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Real-world effectiveness of MET TKI inhibitors versus pembrolizumab ± chemotherapy (pembro±CT) in 1L for patients with *MET* exon 14 skipping alterations in locally advanced or metastatic non-small cell lung cancer

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CONCLUSIONS

- **No statistically significant differences in real world response rate (rwRR), real-world overall survival (rwOS), or real-world progression-free survival (rwPFS) were observed between mesenchymal-epithelial transition (MET) tyrosine kinase inhibitors (TKIs) and pembro±CT in first line (1L) in the United States (US).**
- **MET TKIs showed numerically longer rwPFS and treatment persistence, while pembro±CT showed numerically longer rwOS.**
- **Overall effectiveness was comparable, supporting MET TKIs as an effective and clinically meaningful 1L treatment option in *MET* exon 14 (*MET*ex14) skipping alteration positive non-small cell lung cancer (NSCLC).**
- **Limitations include small, weighted samples, disproportionate follow-up, missing data, response assessment variability, and limited generalizability.**

INTRODUCTION

- NSCLC accounts for 80–85% of lung cancer cases, *MET*ex14 skipping alterations presents in approximately 2–4% of all NSCLC cases [1,2].
- The phase II VISION and GEOMETRY mono-1 trials demonstrated clinically meaningful and durable responses with tepotinib and capmatinib, respectively, in patients with advanced *MET*ex14 skipping alterations NSCLC [2,3].
- MET TKIs (tepotinib/capmatinib) have demonstrated clinical activity in *MET*ex14 NSCLC; however, real-world evidence comparing MET TKIs with immunotherapy-based regimens remains limited [2,4].

OBJECTIVE

This study aims to evaluate the real-world outcomes in patients with advanced or metastatic NSCLC harboring *MET*ex14 treated in 1L with MET TKIs versus pembro±CT in the US.

METHODS

Study Design

- This retrospective cohort study used the ConcertAI PATIENT360 ™ database to include adults with stage IIIB–IV or advanced or metastatic *MET*ex14 positive NSCLC initiating MET TKIs or pembro±CT in 1L across the US. The study period was from February 1, 2020 to October 30, 2024.
- The index date was defined as treatment initiation for each line of therapy (LOT), with a 12-month baseline period within the patient identification window (February 1, 2021 to October 30, 2024).

Patient eligibility criteria

- Patients with epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) rearrangements, multiple primary tumors, or clinical trial participation were excluded **(Supplemental Table 1, Attrition Table)**.

Clinical outcomes

- rwRR, rwOS, rwPFS
- Time-to-event outcomes:
  - Time to treatment discontinuation (rwTTD): time from treatment initiation to discontinuation or death, censored at last activity; death took precedence over subsequent treatment,
  - Time to next treatment or death (rwTTNTD, next treatment or death as event, censored at last known activity),
  - Time to next treatment (rwTTNT): time to next treatment, censored at last known activity, including death.

Statistical analysis

- Baseline characteristics were summarized descriptively and balanced using propensity score weighting with the average treatment effect for the treated (ATT); standardized mean differences were used to assess balance.
- Time-to-event endpoints were analyzed using weighted Kaplan–Meier methods and Cox proportional hazards models.
- Discontinuation included treatment switch, a >63-day treatment gap, or on-treatment death.

RESULTS

- Among 273 eligible patient-LOTs, 179 (65.57%) received MET TKIs in any LOT. Of these, 96 (74.42%) patients were treated with MET TKIs in 1L. The treatment trajectories are shown using the Sankey diagram in **Supplemental Figure 1.**
- Baseline characteristics were well balanced using propensity score weighting, with an effective sample size for pembro±CT being 23.76. Median (interquartile range[IQR]) follow-up duration was 11.8 (6.2–19.4) months for MET TKIs and 18.2 (8.1–28.3) months for pembro±CT **(Table 1)**.

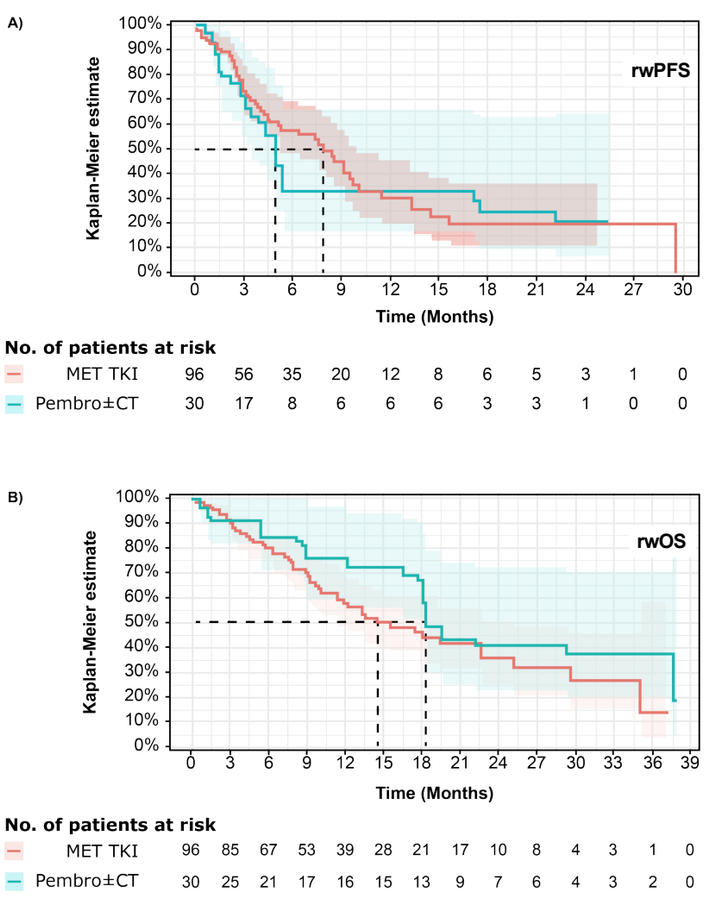
Table 1: 1L, Targeted MET TKI Monotherapy vs. Pembrolizumab ± Chemo

Characteristic	UNWEIGHTED			WEIGHTED		
	Targeted MET TKI Monotherapy (n = 96)	Pembro±CT (n = 30)	SMD*	Targeted MET TKI Monotherapy (ESS = 96)	Pembro±CT (ESS = 23.76)	SMD*
Age at index						
Mean (SD)	74.9 (9.3)	73.6 (5.7)	**0.18**	74.9 (9.3)	73.1 (6.3)	**0.24**
Median (Q1, Q3)	77.0 (72.0, 79.0)	77.0 (70.0, 78.0)		77.0 (72.0, 79.0)	77.0 (70.0, 78.0)	
Gender, %						
Female	46 (47.9)	18 (60.0)	**0.24**	47.9%	53.6%	**0.11**
Race, %						
White	70 (72.9)	26 (86.7)	**0.35**	72.9%	81.5%	**0.22**
Non-White	26 (27.1)	<5		27.1%	18.5%	
Ethnicity, %						
Hispanic or Latino	<5	0 (0.0)	**0.31**	2.1%	0.0%	**0.32**
Not Hispanic or Latino	49 (51.0)	19 (63.3)		51.0%	63.8%	
Unknown	45 (46.9)	11 (36.7)		46.9%	36.2%	
Treatment setting, %						
Academic	14 (14.6)	<5	**0.40**	14.6%	6.5%	**0.29**
Community	82 (85.4)	29 (96.7)		85.4%	93.5%	
ECOG performance score, %						
0-1	52 (54.2)	20 (66.7)	**0.34**	54.2%	64.2%	**0.25**
2+	23 (24.0)	7 (23.3)		24.0%	22.2%	
Unknown	21 (21.9)	<5		21.9%	13.7%	
CCI score (categorical), %						
0-3	63 (65.6)	17 (56.7)	**0.18**	65.6%	59.1%	**0.13**
4+	33 (34.4)	13 (43.3)		34.4%	40.9%	
Smoking history, %						
Smoker/Ex-smoker	49 (51.0)	22 (73.3)	**0.47**	51.0%	55.7%	**0.1**
Non-smoker/Unknown	47 (49.0)	8 (26.7)		49.0%	44.3%	
Tumor mutation burden, %						
Low (≤5 mut/Mb)	28 (29.2)	7 (23.3)	**0.35**	29.2%	22.7%	**0.37**
Intermediate (>5 - ≤20 mut/Mb)	14 (14.6)	6 (20.0)		14.6%	16.8%	
High (>20 - ≤50 mut/Mb)	<5	<5		1.0%	7.6%	
Very high (>50 mut/Mb)	0 (0.0)	0 (0.0)		0.0%	0.0%	
Unknown/Missing	53 (55.2)	15 (50.0)		55.2%	52.8%	
CD274 expression (PD-L1 status), %						
TPS <1%	12 (12.5)	<5	**0.48**	12.5%	2.4%	**0.46**
TPS 1-49%	10 (10.4)	<5		10.4%	16.5%	
TPS ≥50%	20 (20.8)	11 (36.7)		20.8%	31.1%	
Unknown	54 (56.3)	14 (46.7)		56.3%	50.0%	
Evidence of brain metastases, %						
Yes	16 (16.7)	5 (16.7)	**0**	16.7%	18.1%	**0.04**
No	80 (83.3)	25 (83.3)		83.3%	81.9%	
Evidence of liver metastases, %						
Yes	12 (12.5)	6 (20.0)	**0.2**	12.5%	22.6%	**0.27**
No	84 (87.5)	24 (80.0)		87.5%	77.4%	
Stage, %						
Stage 3	5 (5.2)	<5		5.2%	1.6%	
Stage 4	74 (77.1)	25 (83.3)		77.1%	85.3%	
Unknown	17 (17.7)	<5		17.7%	13.2%	
Duration of follow-up (months)						
Mean (SD)	14.0 (10.0)	18.9 (12.3)	**0.44**	14.0 (10.0)	18.8 (12.0)	**0.43**
Median (Q1, Q3)	11.9 (6.2, 19.4)	18.1 (8.1, 29.3)		11.8 (6.2, 19.4)	18.2 (8.1, 28.3)	
Min, Max	0.3, 43.3	0.6, 40.0		0.3, 43.3	0.6, 40.0	

*Absolute values of SMDs are presented
Abbreviations: CCI, Charlson comorbidity index; CD274, cluster of differentiation 274; ECOG, eastern cooperative oncology group; ESS, effective sample size; MET TKI, mesenchymal-epithelial transition tyrosine kinase inhibitor; PD-L1, programmed death-ligand 1; Pembro±CT, pembrolizumab with or without chemotherapy; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); SD, standard deviation; SMD, standardized mean difference; TPS, tumor proportion score

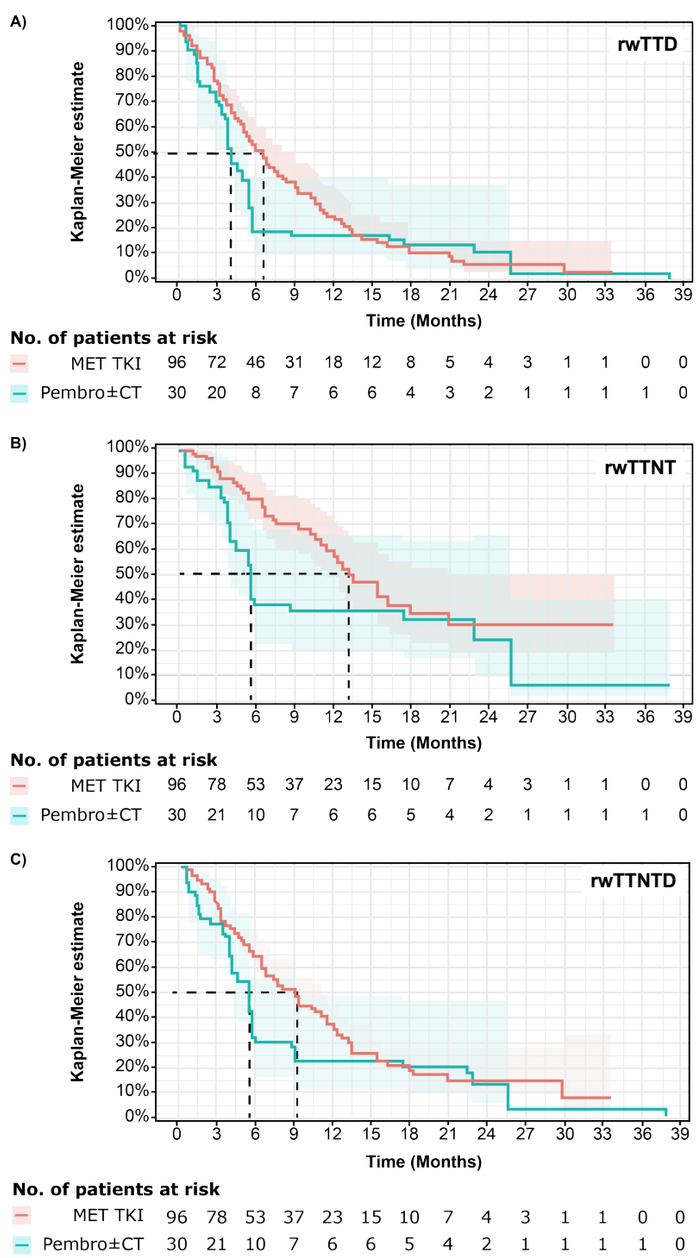
- For MET TKIs vs pembro±CT, rwRR was comparable 0.48 (95% CI: 0.36–0.61) vs 0.48 (0.24–0.72; p=0.97), as were median rwPFS at 7.9 (5.1–10.1) vs 4.9 (3.1–not estimable [NE]) months (HR: 1.15; p=0.66) and median rwOS at 14.5 (11.4–25.2) vs 18.3 (17.6–NE) months (HR: 0.70; p=0.26) **(Figure 1 A & B)**.

Figure 1: Weighted Kaplan-Meier curves in 1L for patients with *MET*ex14+ aNSCLC on Pembro±CT compared to patients on targeted MET TKI monotherapy for (A) rwPFS (B) rwOS



- MET TKIs were associated with numerically longer rwTTD (6.4 [4.9–8.2] vs 3.9 [3.3–5.6] months), rwTTNTD (9.0 [6.4–11.4] vs 5.3 [3.8–8.9] months), and rwTTNT (13.0 [11.3–20.7] vs 5.6 [3.9–25.5] months) than pembro±CT **(Figure 2 A, B, & C)**.

Figure 2: Weighted Kaplan-Meier curves for rwTTD in 1L for patients with *MET*ex14+ aNSCLC on pembro ± CT compared to patients on targeted MET TKI monotherapy for (A) rwTTD (C) rwTTNT (A) rwTTNTD



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DISCLOSURES
MY and **ALP** are employees of EMD Serono, Inc., Boston, MA, USA, an affiliate of Merck KGaA. **CPP** was an employee of Merck, at the time of study. **JH** and **YTY** are employees of Genesis Research Group, Hoboken, NJ. **PKP** disclosed consulting/advisory roles with Merck, Janssen Oncology, Bicara Therapeutics, AstraZeneca, Summit Pharmaceuticals, and AbbVie; honoraria from Merck, Bicara Therapeutics, Janssen Oncology, Summit Pharmaceuticals, AstraZeneca, and AbbVie; and research funding from EMD Serono, Inc., Boston, MA, USA, an affiliate of Merck KGaA, Bicara Therapeutics, Novartis, and Summit Pharmaceuticals.

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