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Matching-adjusted indirect comparison (MAIC) of tepotinib with capmatinib in previously treated advanced non-small cell lung cancer (aNSCLC) with *MET* exon 14 (*MET*ex14) skipping

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CONCLUSIONS

- **This MAIC identifies potential differences in the efficacy profiles of tepotinib and capmatinib**
- **The indirect comparisons confirmed the benefits of tepotinib compared with capmatinib in previously treated patients**
- **There were notable signals of prolonged PFS in favor of tepotinib, however, results must be interpreted cautiously due to possible unobserved confounders**

INTRODUCTION

- Approximately 3–4% of NSCLC tumors harbor *MET*ex14 skipping that can be targeted by selective MET inhibitors[1,2]
- Tepotinib and capmatinib are approved MET TKIs in Europe for the treatment of patients with *MET*ex14 skipping aNSCLC[3,4]
- Evidence for targeted therapies in patients with *MET*ex14 skipping aNSCLC is based on single-arm Phase I/II trial data, however, differences in patient populations between studies make side-by-side comparisons unreliable[5]
- MAIC is a pairwise indirect comparison method that provides a more accurate comparison of study data by adjusting for differences in baseline characteristics[5]

OBJECTIVE

- As the MET TKIs tepotinib and capmatinib are approved in Europe for patients with *MET*ex14 skipping aNSCLC who require further treatment following immunotherapy and/or platinum-based chemotherapy, we compared tepotinib outcomes using MAICs of data from the VISION study, weighted for comparison with capmatinib from the GEOMETRY mono-1 study, in previously treated patients with *MET*ex14 skipping

METHODS

- Data from VISION Cohorts A+C included 61 2L and 88 2L+ patients with *MET*ex14 skipping aNSCLC identified by tissue biopsy with ≥3 months' follow-up, who received tepotinib 500 mg once daily, with a cut-off date of February 1, 2021[6]
- Data from GEOMETRY mono-1 study included 100, 69, and 31 patients with *MET*ex14 skipping aNSCLC from Cohorts 4+6, Cohort 4, and Cohort 6, respectively[7,8] (**Table 1, S1**)
- The data were compared using both unweighted naïve comparison and as a MAIC
  - Patient-level data from VISION were weighted using baseline characteristics prognostic for OS (identified by Cox regression), and compared with the GEOMETRY mono-1 population (**Table S2**)
- ORR, PFS, OS, and DOR were compared between the studies
  - Odds ratios were calculated for ORR comparisons
  - Reconstructed Kaplan–Meier curves or median outcome point estimates calculated by MAIC were used to compare time-to-event endpoints

Table 1. Data sources and cut-off dates

LOT	Comparator	KM data available	Aggregate data available	Duration of follow-up
2L	Capmatinib (Cohort 6)	–	ORR, PFS, DOR (Sep 18, 2020)[7]	Not reported
2L+	Capmatinib (Cohorts 4 and 6)	–	ORR, PFS, DOR (Sep 18, 2020)[7]	Not reported
2L+	Capmatinib (Cohort 4)	OS (Sep 18, 2020)[7] PFS (Jan 6, 2020)[8] DOR (Apr 15, 2019)[9]	ORR (Sep 18, 2020)[7]	Primary analysis conducted when all treated patients in cohorts not stopped for futility had completed at least 6 cycles of treatment (18 weeks) unless patients had discontinued treatment earlier

RESULTS

VISION population weighting

- The VISION population was successfully weighted to match the GEOMETRY mono-1 population; most of the eligible VISION patients were retained (**Table S1, S3, S4**)
  - There were differences in race and smoking history between the cohorts
  - Differences in ECOG PS and histology were much less prominent (**Table S3, S4**)

Tepotinib efficacy outcomes compared with capmatinib in previously treated patients

- In patients treated in 2L only, the point estimate for ORR indicated that there was insufficient data to suggest a superiority of either drug (**Table 2**)
- In the 2L+ population, no consistent difference in ORR was identified between tepotinib and capmatinib (**Table 2**)

Table 2. ORR in previously treated patients

LOT	Comparator	Analysis	ORR with tepotinib, % (n/N)	ORR with comparator, % (n/N)	Odds ratio* (95% CI)
2L	Capmatinib (Cohort 6)	Naïve	52.5 (32/61)	51.6 (16/31)	1.03 (0.43, 2.46)
		MAIC	42.6 (20.1/47.1)		0.70 (0.28, 1.73)
2L+	Capmatinib (Cohorts 4 and 6)	Naïve	47.7 (42/88)	44.0 (44/100)	1.16 (0.65, 2.07)
		MAIC	42.4 (32.3/76.4)		0.93 (0.51, 1.71)
	Capmatinib (Cohort 4)	Naïve	47.7 (42/88)	40.6 (28/69)	1.34 (0.71, 2.53)
		MAIC	43.9 (34.1/77.7)		1.14 (0.59, 2.21)

*Odds ratio >1 favors tepotinib.

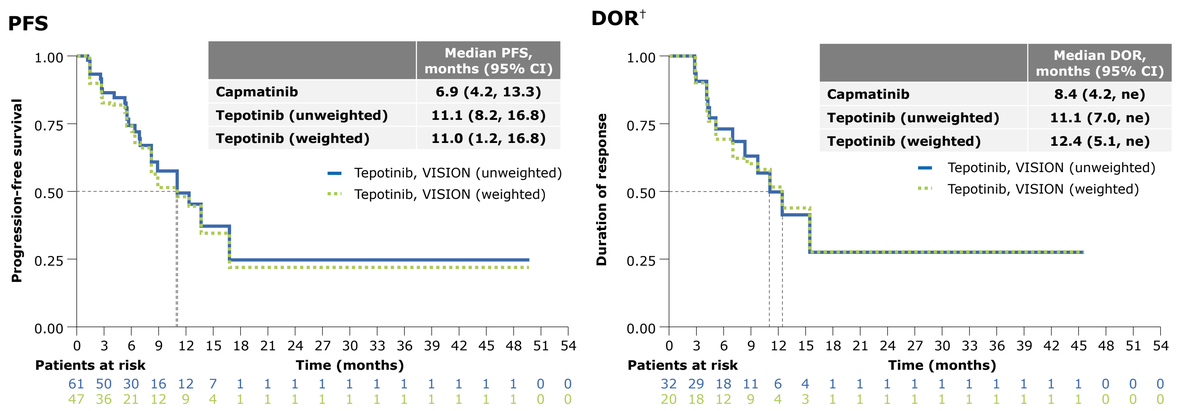
- In the 2L population, the point-estimate comparisons of median PFS and DOR suggested an improvement with tepotinib versus capmatinib (11.0 vs 6.9 months and 12.4 vs 8.4 months, respectively) (**Table 3**)
- In the 2L+ population, the point-estimate comparisons of median PFS suggested a marked increase in median PFS with tepotinib (11.0 vs 5.5 months; **Table 3**)
  - Estimates of median DOR in 2L+ population were similar between tepotinib (11.1 months) and capmatinib (9.7 months; **Table 3**)

Table 3. PFS and DOR in previously treated patients

LOT	Comparator	Endpoint (all IRC-assessed)	Comparator median value, months (95% CI)	Unweighted tepotinib median value, months (95% CI)	Weighted tepotinib median value, months (95% CI)
2L	Capmatinib (Cohort 6)	PFS	6.9 (4.2, 13.3)	11.1 (8.2, 16.8)	11.0 (1.2, 16.8)
		DOR	8.4 (4.2, ne)	11.1 (7.0, ne)	12.4 (5.1, ne)
2L+	Capmatinib (Cohorts 4 and 6)	PFS	5.5 (4.2, 8.1)	11.1 (8.2, 16.8)	11.0 (8.2, 13.7)
		DOR	9.7 (5.6, 13.0)	10.1 (8.3, 15.7)	11.1 (7.0, 15.7)
	Capmatinib (Cohort 4)	DOR	9.7 (5.6, 13.0)	10.1 (8.3, 15.7)	11.1 (7.0, 15.7)

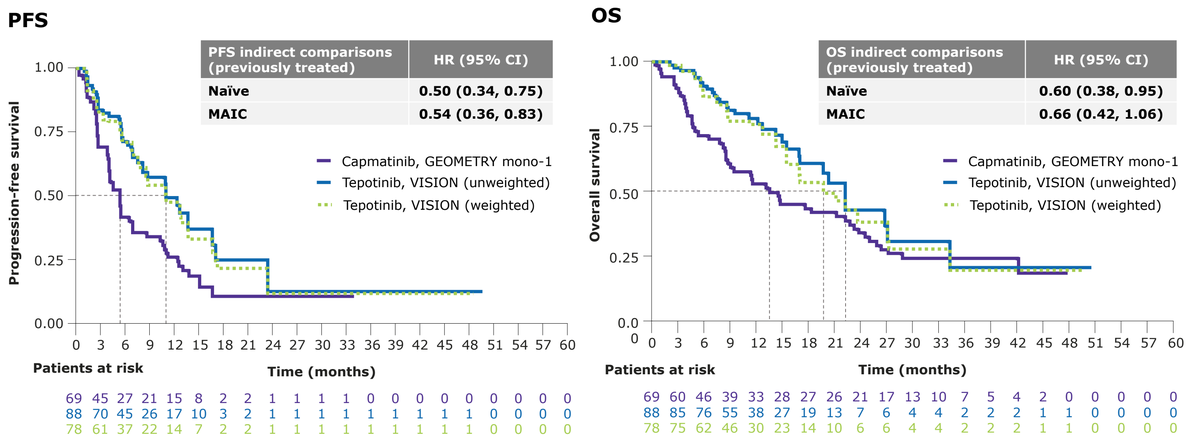
- KM curves for the naïve and MAIC tepotinib 2L and 2L+ populations showed a large degree of overlap (**Figure 1 and 2**)
  - In the 2L population, no KM data were available for capmatinib, therefore naïve and MAIC comparisons were only possible with median PFS and DOR (**Figure 1**)
  - In the 2L+ population, there was a notable separation from the capmatinib KM curves in favor of tepotinib, up to around 24 months (PFS) and 21 months (OS) (**Figure 2**)
  - These suggest an improvement in PFS (HR 0.54; 95% CI: 0.36, 0.83) and OS (HR 0.66; 95% CI: 0.42, 1.06) in favor of tepotinib (**Figure 2**)

Figure 1. Comparison of tepotinib with capmatinib* in patients treated in 2L



*KM data were not available for capmatinib.
†DOR only available for patients who achieved CR/PR.

Figure 2. Comparison of tepotinib with capmatinib in patients treated in 2L+



Abbreviations: 2L, second line; 2L+, second line or later; CI, confidence interval; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRC, independent review committee; KM, Kaplan–Meier; LOT, line of therapy; MAIC, matching-adjusted indirect comparison; MET, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14; ne, not estimable; aNSCLC, advanced non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TKI, tyrosine kinase inhibitor.

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Acknowledgements: This study and the VISION trial were funded by Merck KGaA Healthcare, Darmstadt, Germany. Medical writing assistance (funded by Merck Healthcare KGaA, Darmstadt, Germany) was provided by Syneos Health, London, UK.

Disclosures: PKP holds advisory roles at Calithera, Takeda, Xencor, Mirati, Bicara, CrownBio and EMD Serono, an affiliate of Merck KGaA; his research institution received research expenses from Bicara, Boehringer Ingelheim and EMD Serono, an affiliate of Merck KGaA; BMP is a full-time employee of Merck Healthcare KGaA, Darmstadt, Germany; HV is a full-time employee of Merck Healthcare KGaA, Darmstadt, Germany; MP was supported in co-developing the methodology of this paper with a grant from Merck Healthcare KGaA, Darmstadt, Germany; MP receives further grants and honoraria from various pharmaceutical companies, all unrelated to this research. MP holds stocks in Health-Ecore (Zeist, The Netherlands) and Pharmacoeconomics Advice Groningen (Groningen, The Netherlands).

Presentation number CO58 | Presented at the ISPOR Europe 2022 | 6–9 November | Vienna, Austria and Virtual