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Tepotinib in patients with *MET* exon 14 skipping NSCLC: Primary analysis of the confirmatory VISION Cohort C

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DISCLOSURES

Commercial interest	Relationship(s)
AstraZeneca, BMS, Boehringer, Celgene, Chugai, Lilly, MSD, Novartis, Pfizer, Roche, Takeda	Honoraria: scientific meetings and traveling support
AstraZeneca, BMS, Boehringer, Lilly, MSD, Novartis, Pfizer, Roche, Takeda	Advisory board honoraria
AstraZeneca, BMS, Roche, Takeda	Research funding (institution)

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Tepotinib is a once daily and highly selective MET TKI approved for *MET*ex14 skipping NSCLC based mainly on Cohort A of the multi-cohort Phase II VISION study[1]

Key inclusion criteria

- Advanced NSCLC (*EGFR/ALK* wild-type, all histologies)
- Central confirmation of *MET*ex14 skipping by liquid and/or tissue biopsy
- First, second, or third line of therapy

Cohort A*
***MET*ex14 skipping (primary)**

Cohort C†
***MET*ex14 skipping (confirmatory)**

Tepotinib 500 mg‡ once daily

Selected endpoints

Primary:

Objective response by IRC (RECIST v1.1)

Secondary:

DOR, PFS, OS, Safety

Exploratory RANO-BM analysis§:

BOR per RANO-BM (patients with ≥1 evaluable post-baseline tumor assessment): disease control was defined as CR/PR/SD, or non-CR/non-PD

Here, we report the primary analysis (>9-months' follow-up) of the independent confirmatory Cohort C; data cut-off February 20, 2022‡

*Cohort A enrollment began on September 13, 2016. †Cohort C enrolment began on August 8, 2019. ‡500 mg tepotinib hydrochloride hydrate (active ingredient) contains 450 mg tepotinib free base (active moiety). §Composite of radiographic responses, corticosteroid use, and clinical status, giving a more comprehensive overview of the patient compared with RECIST.[2] For patients with non-measurable lesions only (enhancing and non-enhancing NTLs), non-CR/non-PD was defined as a best objective response of disease control, i.e. persistence of at least one non-progressing NTL. Brain imaging had no mandatory schedule and, as such, data for this analysis were incomplete, and confirmation of response was not required.

ALK, anaplastic lymphoma kinase; BOR, best overall response; CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRC, independent review committee; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; NTL, non-target lesion; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; TKI, tyrosine kinase inhibitor.

1. Paik PK, et al. *N Engl J Med.* 2020;383(10):931–943; 2. Lin NU, et al. *Lancet Oncol.* 2015;16(6):e270–e278.

Patients in the confirmatory Cohort C had a median age of 71 years, about half were male, about half had smoking history, and most had adenocarcinoma histology

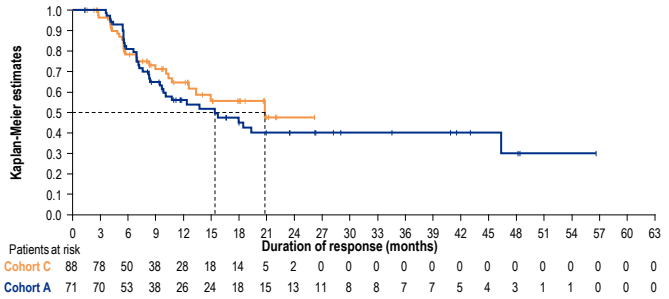
Baseline characteristics		Cohort C (N=161)	Cohort A (N=152)
Median age, years (range)		71.0 (42–91)	73.1 (41–94)
Sex, %	Male	46.6	52.0
Race, %	White/Asian	54.0/42.2	71.1/25.0
ECOG PS, %	0/1	24.8/74.5	27.0/73.0
Smoking history, %	Yes	43.5	52.0
Histology, %	Adenocarcinoma	75.2	86.2
Brain metastases at baseline, %	Yes	21.1	15.1
Line of therapy, %	Treatment-naïve/previously treated	59.0/41.0	45.4/54.6
*MET*ex14 skipping detection*	T+/L+	74.5/49.1	57.9/65.1

*Patients could have had *MET*ex14 skipping detected by both liquid and tissue biopsy and, as such, values do not add up to 100%; testing by both methods was not a requirement for study entry.
ECOG PS, Eastern Cooperative Oncology Group performance status; L+, *MET*ex14 skipping detected in liquid biopsy; *MET*ex14, *MET* exon 14; T+, *MET*ex14 skipping detected in tissue biopsy.

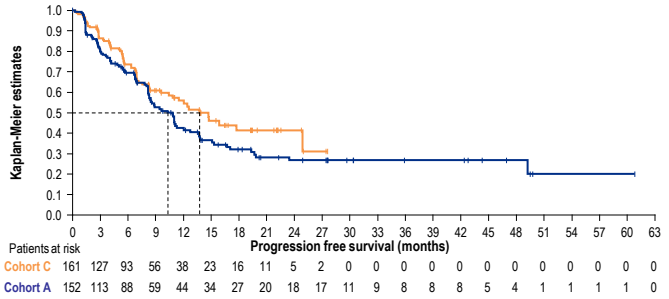
Cohort C primary analysis provided independent confirmation for robust and durable efficacy of tepotinib

	Cohort C (N=161)	Cohort A (N=152)	Cohort A+C (N=313)
ORR, % (95% CI)	54.7 (46.6, 62.5)	46.7 (38.6, 55.0)	50.8 (45.1, 56.5)
DCR, % (95% CI)	80.1 (73.1, 86.0)	72.4 (64.5, 79.3)	76.4 (71.3, 81.0)
mDOR, months (95% CI)	20.8 (12.6, ne)	15.4 (9.7, 46.4)	18.0 (12.4, ne)
mPFS, months (95% CI)	13.8 (10.4, ne)	10.3 (8.2, 12.7)	11.2 (9.5, 13.8)
mOS, months (95% CI)	18.8 (14.4, 25.5)	19.8 (15.2, 22.9)	19.3 (15.8, 22.3)

DOR



PFS

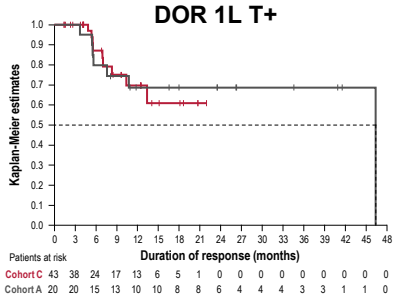


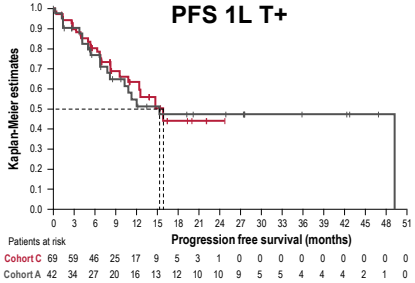
CI, confidence interval; DCR, disease control rate; DOR, duration of response; m, median; ne, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

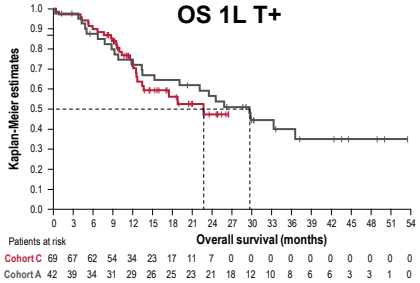
Efficacy was particularly meaningful in treatment-naïve patients enrolled by tissue biopsy

- 74.5% of patients were enrolled in Cohort C based on *MET*ex14 skipping detection by tissue biopsy

1L T+	Cohort C (n=69)	Cohort A (n=42)	Cohort A+C (n=111)
BOR, n (%)			
CR	0	1 (2.4)	1 (0.9)
PR	43 (62.3)	19 (45.2)	62 (55.9)
SD	17 (24.6)	13 (31.0)	30 (27.0)
PD	7 (10.1)	3 (7.1)	10 (9.0)
NE	2 (2.9)	6 (14.3)	8 (7.2)
ORR, % (95% CI)	62.3 (49.8, 73.7)	47.6 (32.0, 63.6)	56.8 (47.0, 66.1)
DCR, % (95% CI)	87.0 (76.7, 93.9)	78.6 (63.2, 89.7)	83.8 (75.6, 90.1)
mDOR, months (95% CI)	ne (10.4, ne)	46.4 (7.6, ne)	46.4 (13.4, ne)
mPFS, months (95% CI)	15.9 (10.8, ne)	15.3 (8.2, ne)	15.3 (11.3, ne)
mOS, months (95% CI)	22.7 (12.7, ne)	29.7 (13.5, ne)	25.9 (17.5, 36.6)



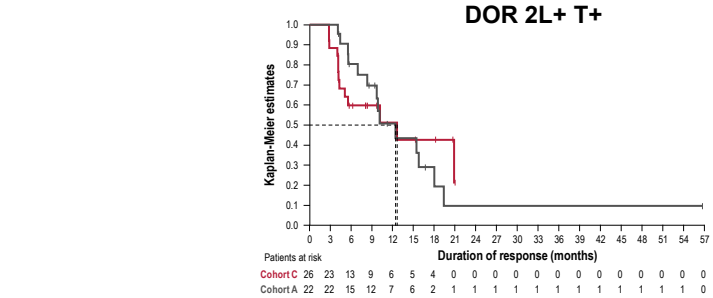


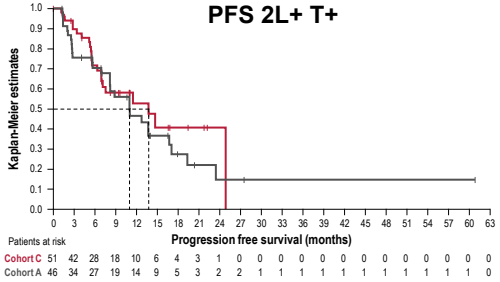


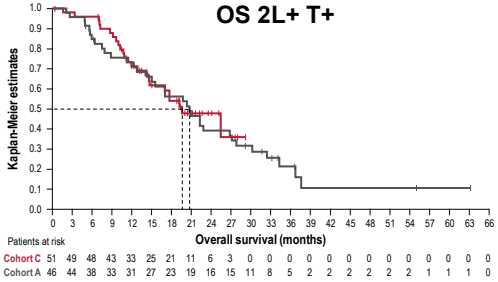
1L, first line; BOR, best objective response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; m, median; *MET*ex14, *MET* exon 14; ne, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T+, *MET*ex14 skipping detected in tissue biopsy.

Efficacy was also robust and durable in previously treated patients enrolled by tissue biopsy

2L+ T+	Cohort C (n=51)	Cohort A (n=46)	Cohort A+C (n=97)
BOR, n (%)			
CR	0	0	0 (0.0)
PR	26 (51.0)	22 (47.8)	48 (49.5)
SD	16 (31.4)	12 (26.1)	28 (28.9)
PD	4 (7.8)	9 (19.6)	13 (13.4)
NE	5 (9.8)	3 (6.5)	8 (8.2)
ORR, % (95% CI)	51.0 (36.6, 65.2)	47.8 (32.9, 63.1)	49.5 (39.2, 59.8)
DCR, % (95% CI)	82.4 (69.1, 91.6)	73.9 (58.9, 85.7)	78.4 (68.8, 86.1)
mDOR, months (95% CI)	12.6 (4.3, ne)	12.4 (7.0, 18.0)	10.2 (8.3, 18.0)
mPFS, months (95% CI)	13.8 (6.9, ne)	11.0 (8.2, 16.8)	11.5 (8.2, 16.8)
mOS, months (95% CI)	19.6 (14.6, ne)	20.8 (14.3, 27.2)	20.4 (17.0, 26.8)





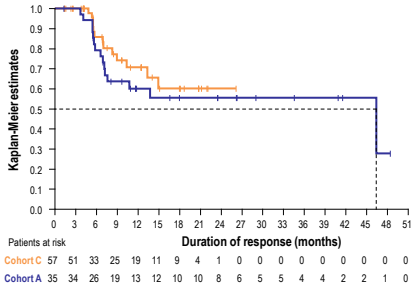


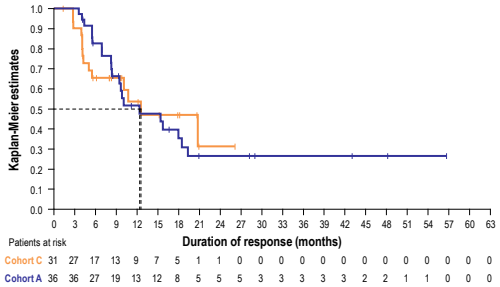
2L+, second-or-later line; BOR, best objective response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; m, median; *MET*ex14, *MET* exon 14; ne, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T+, *MET*ex14 skipping detected in tissue biopsy.

Overall efficacy in Cohort C and Cohort A was robust and durable across therapy lines

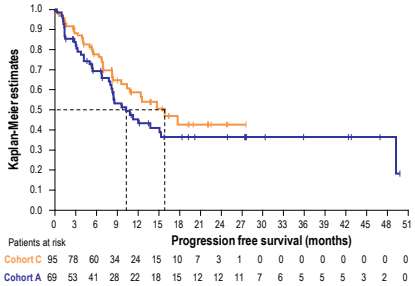
	1L* (T+ and/or L+)		2L+ (T+ and/or L+)	
	Cohort C (n=95)	Cohort A (n=69)	Cohort C (n=66)	Cohort A (n=83)
ORR, % (95% CI)	60.0 (49.4, 69.9)	50.7 (38.4, 63.0)	47.0 (34.6, 59.7)	43.4 (32.5, 54.7)
Median DOR, months (95% CI)	ne (13.4, ne)	46.4 (7.2, ne)	12.6 (5.1, ne)	12.4 (8.4, 18.5)
Median PFS, months (95% CI)	15.9 (10.4, ne)	10.3 (8.0, 15.3)	12.1 (6.9, ne)	10.9 (8.2, 12.7)
Median OS, months (95% CI)	21.1 (12.7, ne)	19.1 (9.9, 25.9)	18.8 (13.5, ne)	19.8 (15.0, 22.3)

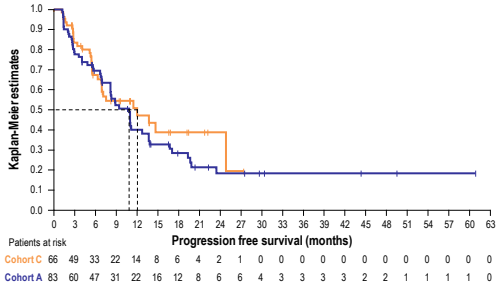
DOR





PFS



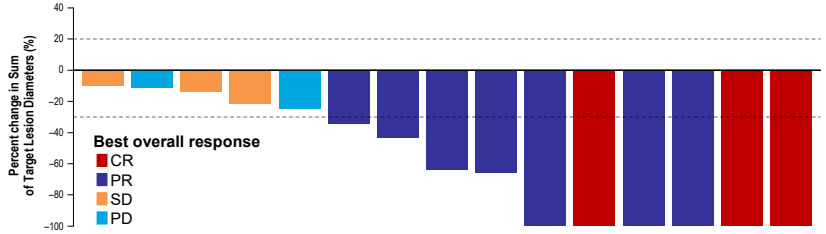


*1L enrollment began approximately 8 months later than 2L+.
1L, first line; 2L+, second-or-later line; CI, confidence interval; DOR, duration of response; L+, *MET*ex14 skipping detected in liquid biopsy; ne, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T+, *MET*ex14 skipping detected in tissue biopsy.

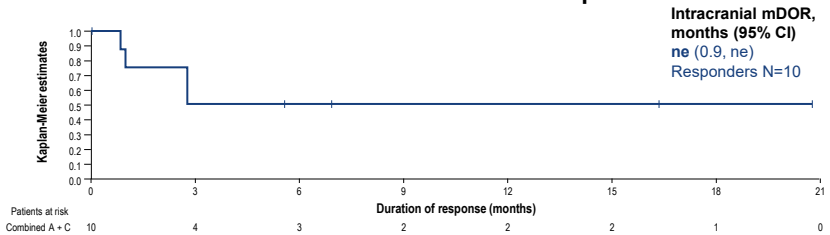
Tepotinib showed promising intracranial activity in patients with brain metastases (RANO-BM analysis)

- Tepotinib crosses the blood brain barrier to a significant extent, leading to concentrations of unbound tepotinib in the brain of 25% compared to plasma ($Kp_{u,u}$=0.25), within a similar range to other CNS–penetrant TKIs[1]
- Across Cohorts A+C, 43 patients with brain metastases were evaluable by RANO-BM (1L, n=23; 2L+, n=20)
- 30 patients (69.8%) received prior brain radiotherapy or surgery
- In patients with target or non-target lesions (n=43), **intracranial disease control rate was 88.4%** (95% CI: 74.9, 96.1) with **intracranial mPFS of 20.9 months** (95% CI: 5.7, ne)
- In patients with target lesions (n=15), **intracranial ORR was 66.7%** (95% CI: 38.4, 88.2) with **intracranial mDOR ne** (95% CI: 0.9, ne)

Intracranial response in patients with target lesions (n=15)



Intracranial duration of response



1L, first line; 2L+, second-or-later line; CI, confidence interval; CNS, central nervous system; CR, complete response; DOR, duration of response; $Kp_{u,u}$, unbound partition coefficient; m, median; ne, not estimable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; TKI, tyrosine kinase inhibitor.

1. Friese-Hamim M, et al. *Lung Cancer.* 2022;163:77–86.

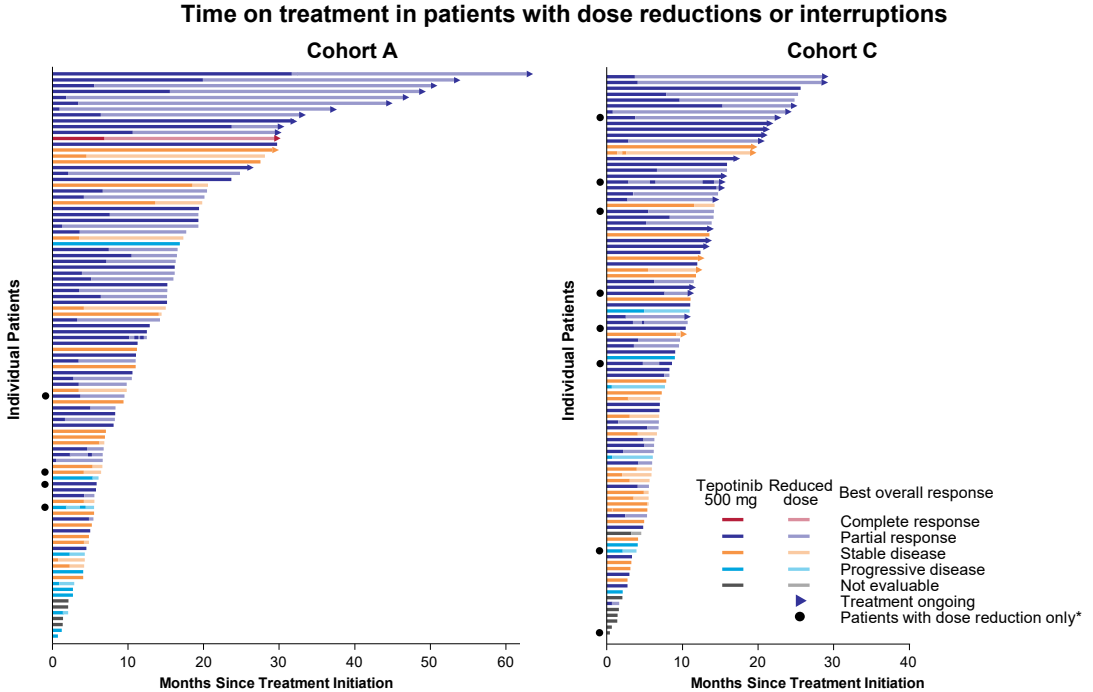
Tepotinib was generally well tolerated, with mostly mild–moderate AEs, and few discontinuations

Treatment-related AEs, %		Cohorts A+C (N=313*)
Any grade		91.7
Grade ≥3		34.2
Leading to dose reduction		33.5
Leading to treatment interruption		42.5
Leading to permanent discontinuation		14.7
Occurring in ≥10% of all patients, %	**Any grade**	**Grade ≥3**
Peripheral edema	66.5	10.9
Nausea	23.3	0.6
Hypoalbuminemia	23.0	3.2
Diarrhea	22.4	0.3
Blood creatinine increase	21.7	0.6
ALT increase	13.1	2.2
Decreased appetite	11.2	0.3

*Safety population comprised all patients from VISION Cohorts A and C.
AE, adverse event; ALT, alanine transaminase.

Patients requiring treatment interruptions and dose reductions were able to continue to benefit from treatment with tepotinib

- To evaluate the impact of treatment modifications, treatment durations were analyzed in patients who had a dose reduction and/or treatment interruption
- The duration of tepotinib treatment across all patients in Cohort A+C (N=313) was:
  - Mean ± SD: 10.35 months ± 9.64
  - Median (range): 7.5 months (0.03–63.2)
  - 48 patients (15.3%) were still receiving treatment
- The duration of tepotinib treatment in patients across Cohort A+C with dose reductions and/or interruption (n=192) was:
  - Mean ± SD: 12.78 months ± 10.46
  - Median (range): 10.5 months (0.7–63.2)
  - 39 patients (20.3%) were still receiving treatment



*Patients indicated with a black circle had no treatment interruptions, patients indicated with solid lines only had no dose reductions, and all other patients had both treatment interruptions and dose reductions.
SD, standard deviation.

Conclusions

- In VISION – the largest clinical trial of a MET TKI in *MET*ex14 skipping NSCLC – the Cohort C primary analysis provided independent confirmation for robust and durable efficacy of tepotinib, with comparable or improved outcomes across endpoints compared to Cohort A
- Efficacy outcomes in Cohort C were particularly durable in treatment-naïve patients identified by tissue biopsy
- In an exploratory RANO-BM analysis, promising intracranial activity was observed, indicating that patients with *MET*ex14 skipping NSCLC with brain metastases benefit from tepotinib treatment
- Safety data confirmed previous observations that tepotinib was generally well tolerated, with mostly mild–moderate AEs, and few discontinuations
- Patients who required treatment interruptions or dose reductions were able to remain on treatment and continue benefiting from treatment with tepotinib

AE, adverse event; MET, mesenchymal-epithelial transition factor; *MET*ex14, MET exon 14; NSCLC, non-small cell lung cancer; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; TKI, tyrosine kinase inhibitor.

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