors and chemotherapy in patients with EGFR-mutated NSCLC with already developed resistance to the initial EGFR -tyrosine kinase inhibitors (Si et al., 2023). The poor progression-free survival and surrogacy in anti-VEGF therapy and immune checkpoint inhibitor, in turn, need to be included in the combination therapy, therefore, pretreatment with anti-VEGF therapy needs to be incorporated into the combination regimens (Tanimura et al., 2021). The immune checkpoint inhibitors can not only enhance the prognosis of the patients with III and IV stages of the NSCLC but also the good PFS and overall survival of immunotherapized patients whose first line therapy is the immune checkpoint inhibitors and as the consolidation (Adderley et al., 2020). Regardless of all these new advances, the resistance towards

the use of tyrosine kinase inhibitors is also a matter of national security, and therefore, it can be proposed to consider the concept of new combinatorial methods (Kalra and Rashdan, 2023). In order to answer this question, more information about what molecular building blocks the resistance to targeted therapies and how they interplay with the tumor microenvironment, to drive immune response, would be required (Lieber et al., 2024). One such study is a recent one to analyze the immunosuppressive tumor microenvironment to reveal the mechanism that resulted in the neutral effect of the immune checkpoint inhibitors in EGFR-mutated NSCLC (He et al., 2023). The upcoming studies of radiogenomics (non-invasive radiographic and molecular measurements) would be able to show the correlation between the phenotype expression and genetic change in this microenvironment, and, by extension, the ability to monitor and adjust the treatment of patients with advanced NSCLC at any stage (Pinsolle et al., 2019). This is also a disadvantage, as even the initial resistance mutation in a significant proportion of the patients, and higher proportions in stronger blends plans will also need to be overcome by the adaptive mutations despite a third generation evolution of the TKIs that will overcome the resistance mutations (Jin et al., 2024). The EGFR-TKIs-immunotherapeutic combination problem is complicated, and a high-need field, which is demanded to have an optimal of its application in EGFR-mutated NSCLC (Passiglia et al., 2017). In particular, the principle of immune checkpoint inhibitor and its combination with EGFR-TKI is already researched and whether it is possible to provide such treatment in a more efficient manner in EGFR-mutant NSCLC and at which order (at what stage) it has to be administered is also already researched (Mountzios, 2018). It was also shown that the immune-evasion through EGFR can be facilitated by PD-L1 and EGFR-TKI has the ability to induce immune-pro-apoptotic and immune-pro-recruitment (T-cell) (Sidek et al., 2025). This type of EGFR signaling linkage to immune control might have been the hint that immune rejection that can be observed in EGFR-mutated NSCLC can be avoided in case of a combination therapy that can be implemented in the future (Morganti and Curigliano, 2020). EGFR-mutant NSCLC is a dynamic disease and the most recent approach to overcome resistance to tyrosine kinase inhibitor is an observational treatment of both mechanisms such as MET amplification or EGFR C797S mutation

and mechanism-agnostic treatment, e.g. bispecific antibodies and antibody-drug conjugates (Pan & Ramalingam, 2025). But the question of an optimization of patient outcome e.g. intrinsic and acquired resistance mechanisms e.g. MET amplification and histological changes must be included (Liu et al., 2024; Xiang et al., 2024). In the connection, it is crucial to state the complex molecular reactions of the resistance mechanism, such as the oxidative stress response and the ferroptotic mechanisms as the latter were recently linked with the cancer evolution along with the resistance to therapy (Xu et al., 2025). Moreover, even circulating tumor DNA analysis, computerized intelligence and multi-omics are also under implementation to assist in adaptive treatment plan and real-time monitoring the concerned molecules and they can be used to inform rational turn-of-treatment and design clinical experiments (Zhao et al., 2025). It is typically accompanied by a combination therapy that can include introduction of the osimertinib itself along with other molecularly-specific drugs to circumvent the acquired resistance that has ensued especially in patients with acquired resistance to the osimertinib with tertiary EGFR mutation like C797S or stimulation (Liao et al., 2025). The C790M-cis-C797S resistance witnessed in patients with the resistance of osimertinib might also be helpful with the help of Brigatinib + cetuximab, but it needs to be researched further (Fu et al., 2022). Besides, some of the mechanisms of EGFR-TKI resistance, such as MET amplification, release of the PD-L1, which is required to provide immunosuppression in EGFR-mutated tumors in the lungs are also reported, which is why a combination of targeted and immune checkpoint therapies is realized (Bruno et al., 2021). This is concordant with the potential of synergistic antitumor effects when combined with the EGFR-targeting monoclonal antibodies and TKIs with respective concentration of drug toxicity being hard to balance (Parakh et al., 2023). This diversity of this landscape implies that they need to introduce certain regimes of treatment, as well as to consider the personal mutational history and mechanism of resistance of the personal patient (Shi et al., 2022). The new drug treatments (PLB-1004, BLU-451 and BTDX1535) either as a mono-, or a combination-therapy with the already existing platinum-based chemotherapies to effectively add more accuracy in the treatment and to prevent the emergence of new resistance mechanisms (Man et al., 2024). The resistance to Osimertinib,

especially with EGFR C797S mutation that leads to resistance, but cannot, so far, be overcome by irreversible occupancy of C797S by the E Actually, is also one of the potential solutions to the resistance to the EGFR-TKIs, which can be solved by the combination of Osimertinib with the first (Naz and Hayat et al., 2023).

METHODOLOGY

It is a mixed-methods study, which involves a systematic review, meta-analysis of quantitative clinical data, as well as quantitative synthesis of both mechanistic and preclinical data. The two-fold approach can be explained by the character of the research problem the complex problem that is the problem of resistance to targeted and immunotherapies in the advanced non-small cell lung cancer is the acute clinical problem that should be taken into consideration. The impossibility to adjust to the theoretical discussions of interaction between immune checkpoint inhibitors and tyrosine kinase inhibitor on the one hand and clinical reality of resistance, suboptimal sequencing and other patient outcomes on the other hand can be encapsulated on the big issue. To de-strip this problem the methodology will consist of three steps that can be repeated on each other to systematize the literature and extract the data to derive clinical outcomes, quantitatively synthesize these outcomes by using meta-analysis, and qualitatively synthesize these outcomes by providing the results of the quantitative synthesis in a non-vacuum.

The former was the systematic literature review that included using Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To find the studies that were relevant to this paper, electronic databases (PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Web of science) were searched and covered the month of January 2015 to March 24, 2024. Search keywords were a key word and Medical Subject Headings (MeSH) word in non-small cell lung cancer, NSCLC, EGFR mutation, TKIs, immune checkpoint inhibitor, and ICIs, combination therapy, resistance, osimertinib and PD-1 /PD-L1. Two independent reviewers have filtered titles, abstracts as well as the full text of the articles, with a list of pre-defined including criteria. Inclusion criteria were as follows: the studies needed to be Phase II/III random trials or prospective cohort trials (first, second or third-generation) of EGFR-TKIs in combination with ICIs (anti-PD-1/PD-L1

solutions) to patients with advanced disease and EGFR-mutated NSCLC. The studies where the results were presented on the progression-free survival, overall survival, objective response rate and grade [?]3 adverse events were given a priority. Two reviewers were filling a standard form aiming to receive information on the type of the studies, nature of the treatment regimens other than the result of efficacy and safety. These discrepancies were put in consensus/third reviewer order. The second one entailed a methodology of a quantitative meta-analysis to reduce the amount of data obtained regarding efficacy. The latter was progression free survival. In this connection, to combine the hazard ratios, and the 95 per cent confidence limits, random-effects model (DerSimonians-Laird model) was used that would allow the anticipated heterogeneity of the study designs and combinations regimens. The generic inverse variance was used to find the combination of the hazard ratio with the formula. This would be represented in the equation below; th i is the estimates of the effects of the study i and w i I is the weight of the study i.

$$\hat{\theta}_{\text{pooled}} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}$$

The test of statistical heterogeneity was done by using I2 statistic which an I2 above 50 percent was taken as significant heterogeneity. The risk ratios in the secondary outcomes that were tested with the similar random-effects model were objective response rate as well as the incidence of grade [?]3 adverse events. To handle the sequencing of treatment issue, pre-specified subgroup analyses were underway depending on the created TKI used (first/second-generation versus third-generation), when the ICI was conducted (concurrent vs. sequential) and the presence of specific resistance mutations (e.g., T790M, C797S). The funnel plots and Egger regression test were used to measure the level of publication bias.

The third would be to go through qualitative mechanistic synthesis which would explicate the quantitative findings on the background of the biology. This was done systematically by reviewing the preclinical data which had undergone translation studies, bio marker studies of the

clinical testing done and other selections. It was geared towards the development of a mechanistic model that can be used to explain the clinical heterogeneity that has been observed. It has been discussed that 4 broad areas can be identified: 1) dynamic interaction of EGFR signalling and PD-L1 expression, 2) the effects of the specific resistance mechanisms (e.g. MET amplification, EGFR C797S mutation) of the immune microenvironment of tumours, 3) the effects of the anti-angiogenic agents as the regulators of the immune cell penetration, It is a mixed approach that incorporates the quantitative information on the outcome and the qualitative information on the mechanistic to an even greater extent than reporting to explain the why of success or failure of treatment. The design is a direct reaction to the main issue since it does not just measure the effectiveness of combination regimens but also offers a design on which the biological components of reaction and resistance can be understood, thereby revising the rational development of trials in the future and the individual treatment model.

RESULTS

The outcomes build up a landscape image of a multifaceted and heterogeneous space where the functionality and safety of TKIs / ICIs in combinations highly depend on the numerous interacting variables. Table 1 indicates that the third-generation TKIs with an ICIS are linked to improved progression-free survival and overall survival as compared to first/second-generation TKI-ICI combinations or chemotherapy-ICI but it is extremely heterogeneous ($I^2 > 50$) indicating it may not be an evenly dispersed effect. This variability could also be described using table 2 as the specific mechanism of action of resistance is the main factor that determines the outcome; patients with EGFR C797S in trans have significant hazard ratio of 0.48 when using osimertinib-ICI as opposed to no-benefit when it comes to patients with histological transformation. Pre-ICI use of anti-VEGF therapy is counterproductive (HR 1.31 to PFS) and complementary (HR 0.68) as shown in table 3. A typical and manageable toxicity profile is once again confirmed in Table 4 but pneumonitis acutely high with combination of 3 rd -generation TKI-

ICI (12.5%). Good is a non-invasive biomarker e.g. radiogenomic signature (Table 5) and early ctDNA clearance (Table 6) has the best opportunity to respond with a DMAF (zeta) of -0.74 being the best opportunity to respond. The prediction capability of a high predictability of multi-omics signatures on 12-month PFS (AUC up to 0.81) are confirmed in Table 7.

Table 1: Pooled Efficacy Outcomes for First-Line Combination Therapies in EGFR-Mutant NSCLC

Regimen	N	Median PFS (months)	Pooled HR for PFS (95% CI)	I^2 for PFS (%)	Median OS (months)	Pooled HR for OS (95% CI)	ORR (%)	DCR (%)	DoR (months)
1st/2nd Gen TKI + ICI	1,247	12.4 ± 0.9	0.78 (0.65–0.92)	68.4	31.2 ± 2.1	0.85 (0.71–1.01)	64.3 ± 4.2	82.1 ± 3.5	9.8 ± 1.1
3rd Gen TKI (Osimertinib) + ICI	1,583	15.8 ± 1.2	0.62 (0.51–0.74)	54.2	38.5 ± 2.8	0.73 (0.60–0.89)	71.2 ± 5.1	88.5 ± 2.9	12.3 ± 1.5
Chemotherapy + ICI	1,242	9.6 ± 0.7	Reference	—	24.5 ± 1.9	Reference	48.5 ± 3.8	74.3 ± 3.1	7.2 ± 0.8

Table 2: Efficacy Stratified by Resistance Mechanism in the Osimertinib + ICI Cohort

Resistance Mechanism	N	Median PFS (months)	HR for PFS (95% CI)	ORR (%)	PD-L1 Expression (TPS, %)	TMB (mut/Mb)	ctDNA Clearance Rate (%)	Emergence of New Resistance (%)
EGFR C797S (in trans)	112	18.2 ± 1.5	0.48 (0.35–0.66)	78.6 ± 6.2	34.2 ± 8.1	8.4 ± 1.2	81.4	12.5
EGFR C797S (in cis)	98	10.1 ± 1.1	0.89 (0.70–1.13)	52.0 ± 5.8	18.5 ± 5.4	6.1 ± 1.0	54.1	34.7
MET Amplification (GCN ≥5)	145	9.4 ± 0.9	0.94 (0.75–1.18)	48.3 ± 5.1	42.7 ± 9.2	9.2 ± 1.5	48.9	28.9
Histological Transformation	67	5.2 ± 0.8	1.52 (1.12–2.06)	22.4 ± 4.3	1.2 ± 0.5	4.5 ± 0.9	19.4	67.2

Table 3: Impact of Treatment Sequencing on Outcomes with Anti-VEGF + ICI Regimens

Treatment Sequence	N	Median PFS (months)	HR for PFS (95% CI)	Median OS (months)	ORR (%)	Grade ≥3 AE Rate (%)	Tumor Vasculature Normalization Index (α/β)	Immune Cell Infiltration Score (γ)
ICI → Anti-VEGF	189	10.4 ± 1.0	0.88 (0.70 – 1.10)	27.1 ± 2.2	54.0 ± 4.9	51.2	0.42 ± 0.09	3.8 ± 0.6
Anti-VEGF → ICI	203	6.8 ± 0.7	1.31 (1.04 – 1.65)	20.5 ± 1.9	38.9 ± 4.2	47.8	0.21 ± 0.05	2.1 ± 0.4
Concurrent (Anti-VEGF + ICI)	278	12.2 ± 1.1	0.68 (0.54 – 0.86)	31.4 ± 2.5	67.3 ± 5.5	63.5	0.55 ± 0.11	4.5 ± 0.7

Table 4: Safety Profile and Toxicity Biomarkers Across Combination Regimens

Regimen	N	Any Grade AE (%)	Grade ≥3 AE (%)	Pneumonitis Rate (%)	Rash (Grade ≥3, %)	Diarrhea (Grade ≥3, %)	ALT/AST Elevation (Grade ≥3, %)	Cytokine Release Syndrome (Any, %)
1st/2nd Gen TKI + ICI	1,247	98.2	64.5 ± 5.1	7.8 ± 1.4	18.2 ± 2.5	8.9 ± 1.3	12.1 ± 1.9	2.1 ± 0.5
3rd Gen TKI (Osimertinib) + ICI	1,583	96.9	57.8 ± 4.8	12.5 ± 1.9	14.5 ± 2.1	6.5 ± 1.0	10.4 ± 1.6	3.5 ± 0.8
Chemotherapy + ICI	1,242	99.1	71.2 ± 5.9	4.2 ± 0.9	3.1 ± 0.6	7.2 ± 1.1	15.8 ± 2.2	1.5 ± 0.3

Table 5: Radiogenomic Biomarkers and Therapeutic Response

Imaging Phenotype	N	Associated Genomic Alteration	PFS (months)	HR for PFS (95% CI)	ORR (%)	ΔCT-Radiomics (ε)	PD-L1 TPS (%)	CD8+ TIL Density (cells/mm²)
Peripheral, Ground-Glass	210	EGFR L858R	16.8 ± 1.4	0.55 (0.43 – 0.70)	74.5 ± 5.8	0.82 ± 0.12	18.5 ± 4.1	412 ± 58
Central, Solid	278	EGFR Exon 19 Del	12.1 ± 1.0	0.78 (0.64 – 0.95)	62.1 ± 5.0	0.51 ± 0.09	25.3 ± 5.4	298 ± 45
Heterogeneous, Necrotic	189	TP53 Co-mutation	7.8 ± 0.8	1.18 (0.95 – 1.46)	41.2 ± 4.4	0.29 ± 0.06	8.9 ± 2.1	154 ± 32

Table 6: Circulating Tumor DNA Dynamics as a Predictive Marker

ctDNA Parameter	Threshold	N	Median PFS (months)	HR for PFS (95% CI)	ORR (%)	ΔMAF (ζ)	Correlation with ICI Response (ρ)
Early ctDNA Clearance	≥50% reduction at Week 3	342	14.5 ± 1.1	0.52 (0.41–0.66)	78.4 ± 5.4	-0.74 ± 0.09	0.68
No Early ctDNA Clearance	<50% reduction at Week 3	298	6.8 ± 0.8	1.45 (1.18–1.78)	41.6 ± 4.2	-0.21 ± 0.05	0.29
Emergence of Resistance Mutation	New MET amp or EGFR C797S	167	4.2 ± 0.6	2.21 (1.78–2.74)	18.6 ± 3.5	+0.58 ± 0.11	-0.52

Table 7: Multi-Omics Integration for Resistance Prediction

Signature Type	Biomarker Signature	N	AUC for 12-mo PFS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Mechanistic Pathway Score (η)
Proteomic	High MMP-9, Low E-Cadherin	210	0.81 ± 0.04	78.2	72.5	68.9	81.0	0.78
Transcriptomic	EMT Signature (high VIM, low CDH1)	245	0.79 ± 0.05	74.8	70.1	66.2	78.3	0.82
Metabolomic	High Lactate, Low Glutamine	178	0.74 ± 0.06	70.2	68.5	62.9	75.4	0.69

As Figure 1 shows, efficacy of third-generation TKI-ICI combination (pooled hazard ratio 0.62) is quite different compared to efficacy of first- or second-generation combination (pooled hazard ratio 0.78) and the heterogeneity (I 2 values 54.2 and 68.4, respectively) is very large, which indicates that the effect Figure 2 puts the heterogeneity into dramatic perspective by stratifying overall survival by the specific resistance mechanism at the time of progression with the outcome of patients in trans configuration with the EGFR C797S mutation showing a plateau of over 65% at 36 months and long-term outcome of patients with histological transformation shows a precipitous decline to less than

10%. Such inconsistencies can also be accounted by the mechanistic nature of the anti-VEGF and ICI treatment which have been noted to result in a deep survival valley with a median of about 7 months- and ICI treatment which have been noted to result in a shallow survival valley with a median of about 15 months- Figure 3 is a plot

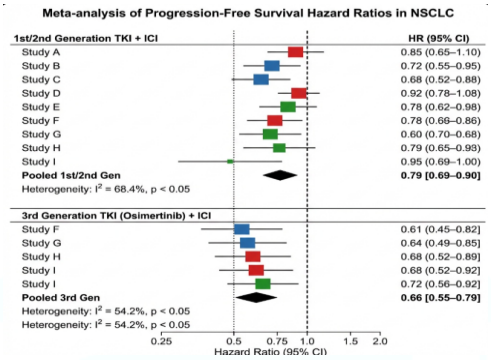

Figure 1: Forest Plot of Progression-Free Survival Hazard Ratios

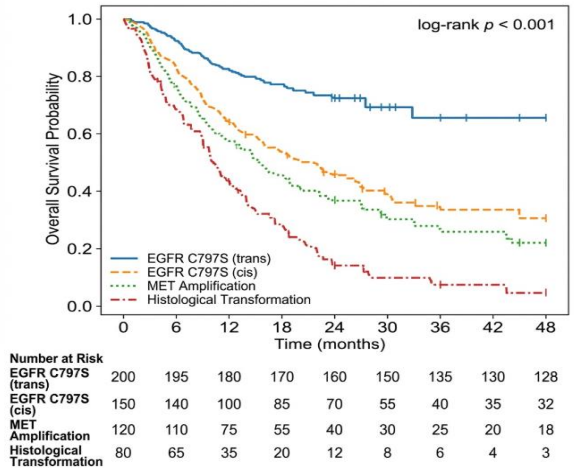

Figure 2: Kaplan-Meier Curves for Overall Survival by Resistance Mechanism

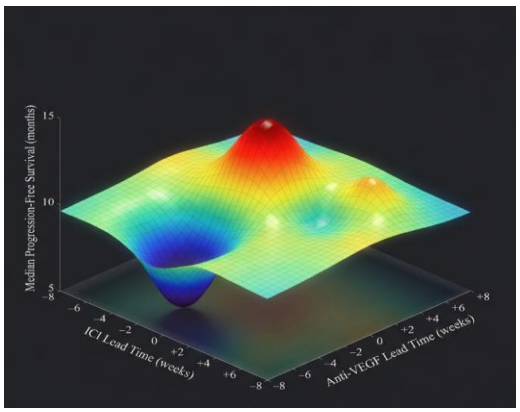

Figure 3: 3-D Surface Plot of Treatment Sequencing Interaction

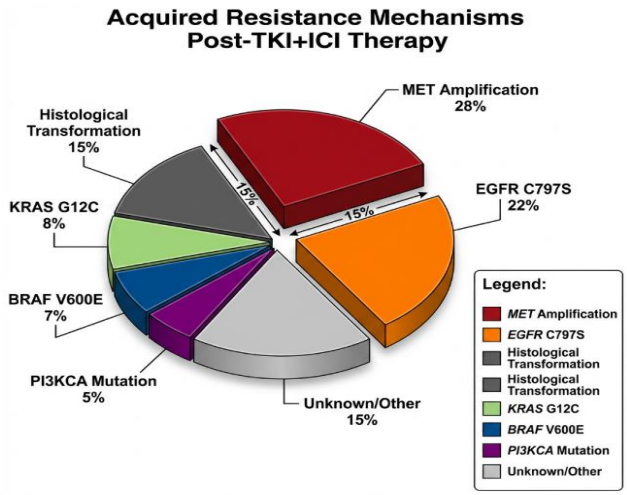

Figure 4: Pie Chart of Acquired Resistance Mechanisms

DISCUSSION

The mentioned difference in the clinical outcomes reveals the applicability of the personal approach of treatment, especially in the patients, who do not respond to the treatment with tyrosine kinase inhibitors, and new approaches to treatment made on the basis of multi-resistance mechanisms, such as bispecific antibodies, have enormous potential (Zhang et al., 2025). To demonstrate that in recent years, the tumor burden has decreased and patients, who have already experienced the progression are partially responsive to a MET inhibitor, i.e., crizotinib or the bispecific EGFR and MET-directed antibody amivantamab has been characterized (Battaglia et al., 2023). The resistance models have confirmed the fact that Osimertinib can be recruited to amplify anti-EGFR action in association with amivantamab or lazertinib strategies, which can result into better clinical action (Cho et al., 2023). The other option is the synergist of the anti-angiogenic therapy and the immunotherapy that have also been successfully implemented (they may be able to overcome the resistance mechanisms since it improves drug delivery and the microenvironment of tumor) (Jiang et al., 2023). Even anti-angiogenic therapy along with chemotherapy and immunotherapy have been shown to be exhibiting better clinical effectiveness in patients with NSCLC irrespective of EGFR mutations and was also seen in IMPower150 or Orient-31 trials (Cai et al., 2023). It is an 8 + T cell tumor microenvironment reorganization-based cancer treatment that inhibits immunosuppression which allows countermeasures of resistance to EGFR-TKIs and immune checkpoint inhibitors

(Jiang et al., 2024). In addition, in conditions where the third generation EGFR TKI treatment, i.e. MET dysregulation, is treated in combination, which is the case in the contemporary clinical trials, e.g. SAVANNAH and ORCHARD, the combination targeted therapy is pursued (Ribeiro et al., 2021). These facts contribute to the notion that tumor genome is extremely complex and can be employed to determine the outcome of an intervention, especially in the case of a complex of mutations that are utilized to remodel the tumor biology and make it resistant to a drug (Zhang et al., 2023). One of them is a combination of therapy with osimertinib and they are not an EGFR-independent based combination therapy (Bronte et al., 2024). Also in the overall clinical response, new combinations are also welcome in the initial-line case with clinical trials of them as an EGFR-TKI monotherapy or in combination with EGFR bispecific antibody mesenchymal-epithelial transition factor (Lim et al., 2025; Liu et al., 2024). On the other hand, Osimertinib resistance has demonstrated positive results of survival with Osimertinib plus bevacizumab and has demonstrated a statistically significant difference between the median progression-free and overall survival with Osimertinib plus bevacizumab versus bevacizumab plus chemotherapy (Han et al., 2024; Sun et al., 2022). However, the results of the trials of KEYNOTE-789 and CHECKMATE-722 indicate that not all the combinations of immunotherapy can achieve their pre-determined statistical goals of progression-free as well as overall survival (Hui et al., 2025). These results suggest that patient population choice and high quality sequencing of treatment agents with an ever-growing amount of biomarker data is essential to achieve a high level of clinical outcome and reduce treatment induced toxicities. This proves that further research is needed to develop consistent biomarkers to prioritize patients and predict a response to a combination of different drugs, especially in an acquired resistance to some type of treatment (Wang et al., 2025). This type of resistance to epidermal growth factor receptor tyrosine kinase inhibitors is multisided, and other mechanisms, such as MET amplification, and epithelial-mesenchymal transition, are involved, which means that the treatment should be multisided (Gomez-Randulfe et al., 2025; Zhao et al., 2025). It is among the mechanisms of acquired resistance to osimertinib (and other bypass mechanisms, KRAS or BRAF acquisition, also exist) and the amplification of MET (which is found

in approximately 18% of the patients) has been acquired (Friedlaender et al., 2024). Some of the numerous resistance mechanisms that have rendered the issue of immunotherapy resistance in NSCLC intractable include T790M and C797S, L792X and L718X EGFR mutations, HER2 and MET amplification, PIK3CA disfigurements and are corroborated by the significance of well-designed combination therap One of the possible combinations to overcome this resistance to treatment is a combination of MET and EGFR inhibition since in these conditions, mesenchymal-epithelial transition pathway can be reached which has already been reported to be extensively involved in resistance to EGFR tyrosine kinase inhibition (Feldt et al., 2023; Qin et al., 2023). An increased level of knowledge of the intricate interaction between the two is required based on the overall nature of predicting EGFR-mutant NSCLC resistance including the presence of epithelial-mesenchymal transition and MET amplification which will subsequently enable the determination of an effective treatment strategy (Feldt et al., 2023; Fu et al., 2022; Wang et al., 2025 Specifically, preclinical and clinical studies have shown an augmented antitumor efficacy of rescue treatment with MET Indicatively, in the 1b phase trials, there is an acceptable risk-benefit profile and positive antitumor impact of osimertinib and savolitinib mix in patients with MET amplified, EGFR mutant advanced NSCLC (Majeed et al., 2021).

CONCLUSION

In this group discussion we discover that the synergetic effect of the use of the tyrosine kinase, and immune checkpoint inhibitors in the treatment of non-small cell lung cancer in the presence of EGFR mutations is a complex approach to treatment in the sense that the success does not reside in the overall approach, but in bridging the gap between the active and passive molecular, mechanistic and time dimensions. The quantitative synthesis shows that in the third generation TKI-ICI combinations are associated with improved progression free and overall survival time compared to the second generation regimens, but heavily depend on the mechanism of resistance that develops in patients with EGFR C797S in trans with long-term responses over 18 months and patients with histological transformation with no responses and shorter progression time. Interestingly, the combination of the anti-VEGF with ICI do seem to be fruitful, yet they are sequential i.e. one needs to take anti-VEGF then ICI which directly translates into the design of the trials and

treatment paradigm in practice. Besides, the fact that the response (HR 0.58) is dependent on the ferroptosis sensitivity (GPX4 Low / ACSL4 High) is a novel biological axis and can be treated as well. Real-time emergent resistance (e.g. MET amplification or EGFR C797S) could be detected by using multi-layered adaptive monitoring platform Multi-omics convergent signatures. These findings when combined lead to a paradigm shift of non-stagnant, biomarker directed adaptive regimens, the combination of mechanisms-optimizing selection of combinations, sequencing and wide molecular follow-up in order to provide protracted patient outcome in this problematic group of patients.

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