A comparison of tepotinib with chemo-immunotherapy in first-line *MET* exon 14 (*MET*ex14) skipping non-small cell lung cancer (NSCLC): Matching-adjusted indirect comparison (MAIC) of VISION in *MET* exon 14 skipping NSCLC and KEYNOTE-189 in wild-type NSCLC

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CONCLUSIONS

Following balancing of populations based on observed patient characteristics, tepotinib appears to have greater PFS than chemo-immunotherapy (C+IO) and marginally better OS

There is considerable uncertainty due to differences in patient characteristics between VISION and KEYNOTE-189 – likely due to the VISION tepotinib study being specific to *MET*ex14 skipping, where patients are notably older with lower smoking rates. This results in low statistical power after reweighting

Multiple studies have shown that *MET*ex14 skipping is associated with worse outcomes in NSCLC. If data in *MET*ex14 skipping NSCLC were available for C+IO, the comparative benefit of tepotinib would be expected to be even greater, which is a limitation of the study

INTRODUCTION

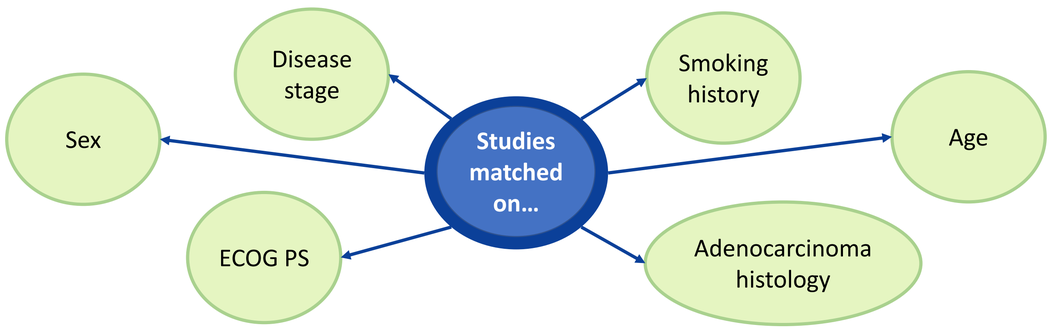
- Tepotinib, a MET tyrosine kinase inhibitor, is approved in multiple countries for the treatment of *MET*ex14 skipping NSCLC, based on the single-arm Phase II VISION trial (NCT02864992; Paik et al., 2020)
- An increasingly used treatment for NSCLC is C+IO, but no head-to-head trials comparing C+IO against tepotinib in *MET*ex14 skipping NSCLC have been conducted
- Thus, a MAIC was conducted to understand the comparative effectiveness of tepotinib compared with C+IO (specifically pembrolizumab + pemetrexed + platinum), adjusting for differences in patient characteristics between studies

OBJECTIVE

This study aimed to compare patient outcomes in VISION (tepotinib) to KEYNOTE-189 (C+IO) in first-line *MET*ex14 skipping NSCLC using MAIC methodologies

METHODS

- MAIC (Signorovitch et al., 2012) was implemented via the R 'maic' package, using the VISION February 2021 data-cut by reweighting patient level data to match published patient characteristics in the KEYNOTE-189 study of first-line pembrolizumab + pemetrexed + platinum chemotherapy in wild-type, non-squamous NSCLC (Rodríguez-Abreu et al., 2021)
- Studies were matched on patient age, sex, ECOG PS, smoking history, adenocarcinoma histology, and disease stage based on input from practicing clinicians, who were then shown patient characteristics after weighting to confirm clinical balance
- Following the MAIC, characteristics and PFS between adjusted VISION and KEYNOTE-189 (the pivotal study for this treatment) were compared



RESULTS

- Only first-line VISION patients were included, as this is the population in KEYNOTE-189. Large differences were observed at baseline between the VISION versus KEYNOTE-189 (Rodríguez-Abreu et al., 2021) populations, such as: patient age (median 72.0 vs 65.0 years), sex (49.3% male vs 62.0%), and smoking history (47.2% vs 88.3%)
- Differences in characteristics were resolved after matching, though this led to a fall in the VISION effective sample size (ESS) from 148 to 38.7 (**Table 1**)
- *MET*ex14 skipping was not measured in the KEYNOTE-189 clinical study, but would be expected to be a low number (<2%) of patients, and thus remains unaccounted for
- Unweighted median PFS was identical between studies: tepotinib 11.9 months (95% CI: 7.1, 12.4) versus C+IO 11.9 months (95% CI: 8.4, 10.9) (**Figure 1**)
- After weighting, tepotinib showed an increase in PFS (median 4.6 months; 95% CI: 10.1, not reached, **Figure 1**), weighted Cox proportional Hazard Ratio (HR) of 0.67 (95% CI: 0.42, 1.07; p=0.091)
- OS results were more uncertain, but again favored tepotinib (weighted median 23.6 vs 22.3 months, weighted Cox HR of 0.71 [95% CI: 0.39, 1.30; p=0.269]; **Figure 1**)

Figure 1. Unweighted and weighted survival curves for tepotinib versus KEYNOTE-189

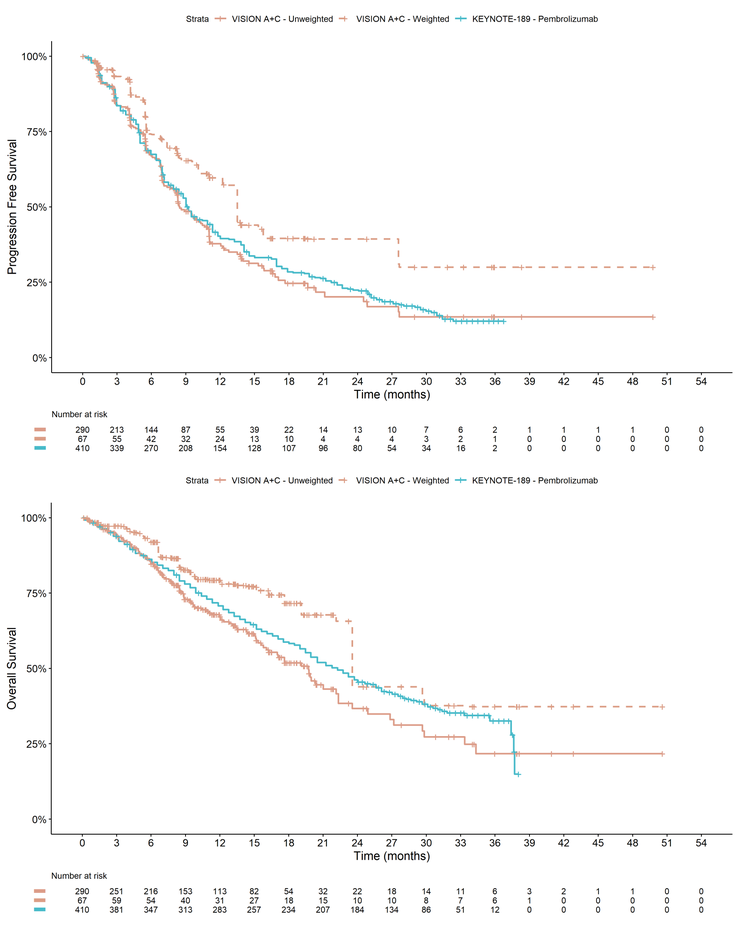


Table 1. Patient characteristics before and after weighting to KEYNOTE-189

	Tepotinib unweighted	Tepotinib weighted	KEYNOTE-189 Pembrolizumab
N/ESS	290	38.7	410
Previously treated, %	49.0	0.0	0.0
Age (mean), years	72.2	68.0	Not reported
Age (median), years	72.0	65.8	65.0
Over 65 years, %	77.9	50.0	Not reported
Male, %	49.3	62.0	62.0
ECOG PS 0, %	26.2	45.1	45.1
Smoking, %	47.2	88.3	88.3
Adenocarcinoma, %	80.7	96.1	96.1
Metastatic/Stage IV disease, %	95.2	99.5	99.5

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival.

References: Paik P, et al. *N Engl J Med.* 2020;383(10):931–943; Rodríguez-Abreu, D. et al. *Ann Oncol.* 2021;32(7):P881–P895; Signorovitch JE, et al. *Value Health.* 2012;15(6):940–947.

Disclosures: HV is an employee of Merck Healthcare KGaA, Darmstadt, Germany, who market tepotinib. AJH, CD, RB & EH are employees of Delta Hat, who were funded by Merck Healthcare KGaA, Darmstadt, Germany, to conduct the analyses. TM & STA are employees of Merck Serono Ltd., Feltham, UK, an affiliate of Merck KGaA, who market tepotinib.