First-Line MET Tyrosine Kinase Inhibitors versus Immunotherapy ± Chemotherapy for Patients with MET Exon 14 Skipping Mutant Metastatic NSCLC

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ABSTRACT

Purpose: First-line treatment options for *MET* exon 14 skipping–mutant metastatic non–small cell lung cancer vary because of differences in drug approvals and clinical experience. This study investigates factors influencing outcomes with first-line MET tyrosine kinase inhibitors (TKI) versus immune checkpoint inhibitors (ICI) ± chemotherapy.

Experimental Design: Clinicopathologic data were collected from patients with metastatic *MET* exon 14 skipping–mutant non–small cell lung cancer treated with first-line MET TKI or ICI ± chemotherapy at five centers. Primary endpoints were real-world progression-free survival (rwPFS) and overall survival (OS) to first-line MET TKI versus ICI ± chemotherapy. Subgroup analyses by clinical and tumor characteristics were performed.

Results: Among 158 patients, 80 received MET TKI and 78 received ICI ± chemotherapy as first-line treatment. Baseline clinicopathologic features were balanced except for a higher proportion of patients with a history of smoking in the ICI ± chemotherapy group ($P = 0.03$). With a median follow-up of 37.9 months, no difference was observed in rwPFS (HR, 0.85; $P = 0.4$) or OS (HR, 0.97; $P = 0.9$) with first-line MET TKI versus ICI ± chemotherapy. In subgroup analyses, first-line ICI ± chemotherapy improved rwPFS in PD-L1 ≥80% (HR, 0.50; $P = 0.03$), whereas MET TKI improved rwPFS (HR, 0.40; $P = 0.005$) and OS (HR, 0.49; $P = 0.03$) in PD-L1 <50%, as well as rwPFS (HR, 0.39; $P = 0.02$) and OS (HR, 0.36; $P = 0.03$) in brain metastases and rwPFS (HR, 0.55; $P = 0.01$) in bone metastases. No significant differences were observed in the incidence of high-grade toxicity ($P = 0.9$) or rates of permanent treatment discontinuation ($P = 0.2$) between first-line MET TKI and ICI ± chemotherapy.

Conclusions: First-line MET TKI improved outcomes in PD-L1 <50% and brain/bone metastases, whereas ICI ± chemotherapy prolonged PFS only in PD-L1 ≥80%, emphasizing the need for personalized treatment selection.

Introduction

MET dysregulation represents a critical oncogenic driver in multiple cancers, including non–small cell lung cancer (NSCLC), promoting tumor invasion, angiogenesis, and metastasis (1–6). Approximately 3% to 4% of advanced NSCLC cases harbor a wide spectrum of genomic alterations in *MET* exon 14 or adjacent intronic regions, disrupting key splicing elements and leading to aberrant exon skipping, loss of the Casitas B-lineage lymphoma (CBL)-binding site, and prolonged MET receptor half-life (1, 2, 7–10).

Several targeted therapies have been developed against *MET* exon 14 skipping (*MET*ex14) alterations and are now used in clinical practice in the treatment of advanced-stage NSCLC (2, 4, 10–12). Two main nonrandomized phase II trials, VISION and GEOMETRY, evaluated the efficacy of tepotinib and capmatinib, respectively, both type Ib MET inhibitors, in patients with advanced *MET*ex14-mutant NSCLC (13, 14). These trials demonstrated

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Clin Cancer Res 2025;31:4802–13

doi: 10.1158/1078-0432.CCR-25-1735

Translational Relevance

Our study provides the first comparison, albeit retrospective, between first-line MET tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI) ± chemotherapy in patients with *MET* exon 14 skipping–mutant metastatic non–small cell lung cancer. In the overall population, first-line MET TKI led to a higher objective response rate, but no significant differences in progression-free survival or overall survival were observed compared with ICI ± chemotherapy. Subgroup analyses indicate that patients with tumors expressing PD-L1 <50% or with baseline brain or bone metastases may experience greater benefit from first-line MET TKI. In contrast, only those with tumors exhibiting very high PD-L1 expression (≥80%) seem to derive greater benefit from first-line ICI ± chemotherapy. Safety profile was comparable between first-line MET TKI and ICI ± chemotherapy in terms of high-grade toxicity and permanent discontinuation. Our study highlights the critical role of personalized treatment strategies in managing first-line *MET* exon 14 skipping–mutant non–small cell lung cancer informed by baseline clinicopathologic factors. Prospective studies are needed to validate these findings and redefine the criteria for first-line treatment strategy.

notable efficacy, particularly in the first-line setting. In MET tyrosine kinase inhibitors (TKI)-naïve patients, capmatinib achieved an overall objective response rate (ORR) of 68% with a median progression-free survival (PFS) of 12.45 months, whereas tepotinib achieved an ORR of 57.3% and a median PFS of 12.6 months in the first-line setting (13, 14). Another MET TKI, savolitinib, approved in China, achieved an ORR of 60% and a median PFS of 13.7 months in the first-line setting (15). In addition, MET TKIs showed intracranial efficacy: in the last update of the GEOMETRY trial, 58% of patients with baseline brain metastases had intracranial complete or partial response to capmatinib, and in the VISION trial, intracranial ORR was 66.7% to treatment with tepotinib (13, 14).

The efficacy of immune checkpoint inhibitors (ICI) is strictly correlated with PD-L1 tumor proportion score (TPS) expression, and increasing PD-L1 TPS levels led to longer PFS and overall survival (OS) in advanced NSCLC, with the greater benefit in patients with very high PD-L1 (≥80% or ≥90%; refs. 16, 17). Previous evidences showed low efficacy of ICIs in *MET*ex14-mutant NSCLC, but these results were limited by small sample size (18).

In the IMMUNOTARGET registry, among patients with a *MET*ex14-mutant metastatic NSCLC receiving ICIs, mostly in second or further lines, disease control rate was achieved in 50%, and *MET*, together with *KRAS*- and *BRAF*-mutant NSCLC, showed the higher proportion of long-term responders, with a 12-month PFS of 23.4%, even if the median PFS was of 3.4 months (19). Another retrospective study investigating the efficacy of ICIs in oncogene-addicted NSCLC showed a median PFS of 2.7 months for *MET*ex14-mutant NSCLC receiving ICIs at any line of treatment (20).

The choice of first-line treatment for *MET*ex14-mutant metastatic NSCLC varies significantly because of differences in drug approvals across countries and physician preference. Whereas MET TKIs have demonstrated efficacy in treatment-naïve NSCLC and currently represent the recommended first-line option for advanced *MET*ex14-mutant NSCLC, some patients also experience prolonged benefit from ICI-based therapy. Recent real-world data from the multicentric Italian ATLAS registry showed a median first-line PFS of 7.2 months with capmatinib or tepotinib, shorter compared with the one observed in the phase II nonrandomized clinical trials with the same MET TKIs and not very different from the median PFS of 6 months reached with first-line chemoimmunotherapy showed by a German multicenter study (21, 22). Currently, no direct comparisons have been made between MET TKIs and immunotherapy ± chemotherapy as first-line treatment for *MET*ex14-mutant NSCLC, and the absence of randomized trials also limits the ability to identify patient subgroups that may benefit more from one approach over the other.

This study aims to identify clinicopathologic factors associated with improved outcomes from MET TKI versus ICI ± chemotherapy in the first-line setting, thereby supporting clinical decision-making and enabling a more tailored therapeutic approach based on individual patient profiles.

Materials and Methods

Study population and primary end point

This is a multicenter, retrospective, observational study including patients with a confirmed diagnosis of advanced NSCLC harboring METex14 alterations from five university hospital centers [Dana-Farber Cancer Institute (Boston, Massachusetts), MD Anderson Cancer Center (Houston, Texas), Sant'Orsola University Hospital (Bologna, Italy), Santa Maria della Misericordia University Hospital (Perugia, Italy), and University Hospital of Geneva (Geneva, Switzerland)]. Consecutive patients diagnosed with metastatic NSCLC between 2014 and 2024 were included in this analysis. Inclusion criteria included the following: (i) age ≥18 years old, (ii) histologically confirmed diagnosis of NSCLC, (iii) metastatic stage, (iv) *MET*ex14 alteration detected by a local laboratory with DNA or RNA next-generation sequencing (NGS) or RT-PCR, using tissue- and/or blood-based samples at each of the participating institutions, according to local standards, and (v) treatment with first-line MET TKI or ICI-based treatment (ICI as monotherapy or in combination with chemotherapy). Clinicopathologic and genomic data, including age, sex, Eastern Cooperative Oncology Group performance status, smoking history, detailed histology, PD-L1 TPS, and baseline metastatic sites, concurrent *MET* amplification according to local sequencing platform used, first-line and subsequent treatments, and relative drug-related toxicities, were retrospectively collected from medical records in each center from patients who met the inclusion criteria and had provided written informed consent to Institutional Review Board–approved correlative research studies at each center. The study was conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki.

The PD-L1 TPS was determined by immunohistochemistry (IHC) by pulmonary pathologists at each center using validated anti–PD-L1 mAbs: E1L3N (Cell Signaling Technology), 22C3 (Dako North America, Inc.), 28-8 (Epitomics, Inc.), or SP263 (Ventana Medical System).

Endpoints

The primary endpoints of the study were real-world PFS (rwPFS) and OS to first-line MET TKI versus ICI ± chemotherapy. Secondary objectives were the assessment of real-world ORR (rwORR) and duration of response to first-line MET TKI versus ICI ± chemotherapy. Investigator-assessed rwORR and rwPFS were determined using RECIST version 1.1 (23). Patients undergoing treatment were monitored with radiologic imaging per routine clinical practice, based on the discretion of their treating physicians.

Investigators were requested to assess disease response using RECIST version 1.1 criteria; however, no formal centralized imaging review was conducted. It is important to note that at each participating center, response evaluations were routinely performed by dedicated, independent thoracic radiologists, who provided detailed RECIST-based assessments as part of standard practice. Additionally, for patients enrolled in clinical trials, formal RECIST evaluations were available through trial documentation at each center. In addition, clinical activity to first-line MET TKI versus first-line ICI ± chemotherapy was assessed in each key patients' subgroups according to age, sex, history of smoke, histology, PD-L1 TPS level, baseline metastatic site, and *TP53* status.

The safety profile of first-line treatment with MET TKI versus ICI ± chemotherapy in patients with METex14-mutant metastatic NSCLC was also evaluated to provide a reliable comparison of the tolerability of currently available treatment strategies in a real-world clinical setting. Treatment-related adverse events (TRAE) were annotated both for MET TKI and ICI ± chemotherapy according to the Common Terminology Criteria for Adverse Events (version 5.0) based on retrospective review of patients' medical records.

Furthermore, we also assessed the PFS and safety of MET TKI or ICI ± chemotherapy when administered in the second-line setting in patients who received both treatments sequentially (first-line and second-line). First-line and second-line PFS were defined as the time from MET TKI or ICI ± chemotherapy initiation to the date of disease progression or death due to any cause. Patients who were alive without evidence of disease progression were censored on the date of their last disease assessment. First-line OS was defined as the time from MET TKI or ICI ± chemotherapy initiation to death due to any cause; patients who were still alive were censored at the date of last contact. Patients who did not have a radiologic follow-up and lacked information on treatment response were excluded from the ORR and PFS analyses.

Statistical analysis

Categorical and continuous variables were summarized using descriptive statistics. The Wilcoxon rank-sum test and Kruskal–Wallis test were used to test for differences between continuous variables, and Fisher exact test was used to test for associations between categorical variables. For the comparison of ORR, a logistic regression model was used to estimate ORs along with their 95% confidence intervals (CI). Log-rank tests were used to test for differences in event–time distributions, and Cox proportional hazards models were fitted to obtain estimates of HRs in univariate and subgroup analyses. Median follow-up was assessed using reverse Kaplan–Meier analysis. All *P* values are two-sided, and CIs are at the 95% level, with statistical significance defined as $P \leq 0.05$. All statistical analyses were performed using R version 3.6.1.

Results

Patient population and tumor characteristics

Among 158 patients with metastatic *MET*ex14-mutant NSCLC considered eligible for this study, 78 received ICI ± chemotherapy and 80 received MET TKI as first-line treatment. Supplementary Fig. S1A and S1B and Supplementary Table S1 report the geographic distribution (United States and Europe) and year of initiation of first-line therapy, stratified also by center location (United Stated vs. Europe). Timing of *MET*ex14 mutation detection according to first-line treatment start is shown in Supplementary Table S2. Considering the whole cohort, PD-L1 TPS was ≥50% in 62.7% of patients ($n = 96/153$ with PD-L1 TPS available pretreatment), and 20.9% ($n = 33$) of patients had baseline brain metastasis (**Fig. 1A** and **B**); regarding detailed first-line treatment choice, the most commonly administered was capmatinib or tepotinib in 33.5% ($n = 53$) of patients, followed by ICI monotherapy (25.9%, $n = 41$), chemoimmunotherapy (23.4%, $n = 37$), crizotinib (13.9%, $n = 22$), and other MET TKIs (3.3%, $n = 5$; **Fig. 1C**).

Looking at baseline clinicopathologic characteristics between patients treated with first-line ICI ± chemotherapy and first-line MET TKI, the percentage of patients with a history of tobacco use was higher in the first-line ICI ± chemotherapy cohort (57.3% vs. 38.8%, $P = 0.03$; **Table 1**). Baseline metastatic sites, in terms of bone, brain, lymph node, and liver metastases, PD-L1 TPS, and concurrent *MET* amplification were also balanced among the two treatment groups (**Table 1**). Clinicopathologic characteristics according to the specific first-line treatment (capmatinib or tepotinib, crizotinib, chemoimmunotherapy, and ICI monotherapy) are summarized in Supplementary Table S3.

Among patients who received first-line ICI ± chemotherapy, 5 (6.41%) were treated within a clinical trial, compared with 15 (18.8%) of those who received first-line MET TKI. Supplementary Table S4 shows clinical trials list with related number of patients enrolled.

PFS and OS to first-line MET TKI versus ICI ± chemotherapy in the overall population

At a median follow-up of 37.9 months (95% CI, 34.5–49.6), rwORR to first-line treatment was 57% with MET TKI versus 40% with ICI ± chemotherapy (OR, 1.99; 95% CI, 1.05–3.80; $P = 0.04$; **Fig. 2A**; Supplementary Table S5), whereas there was no difference in median rwPFS (8.2 months with MET TKI vs. 5.7 months with ICI ± chemotherapy; HR, 0.85; 95% CI, 0.59–1.22; $P = 0.4$) or OS (19.4 months with MET TKI versus 22.1 months with ICI ± chemotherapy; HR, 0.97; 95% CI, 0.65–1.45; $P = 0.9$; **Fig. 2B** and **C**). No difference in the duration of response was observed according to first-line treatment [median rwDoR: 14.0 months (95% CI, 9.2–28.8) with first-line MET TKI versus 19.5 months (95% CI, 12.0–NR) with first-line ICI ± chemotherapy, $P = 0.1$; Supplementary Table S5].

We next evaluated clinical outcomes based on the detailed treatment received in the first line. Although higher rwORRs were observed with capmatinib or tepotinib (57.7%) and crizotinib (63.6%) compared with ICI monotherapy (41.0%) and chemoimmunotherapy (38.9%; Supplementary Fig. S2A; Supplementary Table S6), no significant differences in median rwPFS or OS were identified across the various therapeutic strategies (Supplementary Fig. S2B and S2C).

Key subgroup analyses

Next, subgroup analyses were performed to explore whether certain clinicopathologic features can guide the selection of first-line therapy to benefit specific subgroups of patients.

No significant differences in clinical outcomes were observed between ICI ± chemotherapy and MET TKI treatments across subgroups defined by smoking history, sex, age, and histology (Supplementary Table S7).

Patients with PD-L1 ≥80% benefit more from first-line ICI ± chemotherapy, whereas patients with PD-L1 <50% benefit more from first-line MET TKI

Very high PD-L1 TPS expression is associated with significant prolonged benefit from ICIs therapy in patients with advanced NSCLC (16, 17). First, we evaluated whether patients with high PD-L1

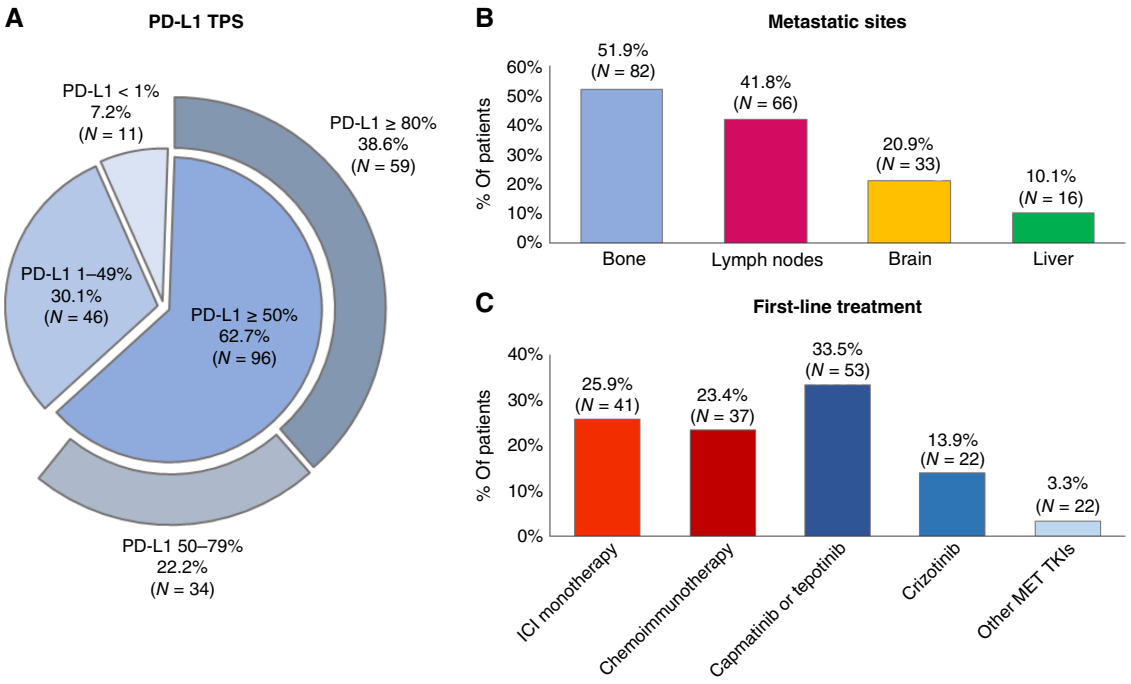


Figure 1.

Baseline PD-L1 TPS, metastatic sites, and first-line treatment choice. **A,** Baseline PD-L1 TPS (in three patients, PD-L1 TPS was reported only as ≥50%), (**B**) metastatic sites (bone, lymph nodes, brain, and liver), and (**C**) first-line treatment choice in metastatic *MET*ex14-mutant NSCLC.

expression (≥50%) experienced longer benefit from ICI-based treatment but found no statistically significant difference according to the type of first-line therapy (Supplementary Table S8). Because a PD-L1 cutoff of ≥50% may not adequately capture ICI efficacy in METex14-mutant NSCLC, we further explored whether progressively higher PD-L1 levels could better identify a subgroup of patients more likely to benefit from ICI (Supplementary Table S8). In patients whose tumors had a PD-L1 TPS ≥80% (n = 59/153, 38.6%), first-line ICIs ± chemotherapy significantly prolonged median rwPFS compared with MET TKI (9.4 vs. 5.0 months, HR, 0.50; 95% CI, 0.27–0.92; P = 0.03). No differences in rwORR were observed between the two first-line regimens (53.6% with first-line ICI ± chemotherapy versus 51.6% with first-line MET TKI, P = 0.9). A numerically longer OS was observed with ICI ± chemotherapy compared with MET TKI, although this did not reach statistical significance (43.8 vs. 15.8 months; HR, 0.52; 95% CI, 0.26–1.04; P = 0.07; **Fig. 3A–C**).

Direct comparison in rwPFS and OS across types of MET TKIs and specific immunotherapy regimen in the PD-L1 TPS ≥80% subgroup is shown in Supplementary Fig. S3A and S3B.

No significant differences in rwORR, rwPFS, and OS were observed according to first-line treatment strategy in patients with a PD-L1 TPS 50% to 79% (**Fig. 3D–F**).

Next, we evaluated patients with tumor having PD-L1 TPS expression <50% (n = 57/153, 37.3%). For PD-L1 TPS 0% to 49%, first-line MET TKI usage, compared with ICIs ± chemotherapy, resulted in significantly longer median rwPFS (12.2 vs. 5.7 months, HR, 0.40; 95% CI, 0.21–0.76; P = 0.005), longer median OS (27.4 months vs. 15.0 months, HR, 0.49; 95% CI, 0.26–0.95; P = 0.03), and numerically higher rwORR (60% vs. 34.6%; OR, 2.83; 95% CI, 0.97–8.71; P = 0.06; **Fig. 3G–I**). Direct comparisons in rwPFS and OS across types of MET TKI and specific immunotherapy regimen in the PD-L1 TPS <50% subgroup is shown in Supplementary Fig. S3C and S3D. To evaluate whether smoking status influenced these results, we examined the distribution of patients with or without a history of smoking across different PD-L1 expression levels, and no significant differences were found (Supplementary Table S9).

Patients with baseline brain metastasis and bone metastasis benefit more from first-line MET TKI

In the GEOMETRY and VISION trials, capmatinib and tepotinib demonstrated central nervous system (CNS) penetrance (13, 14). In this retrospective cohort, MET TKI demonstrated superior outcomes compared with ICI ± chemotherapy in patients with baseline brain metastases. Data regarding any baseline local treatment for brain metastasis and site of brain metastasis are reported in Supplementary Table S10. First-line MET TKI was associated with a higher rwORR (64.7% vs. 20%; OR, 7.33; 95% CI, 1.60–42.82; P = 0.02), as well as longer median rwPFS (11.70 vs. 2.73 months, HR, 0.39; 95% CI, 0.17–0.88; P = 0.02) and longer median OS (32.2 vs. 14.8 months; HR, 0.36; 95% CI, 0.14–0.92; P = 0.03; **Fig. 4A–C**). Whereas the percentage of CNS progression at any time during treatment was similar between the two first-line regimens (9.5% for MET TKI vs. 14.1% for ICI ± chemotherapy, Supplementary Fig. S4A), among patients with baseline brain involvement, CNS disease control was higher in those treated with MET TKI: specifically, CNS progression at any time during treatment occurred in 18.8% of patients receiving first-line MET TKI, compared with 30.8% of those treated with first-line ICI ± chemotherapy (Supplementary Fig. S4B and S4C). Notably, among patients with (n = 11) and without (n = 42) baseline brain metastasis, treated with first-line capmatinib or tepotinib, no brain progression was observed, even if this observation is limited by the small sample size.

Table 1. Baseline clinicopathologic characteristics of patients with metastatic NSCLC harboring *MET*ex14 alterations and treated in the first-line setting with ICI ± chemotherapy or MET TKI.

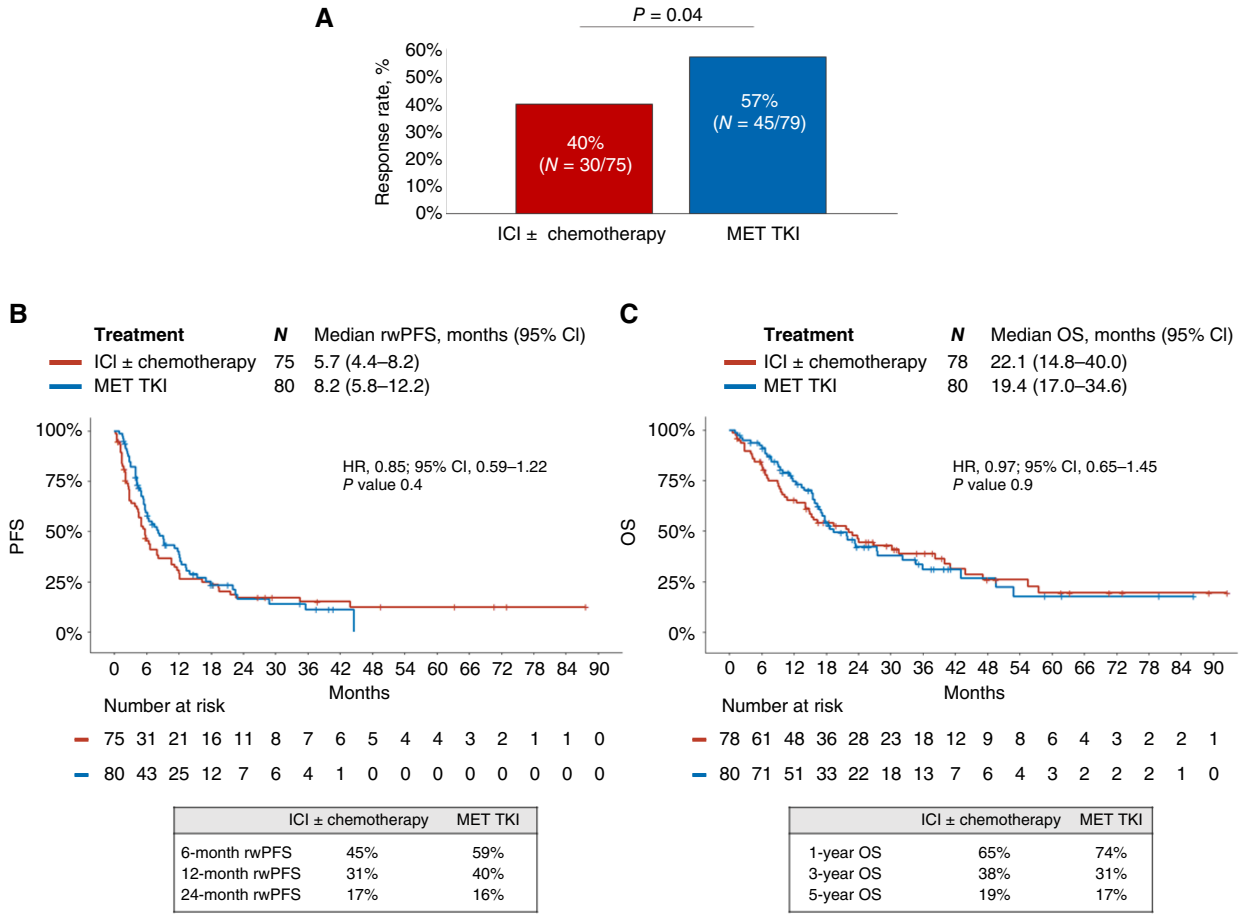
	ICI ± chemotherapy (*N* = 78)	MET TKI (*N* = 80)	*P* value
Age			
Median (minimum, maximum)	71.5 (40.0, 92.0)	71.5 (47.0, 92.0)	0.9
Sex			
Female	43 (55.1%)	47 (58.8%)	0.7
Male	35 (44.9%)	33 (41.3%)	
History of tobacco use			
Patients with a history of tobacco use	43 (57.3%)	31 (38.8%)	**0.03**
Patients without a history of tobacco use	32 (42.7%)	49 (61.3%)	
Unknown	3	0	
Pack-years			
Median (minimum, maximum)	24.0 (1.00, 90.0)	15.0 (1.75, 80.0)	0.2
Histology			
Adenocarcinoma	57 (73.1%)	47 (58.8%)	0.08
Other	21 (26.9%)	33 (41.3%)	
Brain metastasis			
No	62 (79.5%)	63 (78.8%)	1
Yes	16 (20.5%)	17 (21.3%)	
Bone metastasis			
No	40 (51.3%)	36 (45.0%)	0.5
Yes	38 (48.7%)	44 (55.0%)	
Liver metastasis			
No	69 (88.5%)	73 (91.3%)	0.7
Yes	9 (11.5%)	7 (8.75%)	
Lymph nodes metastasis			
No	51 (65.4%)	41 (51.3%)	0.1
Yes	27 (34.6%)	39 (48.8%)	
PD-L1 TPS			
≥50%	50 (64.9%)	46 (60.5%)	0.8
1%–49%	22 (28.6%)	24 (31.6%)	
<1%	5 (6.49%)	6 (7.89%)	
Unknown	1	4	
Eastern Cooperative Oncology Group performance status			
0	27 (35.5%)	35 (46.1%)	
1	41 (53.9%)	33 (43.4%)	0.4
≥2	8 (10.5%)	8 (10.5%)	
Unknown	2	4	
Concurrent *MET* amplification			
No	64 (84.2%)	73 (91.3%)	0.2
Yes	12 (15.8%)	7 (8.7%)	
Unknown	2	0	
Sequential treatment (first- and second-line)			
No	45 (57.7%)	56 (70.0%)	0.1
Yes	33 (42.3%)	24 (30.0%)	

Compared with ICIs ± chemotherapy, first-line MET TKI demonstrated a higher rwORR (58.1% vs. 32.4%; OR, 2.89; 95% CI, 1.17–7.42; $P = 0.02$) and improved median rwPFS in patients with baseline bone metastases (7.89 vs. 4.57 months, HR, 0.55; 95% CI, 0.34–0.88; $P = 0.01$; **Fig. 4D–F**). Detailed HRs for rwPFS and OS according to each first-line therapeutic strategy in subgroups of patients with baseline brain or bone metastatic involvement are presented in Supplementary Fig. S5A–S5D.

Concurrent genomic alterations and impact of *TP53* mutations on clinical outcomes according to first-line treatment strategy

Next, we looked at the genomic landscape of cases with metastatic *MET*ex14-mutant NSCLC included in this study. Among 158 patients, 155 had information regarding type of NGS sample (tumor tissue vs. liquid), and 118 (76.1%) patients had available DNA NGS on tumor tissue. Among those, 101 (85.6%) had *TP53* status available, with 34 (33.7%) of them harboring a deleterious mutation of *TP53*.

Considering the subgroup of patients with concurrent *TP53* mutations, even if a higher percentage of rwORR was observed in patients receiving first-line MET TKI (72.2% vs. 31.3%; OR, 5.72 95% CI, 1.3–27.5; $P = 0.02$), this was not translated into prolonged rwPFS and OS, showing similar clinical outcomes in terms of PFS and OS to first-line MET TKI versus ICIs ± chemotherapy (Supplementary Fig. S6A–S6C). No significant differences in terms of rwORR, rwPFS, and OS were observed in the *TP53* wild-type subgroup based on the type of first-line treatment strategy (Supplementary Fig. S6D and S6F).



	ICI ± chemotherapy	MET TKI
6-month rwPFS	45%	59%
12-month rwPFS	31%	40%
24-month rwPFS	17%	16%

	ICI ± chemotherapy	MET TKI
1-year OS	65%	74%
3-year OS	38%	31%
5-year OS	19%	17%

Figure 2.
Clinical outcomes to first-line treatment in the whole cohort. **A,** rwORR, (**B**) rwPFS, and (**C**) OS of metastatic *MET*ex14-mutant NSCLC according to first-line ICI ± chemotherapy or MET TKI.

Beyond *TP53,* the other most common genomic co-alterations were *MDM2* amplification, detected in 25.5% (n = 24/94) of cases, *CDK4* amplification in 15.5% (15/97), *CDKN2A* copy number loss or inactivating mutations in 11.7% (11/94), and inactivating mutations of *NF1* in 10.6% (10/94) of cases.

Patients with concurrent *MET* amplification

Upregulation of PD-L1 TPS has been described in NSCLC harboring *MET* amplification (24). Therefore, we next asked whether these patients had different outcomes to first-line ICI ± chemotherapy versus MET TKI. In our cohort of patients with METex14-mutant NSCLC with concurrent *MET* amplification (n = 19), clinicopathologic features were not different compared with those of patients without a concurrent *MET* amplification (n = 137; Supplementary Table S11). Among patients with concurrent baseline *MET* amplification, 72.2% (n = 13/18 with PD-L1 TPS available at baseline) had a PD-L1 TPS ≥50%, and 63.2% received first-line ICI ± chemotherapy (Supplementary Fig. S7A and S7B).

Among the seven patients treated with first-line MET TKI, all achieved an objective response as best overall response. Looking at patients treated with ICIs ± chemotherapy, among 11, 6 had an objective response, and two achieved a SD as best overall response; two patients, both with a very high PD-L1 (#1 and #2), were still under treatment after more than 3 years at the time of data cutoff. Supplementary Fig. S7C depicts the 18 patients included in the first-line PFS analysis.

Subsequent treatment strategy

Among 158 total patients included in this study, 90 (57%) underwent a systemic second-line treatment, 55.5% (n = 50/90) received a MET TKI, 27.7% (n = 25/90) received ICI ± chemotherapy, and 11.1% (n = 10/90) received chemotherapy. Sixteen patients, at the time of data cutoff, were still on first-line treatment (**Fig. 5A**).

Fifty-seven (36.7%) patients received both treatments sequentially (first-line and second-line), 33 received MET TKI, and 24 received ICI ± chemotherapy as second-line treatment. There was no difference in second-line rwORR (45.2% for MET-TKI versus 31.8% for ICIs ± chemotherapy, P = 0.3) and second-line median rwPFS between MET TKI versus ICI ± chemotherapy (4.60 vs. 6.61 months; HR, 0.77; 95%; CI, 0.42–1.41; P = 0.4; Supplementary Fig. S8A and S8B).

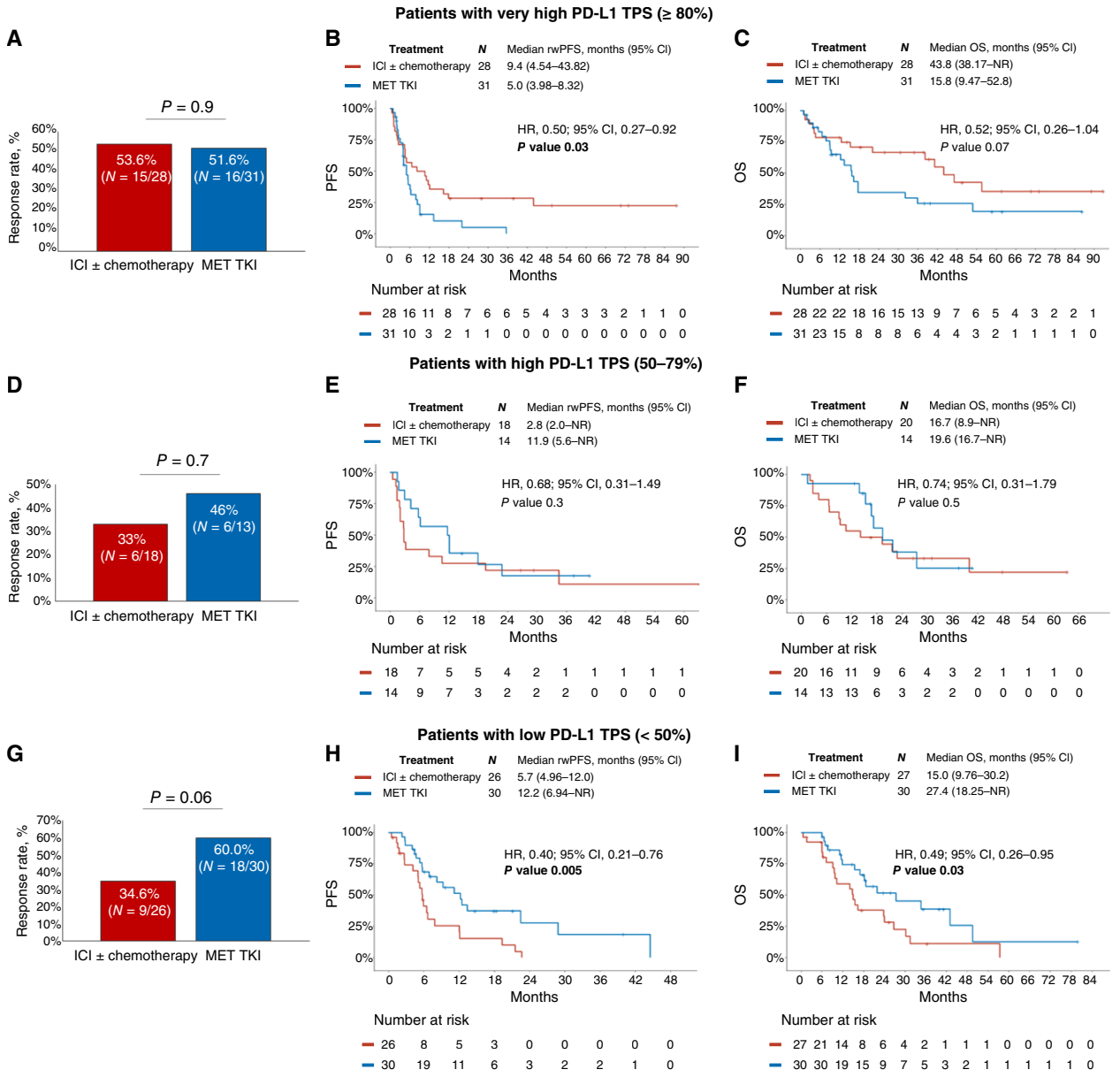


Figure 3.

Clinical outcomes with first-line treatment across subgroups defined by PD-L1 TPS. **A,** rwORR, (**B**) rwPFS, and (**C**) OS of metastatic *MET*ex14-mutant NSCLC according to first-line ICI ± chemotherapy or MET TKI in patients with very high PD-L1 TPS (≥80%), (**D–F**) patients with high PD-L1 TPS (50%–79%), and (**G–I**) patients with low PD-L1 TPS (<50%).

Safety

Next, we examined TRAEs in the first-line setting according to the treatment received. Overall, higher rate of TRAEs of any grade was observed in patients who received MET TKI as first-line therapy compared with ICI ± chemotherapy (60% vs. 35.9%, $P = 0.004$), even if no difference in term of incidence of G3-G4 TRAEs ($P = 0.9$) and permanent discontinuation ($P = 0.2$) between MET TKI and ICI ± chemotherapy was detected (Supplementary Table S12; Supplementary Fig. S9). For patients treated with first-line MET TKI, the most common TRAE was peripheral edema, detected in 34% of cases, whereas among patients treated with first-line ICI ± chemotherapy, the most common TRAEs was pneumonitis, followed by cutaneous and hematologic, both noted in 7.7% of patients (**Fig. 5B**). A detailed spectrum of TRAEs according to specific first-line treatment is shown in Supplementary Table S13. Among patients who received both treatments sequentially (first-line and second-line), the incidence of TRAEs of any grade or high grade (G3–G4) was higher for second-line MET TKI compared with second-line ICI ± chemotherapy (Supplementary Table S12), but the incidence of TRAEs of any grade

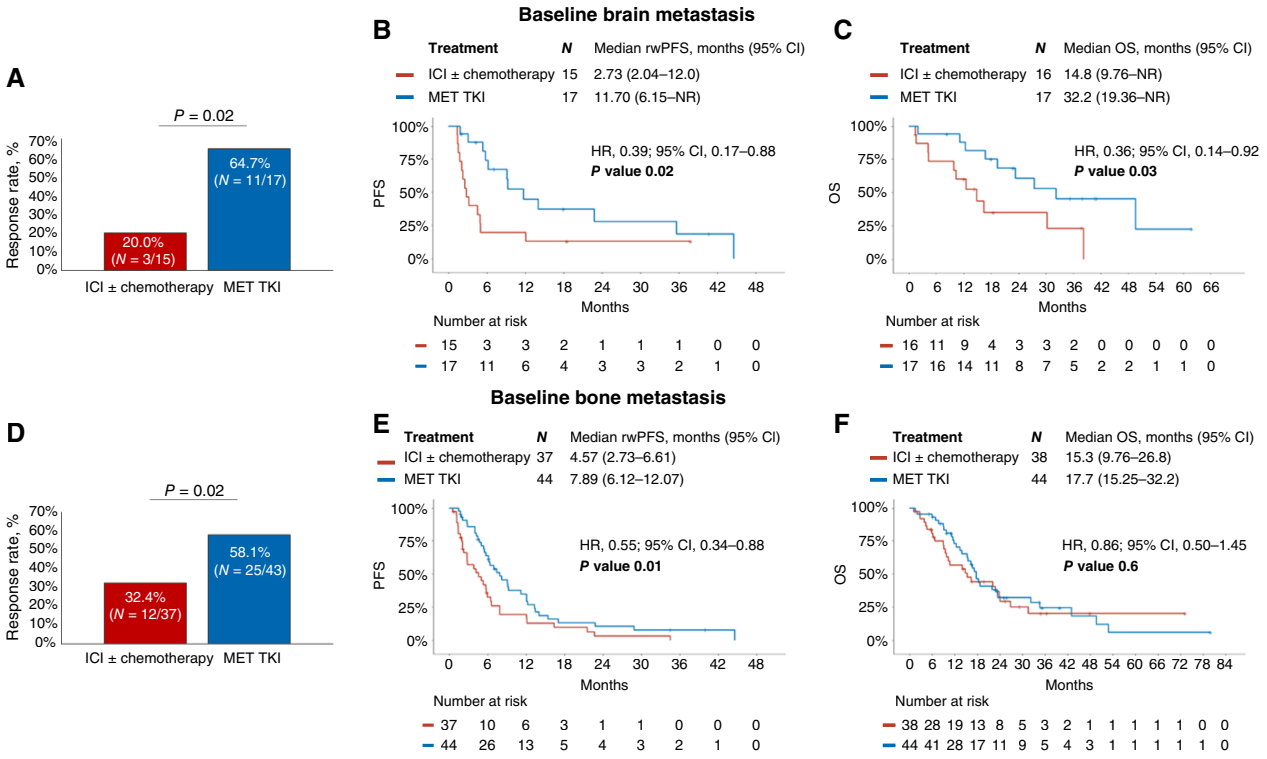


Figure 4.

Clinical outcomes with first-line treatment across subgroups defined by baseline metastatic sites. **A,** rwORR, (**B**) rwPFS, and (**C**) OS of metastatic *MET*ex14-mutant NSCLC treated with first-line ICI ± chemotherapy or MET TKI in patients with baseline brain metastasis and (**D–F**) patients with baseline bone metastasis.

was similar for MET TKI received in first-line setting versus MET TKI received in second-line setting after ICI ± chemotherapy (60% vs. 57.6%; $P = 0.4$) and the same for high-grade TRAEs (14.9% vs. 15.2%; $P = 0.9$). Moreover, the incidence of immune-related AEs was not higher in patients treated with ICI ± chemotherapy in the second line after a first-line MET TKI compared with patients receiving ICI ± chemotherapy in the first line (Supplementary Table S12).

Discussion

This international multicenter retrospective study represents the largest real-world analysis directly comparing first-line MET TKI to ICI ± chemotherapy in *MET*ex14-mutant metastatic NSCLC. We observed practice patterns and complex decision-making processes, emphasizing the nuances of effectiveness among various subgroups of patients and the broader implications for clinical practice. Although there were no significant rwPFS and OS differences in the all comers, subgroup analyses provided some evidence on how to better select patients for a tailored first-line treatment strategy. The rwORR was significantly higher for first-line MET TKI (57%) compared with ICI ± chemotherapy (40%), aligning with the biological rationale of targeting the MET pathway in *MET*ex14-mutant NSCLC, and similar to GEOMETRY and VISION trials results (13, 14). Despite this, rwPFS and OS did not significantly differ between the two strategies, suggesting that, whereas MET TKI may achieve higher immediate response rates, long-term outcomes might be influenced by other factors such as subsequent treatments, patient characteristics, PD-L1 TPS expression, and baseline metastatic sites. As expected, capmatinib and tepotinib were associated with the longest durations of response among MET TKIs, emphasizing their role as preferred MET inhibitors.

Although there was no rwPFS and OS difference in all comers, subgroup analyses showed differential outcomes based on baseline clinicopathologic characteristics. For patients with PD-L1 TPS ≥80%, first-line ICI ± chemotherapy demonstrated a significant rwPFS benefit over MET TKI and, although the OS benefit for ICI ± chemotherapy in this subgroup did not reach statistical significance, there was a striking numerical difference in median OS favoring ICI ± chemotherapy (43.8 vs. 15.8 months). Therefore, ICI ± chemotherapy seems to demonstrate efficacy only in a subset of METex14-mutant NSCLC, supporting PD-L1 TPS as a potential biomarker for selecting first-line ICI-based therapies in *MET*ex14-mutant NSCLC, limited to patients with very high PD-L1 expression (≥80% or ≥90; refs. 16, 17).

Conversely, for patients with PD-L1 TPS <50%, MET TKI provided significantly longer rwPFS (12.2 vs. 5.7 months) and OS (27.4 vs. 15.0 months) compared with ICI ± chemotherapy, supporting the prioritization of first-line MET TKI in patients with low PD-L1 TPS expression (<50%), in which MET pathway dependency may outweigh the benefits of immunotherapy.

Baseline metastatic sites were another critical determinant of treatment outcomes. Among patients with brain metastases, MET TKI outperformed ICI ± chemotherapy in rwORR (64.7% vs. 20%), rwPFS (11.7 vs. 2.73 months), and OS (32.2 vs. 14.8 months), likely reflecting the CNS penetration of certain MET TKIs. Additionally,

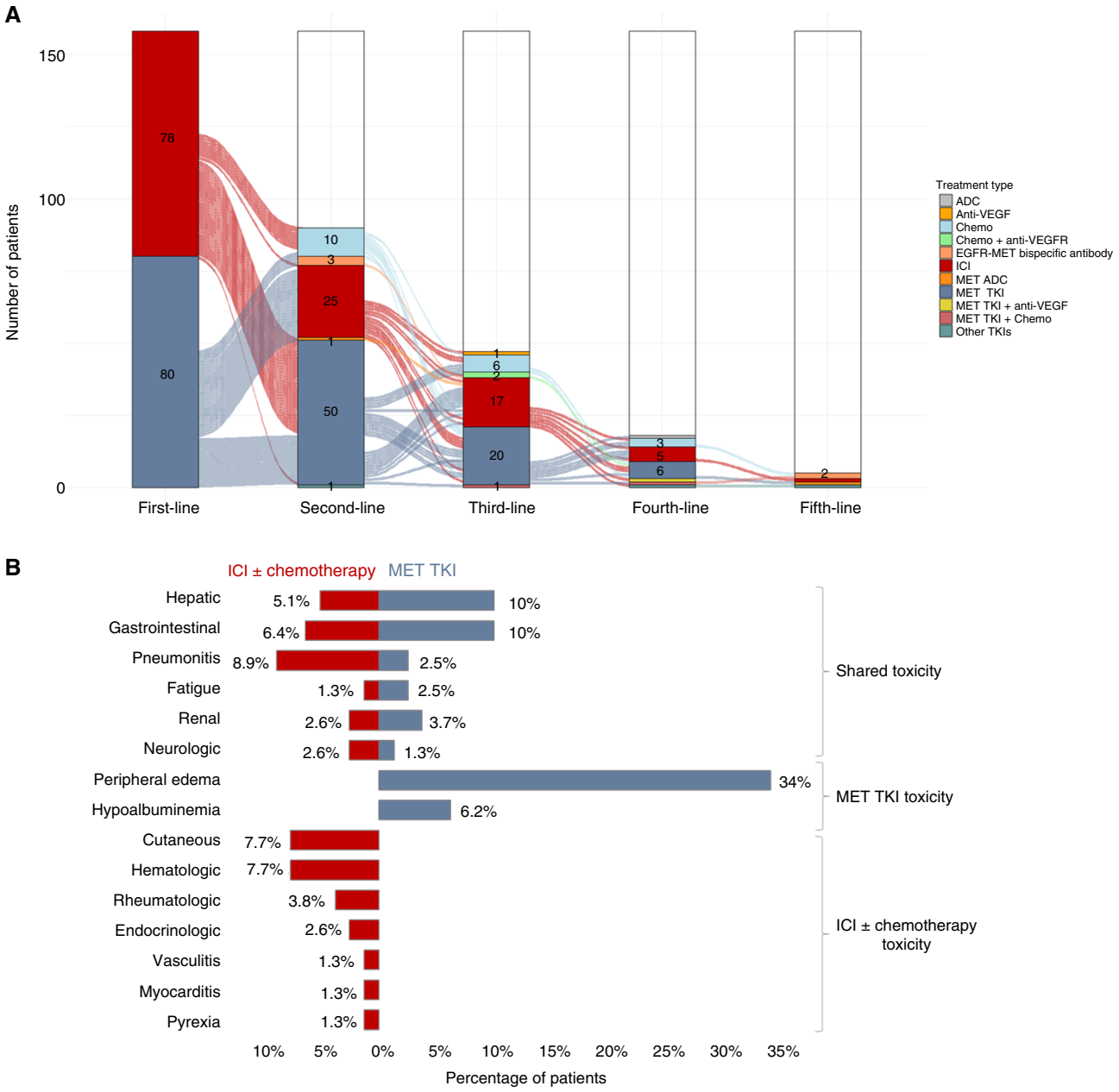


Figure 5.

Sequential lines of treatment after first-line treatment and TRAEs according to first-line treatment. **A,** Sequential lines of treatment in patients with metastatic *MET*ex14-mutant NSCLC. Ninety patients received additional systemic oncologic treatments; 16 patients were still under first-line treatment, three were under the same MET TKI used in first-line therapy beyond progression, six were off-treatment maintaining disease control after first-line interruption; 15 were lost at follow-up; two had pending decision about second-line treatment after progression to first-line; 26 did not receive further active oncologic treatment until death or died under first-line treatment. ADC, antibody–drug conjugate; Chemo, chemotherapy. **B,** TRAEs according to first-line treatment choice (MET TKI or ICIs).

CNS progression was less frequent among patients receiving MET TKI with baseline brain metastasis, suggesting superior intracranial disease control (14, 25). As shown in the GEOMETRY and VISION trials, both capmatinib and tepotinib demonstrated intracranial efficacy, and the same was observed in our retrospective cohort, although we acknowledge the small sample size available for this subgroup analysis, supporting the clinical utilization of these two specific MET TKIs specifically as first-line treatment choice in patients with baseline brain disease involvement.

For patients with baseline bone metastases, compared with ICI ± chemotherapy, MET TKI also demonstrated superior outcomes, with higher rwORR (58.1% vs. 32.4%) and longer rwPFS (7.89 vs. 4.57 months). Patients receiving ICI ± chemotherapy or TKI-based treatments, such as EGFR TKIs, exhibit poorer survival outcomes

when bone metastases are present compared with those without bone involvement. Previous data in patients with renal cell carcinoma showed higher IHC expression of MET on bone metastases, and related preclinical studies have shown the efficacy of MET inhibitors in targeting bone metastases in murine models, highlighting a potential therapeutic avenue for improving outcomes in this subset of patients (26). Whether also in NSCLC is comparable needs further investigation but can partially explain why in our retrospective study patients with baseline bone metastasis respond better to first-line MET TKI compared with first-line ICI ± chemotherapy. These findings underscore the importance of considering baseline metastatic sites when selecting first-line therapies.

In our cohort, more than half of the patients received systemic second-line treatment, with MET TKI and ICI ± chemotherapy being the most common options. Whereas rwORR and rwPFS for second-line treatment were comparable between MET TKI and ICI ± chemotherapy, these results highlight the importance of sequencing therapies to optimize long-term outcomes. Patients who received both MET TKI and ICI ± chemotherapy sequentially may benefit from complementary mechanisms of action, addressing the limitations of each individual therapy.

The safety profiles of first-line MET TKI and ICI ± chemotherapy were generally comparable. Grade 3 to 4 TRAEs occurred in approximately 14% to 15% of patients in both groups, and permanent discontinuation rates were similar. This indicates that both therapies are well-tolerated, enabling clinicians to prioritize efficacy and patient-specific factors when choosing first-line treatment strategy.

As expected, the most common genomic coalteration was represented by *TP53* mutations, as already shown in the literature in larger cohorts (27). *TP53* status did not influence the choice of first-line treatment; however, this finding may be limited by the small sample size, and further genomic biomarkers' investigation in larger cohorts is warranted.

The comparable OS outcomes between MET TKI and ICI ± chemotherapy highlight the importance of tailoring treatment based on individual patient characteristics, including PD-L1 TPS expression and baseline metastatic site. PD-L1 TPS emerges as a critical biomarker for guiding first-line therapy selection, with very high PD-L1 expression favoring ICI ± chemotherapy and low PD-L1 expression favoring MET TKI. The superior intracranial activity of MET TKIs, specifically capmatinib and tepotinib, underscores their role in patients with baseline brain metastases, in which ICI ± chemotherapy may be less effective. The comparable efficacy of MET TKI and ICI ± chemotherapy in the second-line setting supports the potential benefit of sequencing these therapies to achieve optimal outcomes.

The retrospective design of our study inherently carries several limitations, including potential selection bias and incomplete data collection for several variables, lack of centralized independent radiologic revision of treatment response, a probable underestimation of low-grade TRAEs, the heterogeneity of NGS platforms, and the relatively small sample size of certain subgroups, such as patients with concurrent *MET* amplification, CNS metastases, and *TP53*-mutant cases. Moreover, our study has inherent limitations due to international variability in both drug approvals and implementation of molecular diagnostics for *MET*ex14 alterations in clinical practice, leading to variation in the timing of MET TKI availability between the United States and Europe. Differences in regulatory timelines between the FDA and European Medicines Agency have led to asynchronous availability of MET inhibitors across participating centers. For instance, capmatinib received FDA-accelerated approval for advanced *MET*ex14-mutant NSCLC in 2020, whereas in Europe, its use in the first-line setting remains off-label and often accessible only through compassionate use programs, which are not uniformly approved or implemented. Moreover, heterogeneity in sequencing platforms and the inclusion, or lack thereof, of adequate *MET* sequencing, both across and within countries, contributes to variability in *MET*ex14 mutation detection. These discrepancies are further influenced by differences between hybrid capture-based assays (e.g., OncoPanel platform) and other amplicon-based NGS approaches used in different centers, as well as by center-specific practices and timing of *MET* testing over the years. These factors may have affected patient selection, treatment access, and data comparability and should be considered when interpreting our real-world findings from a multicentric international cohort.

National Comprehensive Cancer Network guidelines recommend capmatinib or tepotinib as first-line treatment option for advanced NSCLC with *MET*ex14 mutations while no homogeneous full reimburse in the first-line setting is now available in other parts of the world; therefore, in many countries, patients can have access to MET TKI only after first-line ICI ± chemotherapy. The findings of this study have important implications for the first-line management of metastatic *MET*ex14-mutant NSCLC, providing valuable insights to guide clinical decision-making and supporting the key role of MET TKI. First-line MET TKI therapy led to a higher response rate than ICI ± chemotherapy, supporting its use in patients needing rapid tumor shrinkage and symptom relief. Patients with tumors exhibiting PD-L1 <50%, or with baseline brain metastasis, may derive significant greater benefit from first-line MET TKIs, especially capmatinib or tepotinib. The effective role of first-line ICI ± chemotherapy seems to be restricted only to patients having tumors expressing very high PD-L1 (≥80%). Therefore, prioritizing a treatment associated with higher response rates and numerically longer PFS in the first-line setting strongly supports the upfront use of MET TKIs. Although rwPFS with MET TKIs may be shorter than reported in clinical trials, it remains longer than the rwPFS observed with ICI ± chemotherapy (21, 22). Moreover, not all patients will be eligible for second-line treatment, potentially preventing them from receiving the most effective therapy. Whereas this study provides important real-world evidence, several questions remain unanswered, and prospective randomized studies are needed to validate these findings and explore the mechanisms underlying differential responses to MET TKI and ICI ± chemotherapy. Additionally, the role of novel treatment strategies, such as antibody–drug conjugates, warrants investigation to further improve outcomes in this challenging patient population. In conclusion, our study highlights the need for broader and more consistent reimbursement policies to ensure equitable access to MET TKIs as first-line treatment across different countries, particularly for patients with *MET*ex14 NSCLC who are unlikely to benefit from ICI-based therapies, such as those with low PD-L1 expression or brain/bone metastases. Ensuring timely access to the most effective therapy in the first-line setting is essential to optimize clinical outcomes in this vulnerable patient population.

Authors' Disclosures

F. Pecci reports personal fees from EMD Serono, Inc. outside the submitted work; in addition, F. Pecci is supported by Fondazione Gianni Bonadonna Fellowship 2024, in collaboration with the European School of Oncology. A. Di Federico reports personal fees from Hanson Wade, IQVIA, and Novartis and other support from Johnson & Johnson and Pfizer outside the submitted work. J. Wu reports research grants from NIH, Cancer Prevention and Research Institute of Texas (CPRIT), Break Through Cancer, and Siemens and travel compensation to join academic conferences from ESMO, DAVA Oncology, 3PSOLUTION, and International Summit on Lung Cancer. E. Garbo was supported by an American–Italian Cancer Foundation Post-Doctoral Research Fellowship, year 2024 to 2025. M. Aldea reports grants from Amgen, Owkin, and AstraZeneca outside the submitted work. D. Gibbons reports personal fees from Eli

Lilly, Aktis Oncology, Menarini Ricerche, and Ideology Health and grants from Boehringer Ingelheim and Mirati outside the submitted work. H. Tran reports personal fees from Abion outside the submitted work. F. Paoloni was supported by an American–Italian Cancer Foundation Post-Doctoral Research Fellowship, year 2024 to 2025. F. Gelsomino reports personal fees from Pfizer, Bristol Myers Squibb, Novartis, Regeneron, Eli Lilly, and AstraZeneca outside the submitted work. M. Tiseo reports grants and personal fees from AstraZeneca and Boehringer Ingelheim; grants, personal fees, and nonfinancial support from Roche; personal fees and nonfinancial support from Takeda and Amgen; and personal fees from Pfizer, Eli Lilly, Bristol Myers Squibb, Novartis, MSD, Merck, Johnson & Johnson, Pierre Fabre, Regeneron, BeiOne, Daiichi Sankyo, and Accord outside the submitted work. J. Rotow reports personal fees and other support from Merus, Bristol Myers Squibb, Daiichi Sankyo, AstraZeneca, and Johnson & Johnson; personal fees from BioAtla, Summit, Takeda, Jazz Pharmaceuticals, Amgen, Genentech, Pfizer, Boehringer Ingelheim, Novocure, Gilead, EMD Serono, and Nuvation Bio; and other support from AbbVie, Bicycle Therapeutics, Blueprint, Enliver, EpimAb, LOXO Oncology, ORIC Pharmaceuticals, RedCloud, Black Diamond, Regeneron, ImmunityBio, Altor Bioscience, Duality, and BlossomHill Therapeutics outside the submitted work. A. Ardizzoni reports personal fees from Bristol Myers Squibb, AstraZeneca, MSD, Roche, Eli Lilly, Novartis, Amgen, Pfizer, Regeneron, Takeda, Daiichi Sankyo, AbbVie, Pierre Fabre, Johnson & Johnson, and Gilead outside the submitted work. M.M. Awad reports grants and personal fees from Genentech, Bristol Myers Squibb, AstraZeneca, Lilly, and Amgen and personal fees from Merck, Mirati, Gritstone, EMD Serono, Regeneron, Janssen, Affini-T Therapeutics, Novartis, Coherus, D3Bio, Synthekine, Gilead, and Seagen outside the submitted work. A. Addeo reports personal fees from Bristol Myers Squibb, MSD, Astellas, Roche, AstraZeneca, Pfizer, Eli Lilly, Boehringer Ingelheim, and Regeneron outside the submitted work. M.V. Negrao reports consulting or advisory board relationships with Genentech, Sanofi, Pfizer, Lilly, AstraZeneca, and BMS; speaker's bureau relationships with OncLive, Ideology, BIO Brasil, Medscape, DAVA Oncology, and Targeted Oncology; research funding from Lilly, Mirati, BMS, Novartis, Alaunos, AstraZeneca, Pfizer, Genentech, Navire, and Frontier Medicine; support for travel, accommodation, and expenses from Ideology, DAVA Oncology, and Targeted Oncology; and writing support from ApotheCom and Ashfield Healthcare. P.A. Jänne reports grants and personal fees from Daiichi Sankyo, AstraZeneca, and Eli Lilly and personal fees from SFJ Pharmaceuticals, Voronoi, Biocartis, Sanofi Oncology, Takeda Oncology, Mirati Therapeutics, Transcenta, Silicon Therapeutics, Syndax, Nuvalent, Bayer, Eisai, Allorion Therapeutics, Accutar Biotech, AbbVie, Monte Rosa Therapeutics, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotechnology, Duality Biologics, Blueprint Medicines, Dizal Pharma, GlaxoSmithKline, Myris Therapeutics, Tolremo, Pfizer, Chugai, and Bristol Myers Squibb outside the submitted work; in addition, P.A. Jänne has a patent for EGFR mutations issued, licensed, and with royalties paid from LabCorp. J.V. Heymach reports personal fees from EMD Serono, Novartis, Johnson & Johnson, and AbbVie during the conduct of the study. J. Zhang has acted as a consultant and/or adviser or speaker or received research funding from AstraZeneca, BeiGene, Bicara Therapeutics, Bristol Myers Squibb, Catalyst, GenePlus, Helius, Hengrui Therapeutics, Innovent Biologics, Johnson & Johnson, Merck, Novartis, OrigMed, OncoHost, Roche, Summit, Takeda, and Varian. B. Ricciuti reports personal fees from AstraZeneca, Regeneron, Bristol Myers Squibb, Caris Life Sciences, Amgen, AbbVie, and Targeted Oncology; grants from AstraZeneca; and grants and personal fees from SITC outside the submitted work. X. Le reports personal fees from Eli Lilly, EMD Serono (Merck KGaA), AstraZeneca, Spectrum Pharmaceutics, Novartis, Regeneron, Boehringer Ingelheim, Hengrui Therapeutics, Bayer, Teligene, Taiho, Daiichi Sankyo, Janssen, Blueprint Medicines, Sensei Biotherapeutics, SystImmune, ArriVent BioPharma, Abion, BlossomHill Therapeutics, and AbbVie and grants from Eli Lilly, EMD Serono, ArriVent BioPharma, Dizal Pharma, Teligene, Regeneron, Janssen, Thermo Fisher Scientific, Takeda, and Boehringer Ingelheim outside the submitted work. No disclosures were reported by the other authors.

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Acknowledgments

F. Pecci is supported by Fondazione Gianni Bonadonna Fellowship 2024, in collaboration with the European School of Oncology. E. Garbo is supported by an American–Italian Cancer Foundation Post-Doctoral Research Fellowship, years 2024 to 2025. F. Paoloni is supported by an American–Italian Cancer Foundation Post-Doctoral Research Fellowship, years 2024 to 2025. This study was supported by Team Stuie's Pan-Mass Challenge.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received May 10, 2025; revised July 2, 2025; accepted August 25, 2025; posted first August 27, 2025.

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