Tepotinib and capmatinib in patients with *MET* exon 14 skipping NSCLC: A matching-adjusted indirect comparison (MAIC)

Boris M Pfeiffer[1], Maarten J. Postma[2,3], Anthony Hatswell[4], Helene Vioix[1], Paul K. Paik[5]

[1]Global Evidence and Value Department, Merck Healthcare KGaA, Darmstadt, Germany; [2]Department of Health Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [3]Department of Economics, Econometrics and Finance, University of Groningen, Faculty of Economics and Business, Groningen, The Netherlands; [4]Delta Hat Ltd., Nottingham, United Kingdom; [5]Department of Medicine, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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Merck KGaA
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Disclaimer and intended use

Disclaimer

- Tepotinib is currently under clinical investigation for various indications worldwide. Regulatory approval is dependent on the completion of the study programs and review by local regulatory authorities. Please check the current label status in your respective country.

Intended use

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- If needed, local MLR approval must be sought as per local process

Introduction

- Approximately 3–4% of NSCLC tumors harbor *MET*ex14 skipping that can be targeted by selective MET inhibitors[1]
- Tepotinib and capmatinib are approved in multiple countries for the treatment of patients with metastatic NSCLC harboring *MET*ex14 skipping
- These MET TKI approvals were based on multicenter, non-randomized, Phase II trials[2,3]
- In long-term follow-up from the VISION study of tepotinib (data cut-off: November 2022), among patients with metastatic NSCLC with *MET*ex14 skipping confirmed in tissue biopsies[2]:
  - ORR was 58.6% (95% CI: 48.8, 67.8), mDOR was 46.4 months (95% CI: 15.2, ne), mPFS was 15.9 months (95% CI: 11.0, 49.7), and mOS was 29.7 months (95% CI: 18.8, ne) in 1L patients (n=111)
  - ORR was 49.5% (95% CI: 39.2, 59.8), mDOR was 12.4 months (95% CI: 8.3, 18.0), mPFS was 11.5 months (95% CI: 8.2, 14.7), and mOS was 20.4 months (95% CI: 17.0, 25.5) in 2L+ patients (n=97)
- Differences in patient populations between studies make side-by-side comparisons of individual studies unreliable[1]
- MAIC is a pairwise indirect comparison method that provides a more accurate comparison of study data by adjusting for differences in baseline characteristics subject to possible unobserved, uncontrolled confounding[1]
- Previously published MAIC results of tepotinib with other MET TKIs predicted prolonged PFS and OS of tepotinib compared with crizotinib and capmatinib[1]
- **Here, we report an updated MAIC analysis** using tepotinib outcomes from a larger patient population in VISION with a later data cut-off (November 2022),[2] weighted for comparison with capmatinib (GEOMETRY mono-1) in 1L and 2L+ patients with advanced *MET*ex14 skipping NSCLC

1L, treatment-naïve; 2L+, previously treated; CI, confidence interval; DOR, duration of response; m, median; MAIC, matching-adjusted indirect comparison; MET, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14; ne, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Paik P, et al. *Adv Ther*. 2022;39(7):3159–3179; 2. Mazieres J, et al. *JAMA Oncol*. 2023;e231962. doi:10.1001/jamaoncol.2023.1962 (Epub ahead of print); 3. Wolf J, et al. *N Engl J Med*. 2020;383:944–957.

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Methods

- The MAIC utilized data from patients with advanced *MET*ex14 skipping NSCLC from two trials:
  - VISION (NCT02864992) Cohort A (primary cohort; follow-up ≥35 months) and Cohort C (confirmatory cohort; follow-up ≥18 months); each comprising 1L and 2L+ patients who received tepotinib 500 mg (450 mg active moiety) once daily (data cut-off: November 20, 2022)
  - GEOMETRY mono-1 (NCT02414139) Cohort 5b (1L) and Cohort 4 (2L+), in which patients received capmatinib 400 mg twice daily (data sources[1,2] and cut-offs shown in **Table 1**)

Table 1. Data sources and cut-off dates used for GEOMETRY mono-1 comparisons*

Summary statistics available	Swimmer plots, i.e. individual patient data available	KM data available	Duration of follow-up
ORR, DOR (Sep 18, 2020)[1]	PFS (Jan 6, 2020)[2]	OS (Sep 18, 2020)[1]	Primary analysis conducted when all treated patients in cohorts not stopped for futility had completed at least six cycles of treatment (18 weeks), unless patients had discontinued treatment earlier

*ORR and DOR data were taken from the latest available data cut-off. PFS and OS were taken from the latest available data cut-off with individual patient or KM data, with preference given to swimmer plots over KM data where both were provided due to greater fidelity.
1L, treatment-naïve; 2L+, previously treated; DOR, duration of response; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
1. Wolf J, et al. *J Clin Oncol*. 2021;39(15_suppl):9020–9020; 2. Wolf J, et al. *N Engl J Med*. 2020;383:944–957.

Methods (cont'd)

- Patient-level data for patients from VISION with *MET*ex14 skipping detected in tissue biopsies were reweighted, such that the (reweighted) baseline characteristics matched those of GEOMETRY mono-1 Cohort 5b and Cohort 4
  - Clinical input was taken to act as a gatekeeper in selecting only the most relevant covariates for inclusion (**Figure 1**, next slide)
  - Selected covariates were: age*, sex, ECOG PS 0 vs 1+, smoking history, and adenocarcinoma histology
  - Patients were stratified by 1L and 2L+
  - Compared outcomes were IRC-assessed ORR, DOR and PFS, as well as OS
  - Reconstructed patient-level data were used to compare time-to-event endpoints where possible†
  - Where only aggregate statistics were available for capmatinib, equivalent statistics were recalculated for both unweighted and weighted VISION data

*For 1L patients, mean age was matched; while for 2L+ patients, median age was matched. †Slight differences in the 95% CIs for median estimates between the MAIC and prior reports reflect the impact of digitization.
1L, treatment-naïve; 2L+, previously treated; CI, confidence interval; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; *MET*ex14, *MET* exon 14; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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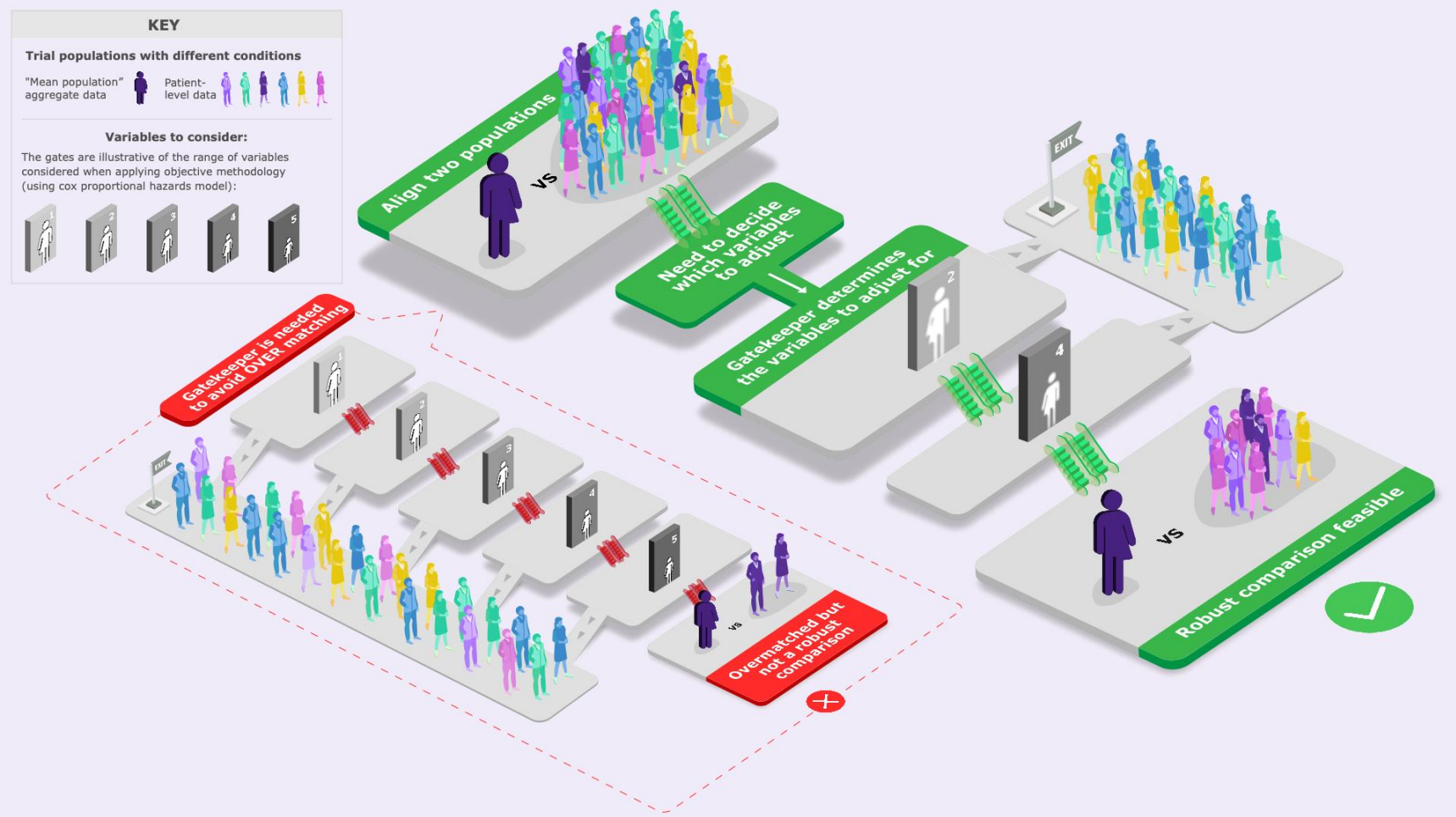
Methods (cont'd)

Figure 1. Methodology to identify covariates for population adjustment



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Results
VISION population weighting

- The patient population from VISION was successfully weighted:
  - 1L: n=111 unweighted, ESS=83.3 weighted to match GEOMETRY mono-1 Cohort 5b (1L, n=28)
  - 2L+: n=97 unweighted, ESS=90.6 weighted to match GEOMETRY mono-1 Cohort 4 (2L+, n=69)
- Summaries of the trials before and after weighting are shown in **Table 2**

Table 2. Major similarities and differences in the study characteristics of the 1L and 2L+ population between VISION and GEOMETRY mono-1

Characteristics	1L patients		2L+ patients	
	Capmatinib (GEOMETRY mono-1 Cohort 5b)[1]	Tepotinib (VISION)[2]	Capmatinib (GEOMETRY mono-1 Cohort 4)[1]	Tepotinib (VISION)[2]
Single-arm, Phase II, multi-cohort	Similar		Similar	
aNSCLC patients with *MET*ex14 skipping	Similar		Similar	
Stage IIIb or IV at the time of study entry	Similar		Similar	
International study*	Similar		Similar	
Number of patients in comparison†	28	111 (ESS 83.3)	69	97 (ESS 90.6)
Age of patients, years‡	72.4	74.2 (weighted 72.4)	71.0	70.3 (weighted 71.0)
ECOG PS 0, %	25.0	28.8 (weighted 25.0)	23.2	25.8 (weighted 23.2)

*Participating countries for GEOMETRY mono-11: Argentina, Austria, Belgium, France, Germany, Israel, Italy, Japan, Lebanon, Mexico, Norway, Republic of Korea, Russia, Singapore, Spain, Sweden, Taiwan, The Netherlands, UK, and USA. Participating countries for VISION[2]: Belgium, China, France, Germany, Israel, Italy, Japan, Poland, Republic of Korea, Spain, Switzerland, Taiwan, The Netherlands, and USA. †Addressed by weighting. ‡For 1L patients, mean age was matched; while for 2L+ patients, median age was matched.

1L, treatment-naïve; 2L+, previously treated; aNSCLC, advanced non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; *MET*ex14, *MET* exon 14.

1. Wolf J, et al. *N Engl J Med*. 2020;383:944–957; 2. Mazieres J, et al. *JAMA Oncol*. 2023:e231962. doi:10.1001/jamaoncol.2023.1962 (Epub ahead of print).
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Results
Comparison of efficacy outcomes with tepotinib versus capmatinib in 1L patients

- In the matched 1L population versus Cohort 5b (**Table 3**):
  - The ORR by IRC was:
    - 59.3% (95% CI: 50.1, 68.5) in the weighted population for tepotinib
    - 67.9% (95% CI: 49.5, 83.1) in GEOMETRY mono-1 Cohort 5b
  - mDOR was 46.4 months (95% CI: 46.4, ne) versus 12.6 months (95% CI: 5.6, ne), respectively
  - Tepotinib appeared to be associated with prolonged PFS and OS compared with capmatinib:
    - mPFS was 22.0 months (95% CI: 11.3, ne) versus 12.3 months (95% CI: 8.2, ne)
    - mOS was 29.7 months (95% CI: 14.2, ne) versus 20.7 months (95% CI: 12.5, ne)

Table 3. Efficacy of tepotinib versus capmatinib in 1L patients

Variables	Tepotinib, VISION (unweighted)	Tepotinib, VISION (weighted)	Capmatinib, GEOMETRY mono-1 Cohort 5b[1,2]
n or ESS	111	83.3	28
ORR by IRC, % (95% CI)	58.6 (49.3, 67.5)	59.3 (50.1, 68.5)	67.9 (49.5, 83.1)
mDOR by IRC, months (95% CI)	46.4 (19.4, ne)	46.4 (46.4, ne)	12.6 (5.6, ne)
mPFS by IRC, months (95% CI)	15.9 (11.3, ne)	22.0 (11.3, ne)	12.3 (8.2, ne)
mOS, months (95% CI)	29.7 (19.1, ne)	29.7 (14.2, ne)	20.7 (12.5, ne)

1L, treatment-naïve; CI, confidence interval; DOR, duration of response; ESS, effective sample size; IRC, independent review committee; m, median; ne, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Wolf J, et al. *J Clin Oncol*. 2021;39(15_suppl):9020–9020; 2. Wolf J, et al. *N Engl J Med.* 2020;383:944–957.
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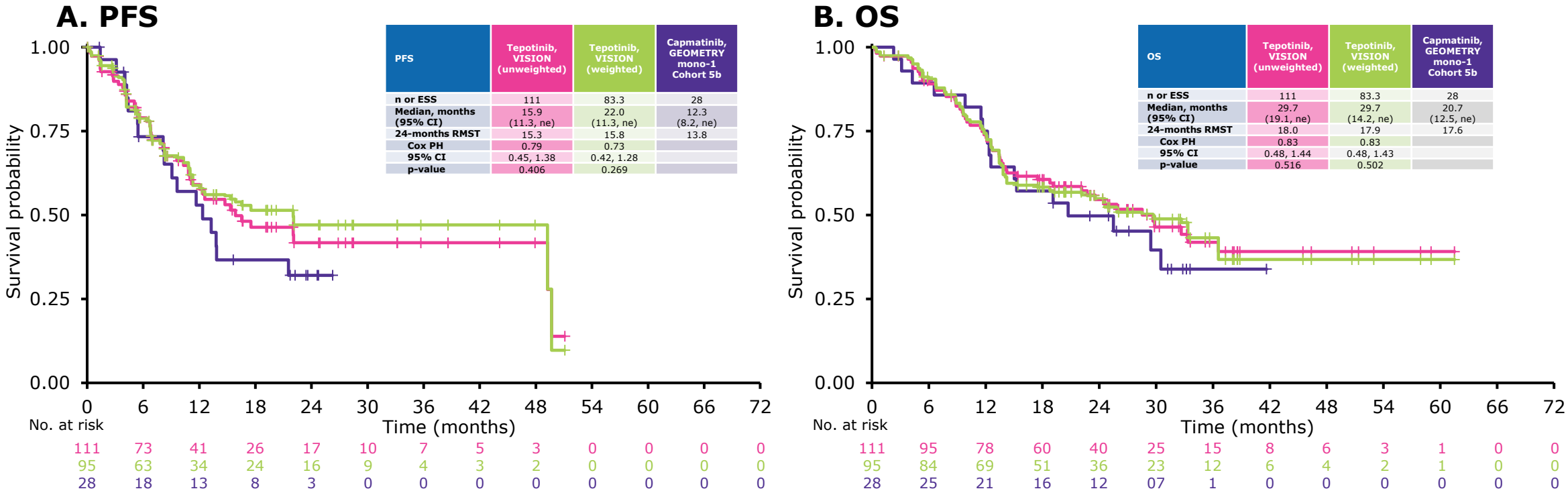
Results

Comparison of efficacy outcomes with tepotinib versus capmatinib in 1L patients (cont'd)

- For both the unweighted and (MAIC) weighted tepotinib 1L population, there was a trend in favor of tepotinib from 12 months in PFS (**Figure 2A**), and 19 months in OS (**Figure 2B**)
- Numerically higher medians, Cox and restricted mean analyses favored tepotinib

Figure 2. PFS and OS with tepotinib versus capmatinib in 1L patients



PFS	Tepotinib, VISION (unweighted)	Tepotinib, VISION (weighted)	Capmatinib, GEOMETRY mono-1 Cohort 5b
n or ESS	111	83.3	28
Median, months (95% CI)	15.9 (11.3, ne)	22.0 (11.3, ne)	12.3 (8.2, ne)
24-months RMST	15.3	15.8	13.8
Cox PH	0.79	0.73	
95% CI	0.45, 1.38	0.42, 1.28	
p-value	0.406	0.269	

OS	Tepotinib, VISION (unweighted)	Tepotinib, VISION (weighted)	Capmatinib, GEOMETRY mono-1 Cohort 5b
n or ESS	111	83.3	28
Median, months (95% CI)	29.7 (19.1, ne)	29.7 (14.2, ne)	20.7 (12.5, ne)
24-months RMST	18.0	17.9	17.6
Cox PH	0.83	0.83	
95% CI	0.48, 1.44	0.48, 1.43	
p-value	0.516	0.502	

1L, treatment-naïve; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; ne, not estimable; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; RMST, restricted mean survival time.

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Results
Comparison of efficacy outcomes with tepotinib versus capmatinib in 2L+ patients

- In the matched 2L+ population versus Cohort 4 (**Table 4**):
  - The ORR by IRC was:
    - 49.4% (95% CI: 39.4, 59.4) in the weighted population for tepotinib
    - 40.6% (95% CI: 29.5, 52.4) in GEOMETRY mono-1 Cohort 4
  - mDOR was 10.2 months (95% CI: 8.3, 19.4) versus 9.7 months (95% CI: 5.6, 13.0), respectively
  - Tepotinib appeared to be associated with prolonged PFS and OS compared with capmatinib:
    - mPFS: 11.5 months (95% CI: 8.2, 17.1) versus 5.4 months (95% CI: 4.2, 8.2)
    - mOS: 19.7 months (95% CI: 17.0, 26.5) versus 13.7 months (95% CI: 8.9, 23.4)

Table 4. Efficacy of tepotinib versus capmatinib in 2L+ patients

Variables	Tepotinib, VISION (unweighted)	Tepotinib, VISION (weighted)	Capmatinib, GEOMETRY mono-1 Cohort 4[1,2]
n or ESS	97	90.6	69
ORR by IRC, % (95% CI)	49.5 (39.6, 59.4)	49.4 (39.4, 59.4)	40.6 (29.5, 52.4)
mDOR by IRC, months (95% CI)	12.4 (9.7, 19.4)	10.2 (8.3, 19.4)	9.7 (5.6, 13.0)
mPFS by IRC, months (95% CI)	11.5 (8.2, 16.8)	11.5 (8.2, 17.1)	5.4 (4.2, 8.2)
mOS, months (95% CI)	20.4 (17.1, 26.8)	19.7 (17.0, 26.5)	13.7 (8.9, 23.4)

2L+, previously treated; CI, confidence interval; DOR, duration of response; ESS, effective sample size; IRC, independent review committee; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Wolf J, et al. *J Clin Oncol*. 2021;39(15_suppl):9020–9020; 2. Wolf J, et al. *N Engl J Med*. 2020;383:944–957.

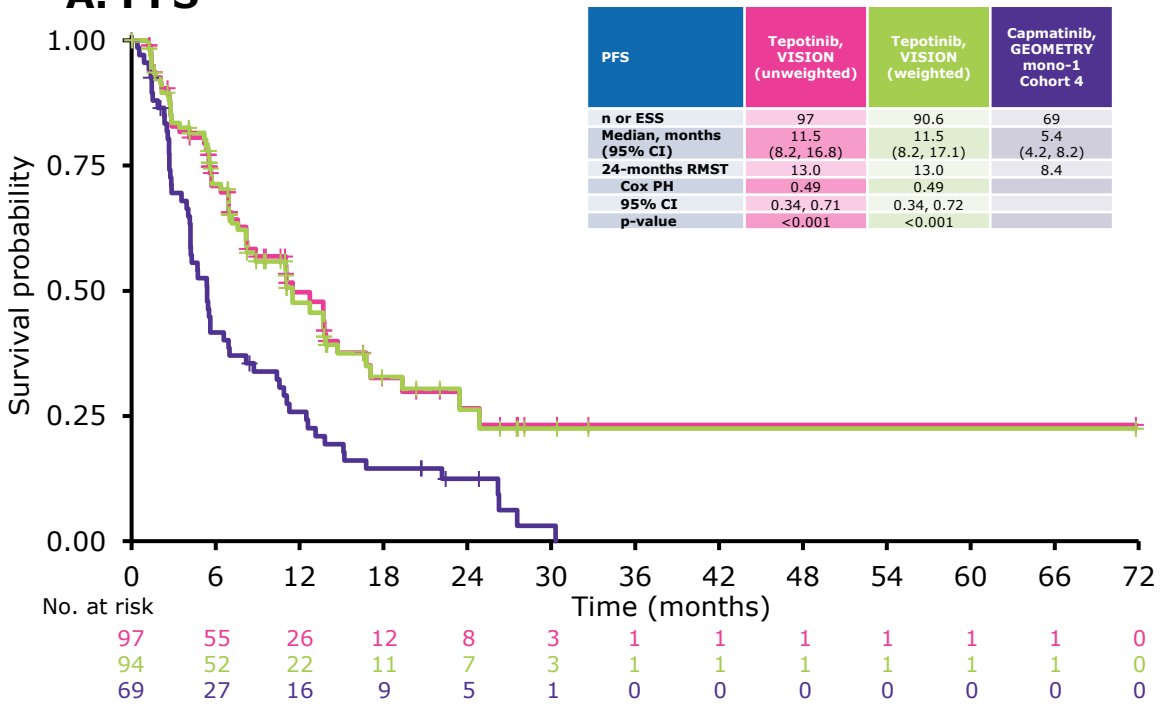
Results

Comparison of efficacy outcomes with tepotinib versus capmatinib in 2L+ patients (cont'd)

- For both the unweighted and (MAIC) weighted tepotinib 2L+ population, there were trends in favor of tepotinib in PFS (**Figure 3A**), and potentially also OS (**Figure 3B**)
- Numerically higher medians, Cox and restricted mean analyses favored tepotinib

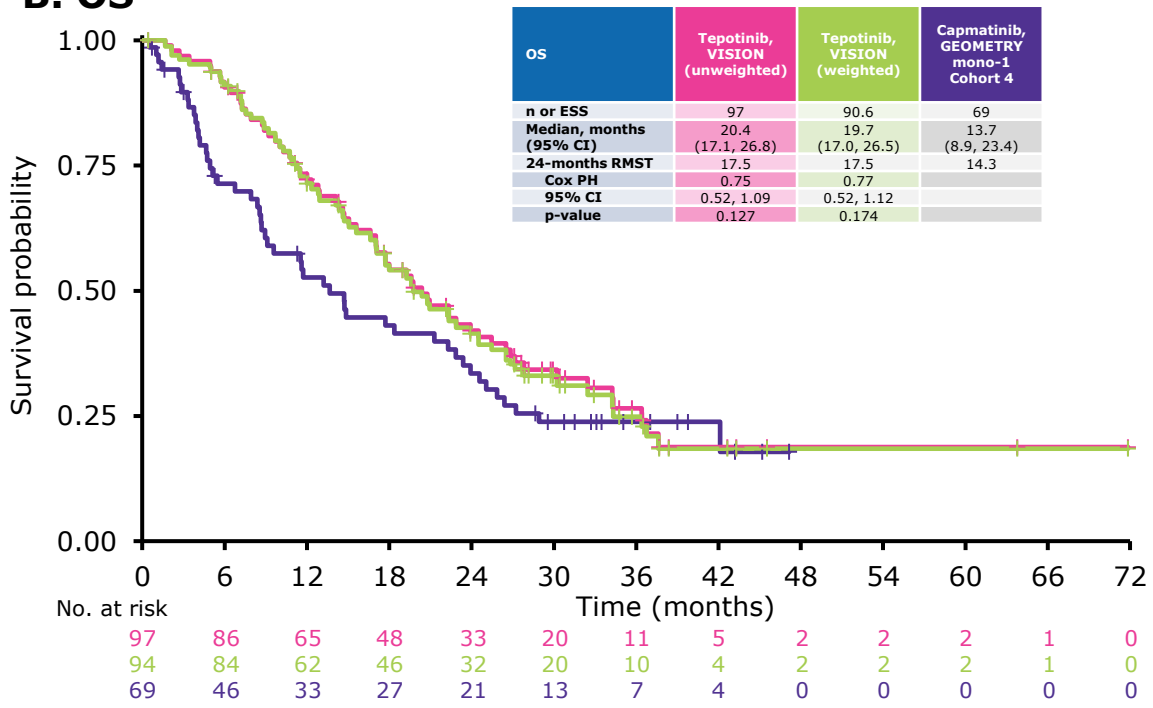
Figure 3. PFS and OS with tepotinib versus capmatinib in 2L+ patients

A. PFS



PFS	Tepotinib, VISION (unweighted)	Tepotinib, VISION (weighted)	Capmatinib, GEOMETRY mono-1 Cohort 4
n or ESS	97	90.6	69
Median, months (95% CI)	11.5 (8.2, 16.8)	11.5 (8.2, 17.1)	5.4 (4.2, 8.2)
24-months RMST	13.0	13.0	8.4
Cox PH	0.49	0.49	
95% CI	0.34, 0.71	0.34, 0.72	
p-value	<0.001	<0.001	

B. OS



OS	Tepotinib, VISION (unweighted)	Tepotinib, VISION (weighted)	Capmatinib, GEOMETRY mono-1 Cohort 4
n or ESS	97	90.6	69
Median, months (95% CI)	20.4 (17.1, 26.8)	19.7 (17.0, 26.5)	13.7 (8.9, 23.4)
24-months RMST	17.5	17.5	14.3
Cox PH	0.75	0.77	
95% CI	0.52, 1.09	0.52, 1.12	
p-value	0.127	0.174	

2L+, previously treated; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; RMST, restricted mean survival time.

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Conclusions

- The updated data including a greater number of patients from VISION increase the robustness of the MAIC with capmatinib, and confirm previous findings[1]
- The indirect comparisons confirmed the clinical benefit of tepotinib in comparison with capmatinib in patients with advanced *MET*ex14 skipping NSCLC treated in 1L
  - The differences in the objective response rate of tepotinib (weighted population: 59.3% [95% CI: 50.1, 68.5]) versus capmatinib (67.9% [95% CI: 49.5, 83.1]) may be explained by the specific characteristics of the population enrolled in the GEOMETRY mono-1 trial
- In the 2L+ setting, PFS was longer with tepotinib versus capmatinib, and there was also a notable signal of benefit for tepotinib for OS
- This analysis will be further updated as new data sets become available from ongoing studies

1L, treatment-naïve; 2L+, previously treated; CI, confidence interval; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

1. Paik P, et al. *Adv Ther*. 2022;39(7):3159–3179.

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MAIC, matching-adjusted indirect comparison.

Disclosures

Boris M. Pfeiffer: Employee of Merck Healthcare KGaA Darmstadt, Germany

Maarten J. Postma: Holds stocks in health-economic consultancies Health-Ecore (Zeist, The Netherlands) and PAG BV (Groningen, The Netherlands)

Anthony Hatswell: Employee of Delta Hat Ltd

Helene Vioix: Employee of Merck Healthcare KGaA, Darmstadt, Germany

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