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Exploring practical experience with different treatments in NSCLC patients with MET-deregulated: a retrospective analysis from the real world

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Abstract

Background Mesenchymal to epithelial transition factor (MET) dysregulation in non-small-cell-lung-cancer (NSCLC) is understudied, with scant data on treatment outcomes.

Methods We retrospectively examined 160 NSCLC patients: 125 with primary MET mutations (further classified into MET exon 14 (METex14) skipping mutations and primary MET amplifications) and 35 with secondary MET amplifications. Patients underwent varied treatments: Chemotherapy, Immune monotherapy, Crizotinib, or Savolitinib. Secondary MET amplification patients were grouped by treatment: Group A (Class Ib MET-TKI with third-generation EGFR-TKI), Group B (Crizotinib with first-generation EGFR-TKI), and Group C (Crizotinib alone). One hundred and thirty patients have completed the whole treatment process. Their data were included in the study's survival analysis (included 95 patients with primary MET mutations and 35 patients with secondary MET amplifications).

Results Among METex14 skipping mutations patients ($n=57$), median progression free survival (PFS) was: Chemotherapy 7.64 m, Crizotinib 8.5 m, Savolitinib 9.3 m, and Immunotherapy 3.87 m. Targeted therapies and chemotherapy significantly outperformed Immunotherapy. Sub-group analysis indicated splice donor region mutations benefited more than those at the polypyrimidine tract (9.23 m vs. 4.03 m, $P=0.038$). For primary MET amplifications ($n=38$), PFS was: Chemotherapy 2.84 m, Crizotinib 3.80 m, Savolitinib 5.23 m, and Immunotherapy 3.30 m. Patients with copy number (CN) > 5 had longer PFS than CN ≤ 5 (5.17 m vs. 3.44 m, $P=0.039$). In secondary MET amplifications ($n=35$), Group A and B had similar PFS (6.77 m and 6.57 m) versus Group C (3.13 m). Dual-target therapy PFS showed no difference between CN ≤ 5 and CN > 5 (8.63 m vs. 6.27 m, $P=0.29$).

Conclusion NSCLC patients with METex14 skipping mutations benefit more from targeted therapies, especially those with splice donor mutations. MET amplification patients benefit universally from targeted therapies; primary MET amplifications show higher benefits with increased copy numbers. For secondary MET amplifications post-EGFR-TKI resistance, dual-target therapy surpasses Crizotinib monotherapy, independent of MET copy number.

Keywords Mesenchymal-epithelial transition factor, Non-small cell lung cancer, Crizotinib, Savolitinib

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Introduction

NSCLC represents approximately 80% of all lung cancer cases, with a sobering 5-year survival rate of around 22% [1]. Nonetheless, the past decade has witnessed a transformative shift in NSCLC management due to significant advancements in immunotherapy and targeted therapies [1]. Among the recently identified oncogenic mutations in NSCLC, METex14 skipping mutations and high-level MET amplifications stand out [2, 3]. METex14 mutations occur in an estimated 3% of lung cancer cases [4], while primary MET amplifications are found in 1–5% of NSCLC patients [2]. Notably, MET amplification has also been highlighted as a pivotal mechanism underlying acquired resistance to first and second-generation EGFR-TKIs, a significance that amplifies post-resistance to third-generation EGFR-TKIs [5]. Historically, MET abnormalities have shown limited responsiveness to conventional treatment strategies [6–12], underscoring the imperative to refine therapeutic approaches.

With the burgeoning interest in targeted interventions, emerging evidence, both preclinical and clinical, indicates heightened sensitivity of METex14 skipping mutations and MET amplifications to tyrosine kinase inhibitors (TKIs). This includes broad-spectrum inhibitors like Crizotinib[13]and specialized inhibitors such as Tepotinib [14, 15], Savolitinib [16], and Capmatinib [17].

Despite the clinical importance, MET mutations are infrequent, and treatment options remain intricate and multifaceted. Real-world data concerning MET mutations, especially beyond the confines of clinical trials, is notably sparse. This gap emphasizes the urgency of acquiring tangible insights from routine clinical practice. Our study delves into the biological profiles of patients manifesting METex14 skipping mutations, primary MET amplifications, and secondary MET amplifications post-EGFR-TKI progression. We aim to discern the therapeutic effectiveness across MET mutation-positive NSCLC subsets, furnishing valuable guidance for clinical decision-making.

Materials and methods

Patient enrollment

This study encompassed 160 NSCLC patients exhibiting MET abnormalities, all treated at the Affiliated Cancer Hospital of Zhengzhou University over an 8-year span. The inclusion criteria were as follows: a) Age of 18 years or older; b) Histological or pathological confirmation of lung cancer; c) Existence of MET mutations; d) Identifiable lesions as per the Solid Tumor Response Evaluation Criteria (version 1.1); e) A comprehensive treatment journey with follow-up. Conversely, patients were excluded based on the following: a) Being younger than 18 years; b) Concurrent diagnosis of an alternative cancer; c) Significant impairment of crucial organs (namely heart, liver, or kidney); d) Inadequate patient data. For those presenting with secondary MET amplification, the following criteria were imperative: a) Presence of baseline EGFR mutations; b) Progression post-EGFR-TKI treatment necessitating re-biopsy from tissue, blood, or other biological specimens for NGS evaluation; c) Verified EGFR mutation status coupled with MET amplification post-first or subsequent line of EGFR-TKI treatment. Notably, those displaying MET amplification at the outset or those previously administered MET-TKIs, including Crizotinib, were not part of this study.

The designated follow-up cut-off was February 5, 2023. This study's primary metric was the median progression-free survival (mPFS), with secondary endpoints including objective response rate (ORR), disease control rate (DCR), and median overall survival (mOS). For those absent at follow-up, the endpoints for OS and PFS corresponded to their last recorded visit.

Methods

We included 160 patients with MET mutation for NSCLC from July 5, 2015, to February 5, 2023. Patients are divided into two groups: primary MET mutations ($n=125$) and the secondary MET Amplification ($n=35$). A total of 125 patients with primary MET mutations were classified as METex14 skipping mutations ($n=76$) or primary MET amplification($n=49$) according to MET mutation mode, and 95 of these patients with different treatments and complete course of treatment were included in the primary MET mutation's retrospective analysis (included 57 patients with MET exon 14 skipping mutation and 38 patients with primary MET amplification). The cohort's distribution is visualized in Fig. 1.

Fifty-seven MET exon 14 skipping mutations (22 Chemotherapy, 15 Crizotinib, 11 Savolitinib, 9 immune monotherapy), they are all first-line treatment. We also counted second-line treatments among patients with MET exon 14 skipping who were treated with first-line chemotherapy or ICI. Among them, 5 patients (2 Crizotinib, 3 Savolitinib) who received second-line targeted therapy were included in the survival analysis of targeted therapy group, with a total of 31 patients (17 Crizotinib and 14 Savolitinib).

Thirty-eight primary MET amplification (18 chemotherapy, 9 Crizotinib, 7 Savolitinib, 4 immune monotherapy). We also counted second-line treatments among patients with de novo MET amplification who were treated with first-line chemotherapy or ICI. Among them, 4 patients (3 Crizotinib, 1 Savolitinib) who received second-line targeted therapy were included in the survival analysis of targeted therapy group, with a total of 20 patients (12 Crizotinib and 8 Savolitinib).In the targeted

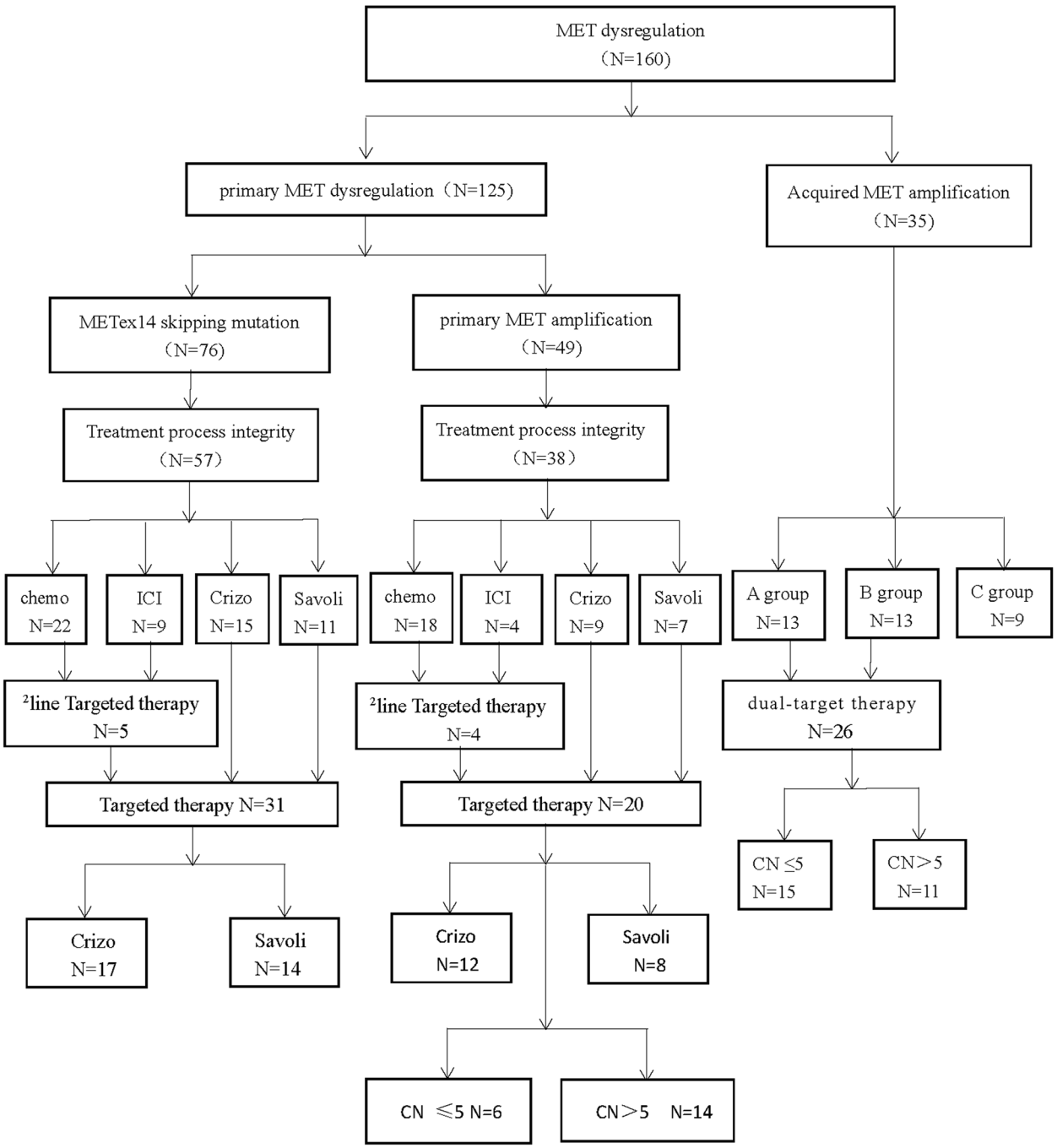

Fig. 1 Flow-chart of patient selection. Abbreviation: MET, Mesenchymal-Epithelial Transition; Chemo, Chemotherapy; METex14，MET exon 14; ICI, immune-checkpoint-inhibitor; Crizo, Crizotinib; Savoli, Savolitinib; CN, Copy number

therapy group ($n=20$), patients were divided into NGS CN≤5 ($n=6$) and NGS CN>5 ($n=14$) according to the NGS copy number (CN).

A total of 35 patients with secondary MET amplification were included and divided into group A (Ib MET-TKI combined with third- generation EGFR-TKI, $n=13$), group B (Crizotinib combined with first-generation EGFR-TKI, $n=13$), and group C (Crizotinib monotherapy, $n=9$) according to treatment regimen. At the same time, group A and group B were called double target treatment groups ($n=26$). In the dual target treatment group, patients were divided into NGS CN≤5 ($n=15$)

and NGS CN > 5 ($n = 11$) according to the NGS copy number (CN).

Ultimately, the data from 130 patients were included in the study's survival analysis (included 95 patients with primary MET mutations and 35 patients with secondary MET amplifications).

Statistical analysis

Statistical analyses were conducted using SPSS version 24 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 7 (GraphPad Software, La Jolla, CA, USA). Disparities in the clinical attributes of patient cohorts were assessed through the Fisher's exact test or the chi-squared test. Survival outcomes were evaluated using the Kaplan–Meier method and contrasted via the log-rank test. All tests were two-tailed, with a p-value of < 0.05 denoting statistical significance.

Results

Baseline characteristics of the study population

A total of 160 NSCLC patients with MET dysregulations were evaluated. The baseline demographics are visualized in Additional Table 1A and Additional Table 1 B respectively.

Clinical and pathological features of the MET dysregulated population

In patients with primary MET mutations, the median age at lung cancer diagnosis is 68 years (range 35–87 years). Notably, the METex14 skipping mutation subgroup had a higher proportion of individuals aged over 65 years (76.35% vs 40.8%, $p < 0.001$). The majority are male (71.2%), with 64.8% being non-smokers or former smokers. Advanced-stage lung cancer is prevalent in 88.0% of these patients, with brain metastases observed in 20%. There's no significant difference between the skipping mutation and primary amplification groups in terms of brain metastasis occurrence. Adenocarcinoma is the dominant histological subtype (77.6%). With respect to PD-L1 expression, the METex14 skipping mutation group exhibits a notably higher percentage of PD-L1 $\geq 1\%$ (83.3% vs 52.1%, $P = 0.007$) (refer to Additional Table 1A).

For the secondary MET amplification cohort, the median age stands at 57 years, ranging from 34 to 71 years. Females comprise 54.3% of this group. Non-smokers or ex-smokers constitute 65.7%, with brain metastases present in 37.1%. Adenocarcinoma remains the sole histological classification reported (refer to Additional Table 1B).

In comparison to the primary MET amplification subgroup, the METex14 skipping mutation group tends to be older, with a median age of 71 years. It also has a more significant fraction of individuals aged over 65 years (76.35% vs 40.8%, $p < 0.001$). Gender distribution in the METex14 skipping mutation group is relatively balanced, with a slight male predominance, whereas the primary MET amplification group is predominantly male (98% vs 54.0%, $P < 0.001$). More patients in the primary MET amplification group are current smokers (59.2% vs 19.7%, $P < 0.001$). Both subgroups share comparable rates of brain metastasis, are chiefly adenocarcinomas, and the majority are staged at TNM IIIB-IV. The METex14 skipping mutation subgroup presents a higher PD-L1 positivity rate (83.3% vs 52.1%, $P = 0.007$), while the MET amplification subgroup displays a heightened TP53 positivity rate (71.4% vs 38.1%, $P = 0.03$) (refer to Additional Table 1A).

Mutation characteristics of MET dysregulated population

In our analysis, 45 MET-specific splicing sites were identified. Of these, 28 individuals (62.2%) exhibited MET splice donor site mutations, predominantly as base substitutions (51.1%). Polypyrimidine tract mutations were observed in 13 individuals (28.9%), mainly as insertions/deletions (26.7%). Two cases showed splice acceptor site mutations: one with the Y1003F mutation and another with a complete exon 14 deletion. (Additional Table 1A).

For the primary MET amplification cohort, the median copy number (CN) was 5.68 (range 2.51–23.68). Notably, 67.3% had a CN above 5 and 12.2% exceeded 10 (Additional Table 1A). In the secondary amplification group, the median CN was 5.1 (range 2.80–15.63), with 51.4% above 5 and 17.1% surpassing 10 (Additional Table 1B).

Efficacy and survival analysis

As of the last follow-up in this study (February 5, 2023), the median follow-up times for the METex14 skipping mutation group, primary MET amplification group, and secondary MET amplification group were 30.6 months, 23.8 months, and 41.4 months, respectively. Detailed survival analysis results are as follows:

Efficacy analysis of METex14 skipping mutation group patients

In the METex14 skipping mutation cohort ($n = 57$), treatment ORRs were observed as follows: Chemotherapy (31.8%), Crizotinib (53.3%), Savolitinib (45.5%), and Immune monotherapy (22.2%) (Table 1). Median PFS durations aligned as 7.64 months, 8.5 months, 9.3 months, and 3.87 months, respectively (Fig. 2A). The PFS for the immunotherapy group was notably shorter (Table 2).

For first and second-line targeted therapies, there was no significant PFS difference between the Crizotinib

Table 1 The efficacy of different first-line treatments in the METex14 skipping mutation cohort (*N*=57)

	Chemo (*N*=22)	Crizotinib (*N*=15)	Savolitinib (*N*=11)	ICI (*N*=9)
PR	7	8	5	2
SD	13	6	5	5
PD	2	1	1	2
ORR, (%)	31.8%	53.3%	45.5%	22.2%
DCR, (%)	90.9%	93.3%	90.9%	77.8%

Abbreviation: *PR* Partial response, *SD* Stable disease, *PD* Progressive disease, *ORR* Objective response rate, *DCR* Disease control rate

(*n*=17) and Savolitinib (*n*=14) groups, with durations of 8.5 and 9.3 months, respectively (*P*=0.83) (Fig. 2B). Further delineation indicated that patients with splice donor region mutations (*n*=11) derived greater benefit from targeted therapies compared to those with polypyrimidine tract mutations (*n*=5), displaying PFS of 9.23 months versus 4.03 months (*P*=0.038) (Fig. 2C).

Efficacy analysis of primary MET amplification group patients

In the primary MET amplification cohort (*n*=38), treatment ORRs were as follows: chemotherapy (16.7%), Crizotinib (22.2%), Savolitinib (42.9%), and Immune monotherapy (25%) (Table 3). Median PFS durations were 2.84 months, 3.80 months, 5.23 months, and 3.30 months, respectively (Fig. 3A). The targeted therapy group displayed a significantly prolonged PFS compared to the chemotherapy group (Table 2).

Regarding first and second-line targeted therapies, there was no substantial PFS difference between the Crizotinib (*n*=12) and Savolitinib (*n*=8) groups, with 3.64 months and 5.23 months, respectively (*P*=0.052) (Fig. 3B). Notably, patients with CN>5 (*n*=14) exhibited a longer median PFS than those with CN≤5 (*n*=6),

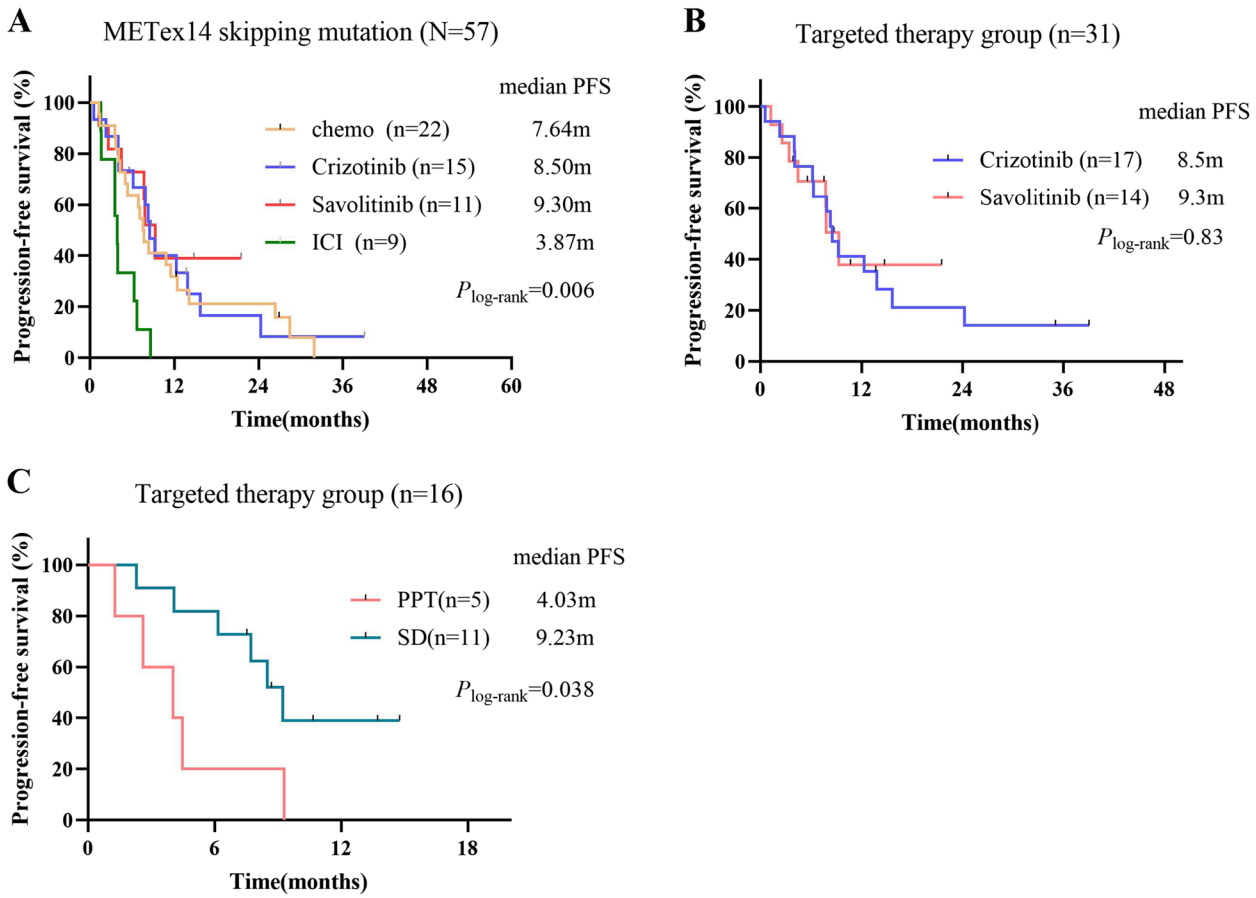

Fig. 2 Survival analysis of patients with METex14 skipping mutations. The PFS of different first-line treatment regimens were compared (**A**); The PFS for Crizotinib and Savolitinib in the targeted therapy group (**B**); In the targeted therapy group, The PFS in patients with the polypyrimidine tract and splice donor region mutations were compared (**C**)

Table 2 The PFS of different first-line treatment regimens were compared in METex14 skipping mutation group and the primary MET amplification group

Treatment	METex14 ($n=57$)		Primary MET amp ($n=38$)	
	mPFS (m)	*P*-value	mPFS (m)	*P*-value
Chemo vs Crizotinib		0.783		0.031
Chemo	7.64		2.84	
Crizotinib	8.50		3.80	
Chemo vs Savolitinib		0.581		0.013
Chemo	7.64		2.84	
Savolitinib	9.30		5.23	
Chemo vs ICI		0.004		0.209
Chemo	7.64		2.84	
ICI	3.87		3.30	
Crizotinib vs Savolitinib		0.678		0.331
Crizotinib	8.50		3.80	
Savolitinib	9.30		5.23	
Crizotinib vs ICI		0.004		0.745
Crizotinib	8.50		3.80	
ICI	3.87		3.30	
Savolitinib vs ICI		0.008		0.372
Savolitinib	9.30		5.23	
ICI	3.87		3.30	

marked at 5.17 months versus 3.44 months ($P=0.039$) (Fig. 3C).

Efficacy analysis of patients with secondary MET amplification

Our study observed that within the group showing secondary MET amplification post EGFR-TKI progression ($n=35$), the ORR for Group A (Class Ib MET-TKI with third-generation EGFR-TKI), Group B (Crizotinib with first-generation EGFR-TKI), and Group C (Crizotinib alone) were 46.2%, 46.2%, and 33.3% respectively (Table 4). The median PFS were 6.77 months, 6.57 months, and 3.13 months, respectively (Fig. 4A). Compared to Group C, the difference was statistically significant (Table 5). Since the median PFS of Groups A and B showed no difference, our study combined them as a dual-target therapy group ($n=26$). Further analysis revealed that there was no difference in the median PFS of patients with CN ≤ 5 and CN > 5 undergoing dual-target treatment (CN ≤ 5 vs CN > 5: 8.63 months vs 6.27 months, $P=0.29$) (Fig. 4B).

Table 3 The efficacy of different first-line treatments in the primary MET amplification cohort (*N*=38)

	Chemo (*N*=18)	Crizotinib (*N*=9)	Savolitinib (*N*=7)	ICI (*N*=4)
PR	3	2	3	1
SD	8	5	4	2
PD	7	2	0	1
ORR, (%)	16.7%	22.2%	42.9%	25.0%
DCR, (%)	61.1%	77.8%	100.0%	75.0%

Discussion

In patients with NSCLC harboring MET mutations, MET-TKIs have been proven to be effective. However, the relative efficacy of different treatment methods for primary NSCLC patients with MET mutations and the treatment choices for patients with acquired MET amplification after EGFR-TKIs remain unclear. We reported the biological and pathological characteristics of various types of MET mutations and analyzed their efficacy in different treatments.

Consistent with most previous studies [18, 19], patients with METex14 skipping mutations were more likely to be older, non-smokers or former smokers, and the pathological type was mostly adenocarcinoma. The positive rate of PD-L1 was 83.3%, which is a common phenomenon in patients with positive driver genes [20]. In addition, our data show that the most common splice site mutation is the splice donor site mutation (55.3%), followed by the polypyrimidine tract mutation (23.4%), which is similar with published data [19]. Compared with METex14 jump mutations, those with primary MET amplification were more common in men, smokers, and younger adults, Moreover, the positive rate of PD-L1 was lower, but the positive rate of TP53 (71.4%) was higher in people with primary MET amplification, which has also been reported in the previous literature [21].

In our study, among METex14 skipping mutations patients ($n=57$), median PFS was: Chemotherapy 7.64 m ($n=22$), Crizotinib 8.5 m ($n=15$), Savolitinib 9.3 m ($n=11$), and Immune monotherapy 3.87 m ($n=9$). patients harboring METex14 skipping mutations demonstrated a moderate response to chemotherapy and targeted therapy, yet a limited efficacy with immunotherapy. Among the targeted treatment cohort, those with splicing donor region mutations derived greater benefit from targeted therapies compared to their counterparts with polypyrimidine tract mutations. Although METex14 skipping mutation has been recognized as an unfavorable prognostic marker for NSCLC [9, 10], few studies have reported on its chemotherapy treatment PFS, which generally demonstrates limited efficacy with a median PFS close to 4 months [22–24]. Notably, our study, encompassing a larger patient cohort all undergoing first-line treatment, diverges from previous findings. This offers clinicians an enhanced perspective, suggesting

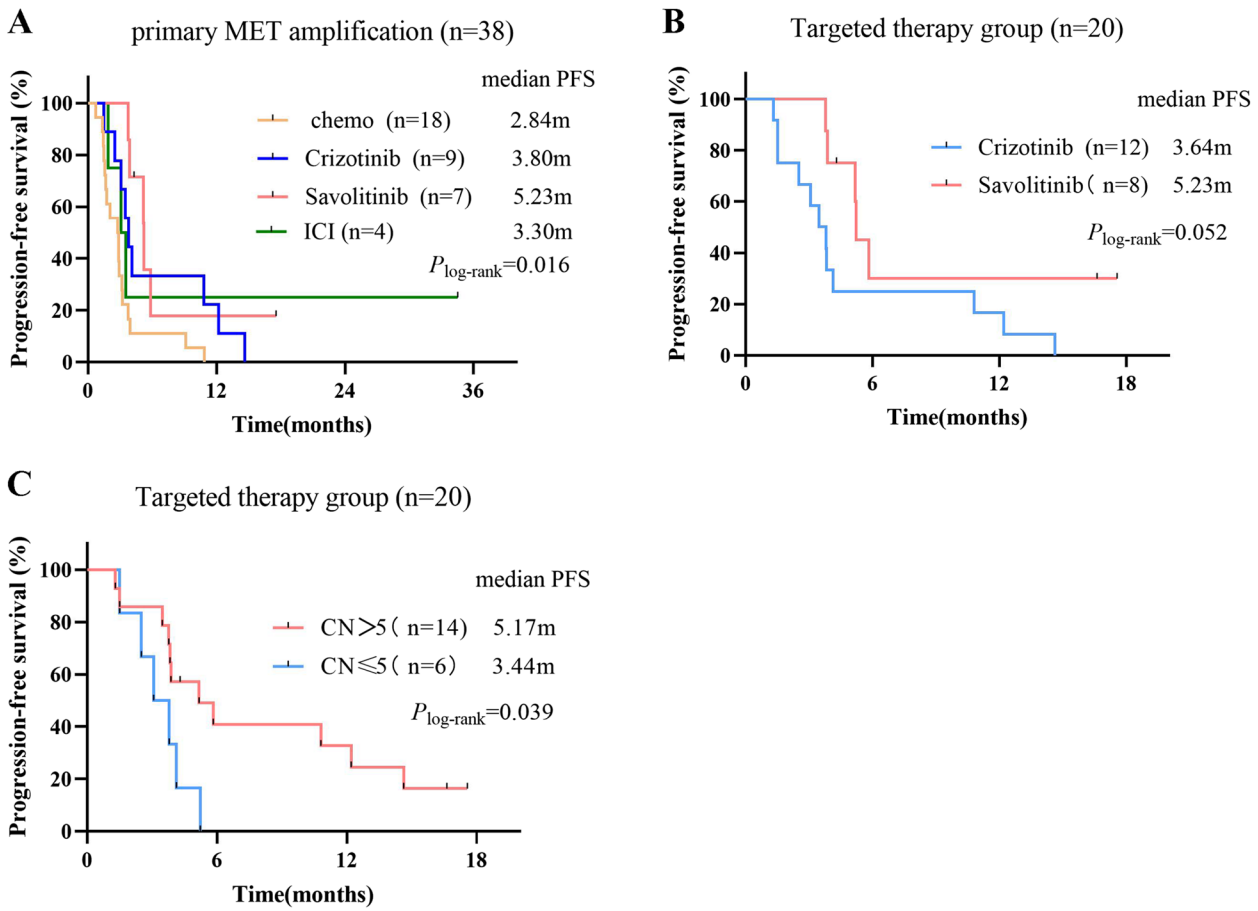

Fig. 3 Survival analysis of patients with primary MET amplification. The PFS of different first-line treatment regimens were compared (**A**); In the targeted therapy group, the PFS in patients receiving Crizotinib and Savolitinib were compared (**B**); In the targeted therapy group, the PFS in patients with CN ≤ 5 and CN > 5 were compared (**C**)

that tailored treatment choices based on patient-specific scenarios might be more efficacious. For patients with financial constraints, chemotherapy emerges as a viable treatment option. Earlier studies highlighted MET activation's role in upregulating several negative immune response checkpoint regulators, such as PD-L1, PDCD1LG2, and SOCS1R, marking it as an independent determinant of PD-L1 expression in lung cancer [25]. Previous research has underscored the limited efficacy of immunotherapy in METex14 skipping mutation cases [12, 26], our findings align with this observation.

Although the clinical trial results for Savolitinib are promising, there are few real-world reports on Savolitinib, and most are case reports [27, 28]. A retrospective analysis revealed fifteen (68.1%) of the 22 patients treated with crizotinib or savolitinib had a partial response [29], but this study did not calculate survival data. In our research, Savolitinib showed significant PFS. Many clinical reports prove that Crizotinib is effective in advanced NSCLC patients with METex14 skipping mutations, with a median PFS of about 7 months [13, 18, 30], consistent with our research on Crizotinib's PFS. We also explored the differences in targeted therapy between different METex14 skipping mutation splicing sites and found that patients with splicing donor region mutations benefit more from targeted therapy compared to those with polypyrimidine tract mutations. This finding, not reported in previous studies, suggests that for more precise treatment, patients with METex14 skipping mutations need further classification at the genetic level.

In our study, among primary MET amplifications ($n=38$), median PFS was: Chemotherapy 2.84 m ($n=18$), Crizotinib 3.8 m ($n=7$), Savolitinib 5.23 m ($n=7$), and Immune monotherapy 3.3 m ($n=9$). MET-TKIs represented by Crizotinib and Savolitinib demonstrate better efficacy than chemotherapy, and the higher the copy number, the better the efficacy. Primary MET amplification is genetically more heterogeneous than METex14 skipping mutations, with a wide range of MET gene copy numbers and frequent co-mutations [31]. Consequently,

Table 4 Efficacy analysis of patients with secondary MET amplification (*N* = 35)

	Ib MET-TKI + 3rd EGFR-TKI (*N* = 13)	Crizotinib + 1st EGFR-TKI(*N* = 13)	Crizotinib (*N* = 9)
Treatment line for study regimens			
2	6	7	4
3	2	4	2
≥ 4	5	2	3
Pre-medication details,			
1st EGFR-TKI	7	13	8
2nd EGFR-TKI	1	0	0
3rd EGFR-TKI	10	0	3
Multiple application of EGFR-TKI	5	0	2
Response			
PR	6	6	3
SD	5	6	2
PD	2	1	4
ORR (%)	46.20%	46.20%	33.30%
DCR (%)	84.60%	92.30%	55.60%

Abbreviation: EGFR-TKI Epidermal growth factor receptor tyrosine kinase inhibitor, *1st* first generation, *2nd* second generation, *3rd* third generation

clinical trials have shown inconsistent efficacy of MET inhibitors in tumors with primary MET amplification [32, 33]. As early as the 2014 ASCO annual meeting, the clinical outcomes of Crizotinib treatment for primary MET-amplified non-small cell lung cancer (NSCLC) were reported [33]. This is one of the earliest studies investigating the activity of MET-targeted therapy in tumors. The results showed that Crizotinib was only effective for medium to high levels of MET amplification. After the concept of MET amplification level classification was proposed by this study, many subsequent studies confirmed that the efficacy of MET TKIs is related to the amplification copy number [17, 32, 34–36]. The Clinical study of Savolitinib did not include patients with primary MET amplification [37]. Our result shows the significant efficacy of Savolitinib in this patient population. Even though there is no statistical significance when compared with Crizotinib, from the statistical charts, it can be seen that there is a trend of greater benefit with Savolitinib. Similarly, Savolitinib showed better efficacy than Crizotinib (mPFS: 7.1 m vs 1.4 m, $P = 0.05$) in a Chinese small sample size, single-center retrospective clinical study [38]. We included all patients regardless of copy number in the survival analysis and divided targeted therapy into two groups based on a copy number of ≤ 5 and > 5. We found that patients with a copy number of > 5 had

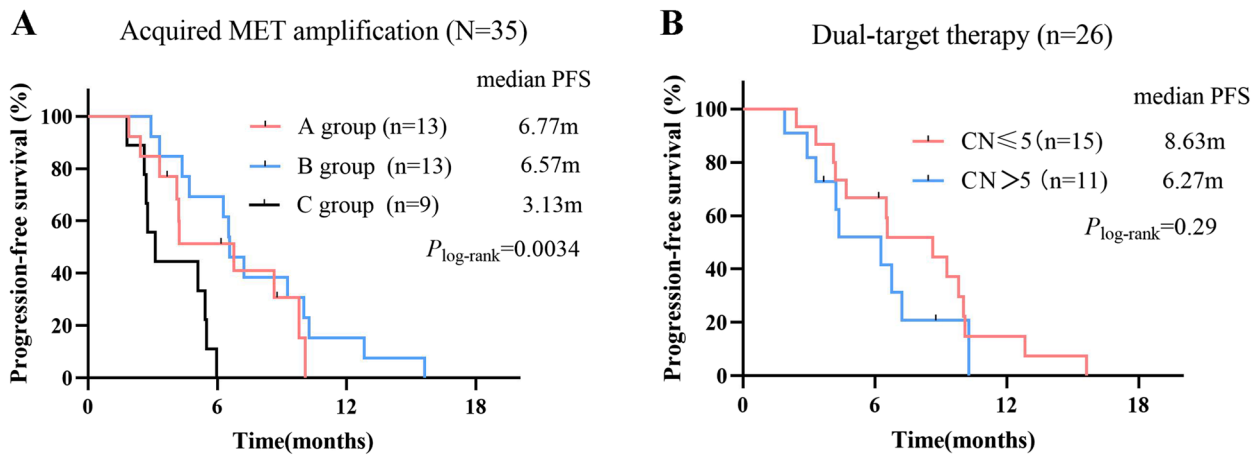

Fig. 4 The survival analysis of patients with acquired MET amplification. The PFS of different treatment regimens were compared (**A**); In the dual-target treatment group (*n* = 26), The PFS in patients with NGS CN ≤ 5 and NGS > 5 were compared (**B**)

Table 5 The efficacy analysis of patients with secondary MET amplification in different ways of treatment

Treatment	Acquired MET amp ($n = 35$)	
	mPFS (m)	*P*-value
A vs B		0.331
A	6.77	
B	6.57	
A vs C		0.03
A	6.77	
C	3.13	
B vs C		0.001
B	6.57	
C	3.13	

Abbreviation: A Class Ib MET-TKI with third-generation EGFR-TKI, *B* Crizotinib with first-generation EGFR-TKI, *C* Crizotinib alone

better therapeutic effects. However, even with MET-TKI treatment, the median PFS was only 3–5 months [15, 17]. Thus, primary MET amplification seems to be a predictive factor for poor response to the aforementioned treatments, and we need to explore new therapeutic methods in the hope of providing more choices for these patients.

Lastly, in our comparison of treatment efficacy in NSCLC patients with MET amplification post-EGFR-TKI progression, dual-target therapy (Group A: 6.77 m and Group B: 6.57 m) yielded a longer PFS compared to Crizotinib monotherapy (Group C 3.13 m). Within the dual-target cohort, the median PFS showed no distinction between NGS CN ≤ 5(PFS:8.63 m) and CN > 5 groups (PFS:6.27 m), indicating the potential of combined EGFR and MET inhibitors, regardless of copy number. While Crizotinib proves effective for primary MET amplification, its utility post-resistance to EGFR-TKI is less studied and typically displays suboptimal outcomes [39, 40]. A prominent 2021 Chinese study [41] corroborated our findings, indicating a mere 2.3-month median PFS in Crizotinib-treated patients. Such data highlights the discrepancy between Crizotinib's theoretical promise and actual clinical efficacy. MET amplification in EGFR-TKI-treated patients triggers ErbB3 phosphorylation, thereby activating the PI3K/AKT pathway [42, 43]. This emphasizes the potential of dual-target therapy, targeting both EGFR and C-MET, to counteract EGFR resistance. The growing utilization of third-generation EGFR-TKIs and the consequent emergence of resistance underpin the urgency for complementary therapeutic strategies. Notable trials like TATTON [35, 44–46], SAVANNAH [47], and NCT04338243 [48] have accentuated the efficacy of combining Savolitinib, Gumarontinib, and Osimertinib, with PFS ranging from 5.5 to 11.1 months. Our data align with these findings. Notably, while most clinical trials focus solely on MET amplification-positive criteria, our research encompassed all secondary MET amplification cases. Irrespective of copy number, we found consistent efficacy in dual-target therapy, indicating its potential for patients with MET resistance post-EGFR-TKI use, even with a lower copy number.

This study has several limitations. Firstly, due to its single-center, retrospective nature, the data is limited, and some clinical information is incomplete. Moreover, The targeted therapy group included patients with first-line targeted therapy and second-line targeted therapy, sequential treatment is likely to have altered PFS, this is a major limitation. Hence a large prospective study is needed to further confirm our results.

Conclusion

In summary, our clinical evidence suggests that patients with advanced lung cancer harboring METex14 skipping mutations can benefit from both chemotherapy and targeted therapies. Compared to patients with mutations at multiple pyrimidine sites, those with mutations in the METex14 splicing donor region derive greater benefits from targeted therapies. For patients with primary MET amplification, MET-TKIs represented by Crizotinib and Savolitinib demonstrate better efficacy than chemotherapy, and the higher the copy number, the better the efficacy. Among patients with secondary MET amplification following resistance to EGFR-TKI, combination dual-target therapy shows better efficacy compared to Crizotinib alone, and patients benefit from dual-target therapy regardless of MET copy number. These findings can provide references for the clinical treatment of patients with MET dysregulation.

Abbreviations

MET	Mesenchymal to epithelial transition factor
NSCLC	Non-small-cell-lung-cancer
METex14	*MET* Exon 14
NGS	Next Generation Sequencing
CN	Copy number
mPFS	Median progression free survival
mOS	Median overall survival
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
DCR	Disease control rate
ORR	Objective response rate
TKI	Tyrosine kinase inhibitors
PD-L1	Programmed death-ligand 1
EGFR	Epithelial growth factor receptor
Chemo	Chemotherapy
ICI	Immune-checkpoint-inhibitor
Crizo	Crizotinib
Savoli	Savolitinib
1st	First generation
2nd	Second generation
3rd	Third generation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03437-4.

Supplementary Material 1.

Supplementary Material 2.

Authors' contributions

All authors' contributed to the study conception and design. Material preparation, data collection and analysis were performed by LMM, XRY and HJY. The first draft of the manuscript was written by LMM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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