Activity of tepotinib in brain metastases: Preclinical models and clinical data from patients with *MET* exon 14 skipping NSCLC

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CONCLUSIONS

- **Tepotinib administration resulted in tumor regression in MET-driven PDX models obtained from lung cancer brain metastases**
- **PDXs implanted orthotopically in the brain regressed upon treatment with tepotinib, supporting the activity of tepotinib in the brain**
- **The efficacy and safety profile of tepotinib in patients with brain metastases was comparable to the overall *MET* exon 14 skipping population in VISION Cohort A**
- **Activity of tepotinib in patients with brain metastases will be assessed in further detail by follow-up brain scans in the confirmatory VISION Cohort C**

INTRODUCTION

- Brain metastases occur in up to 40% of patients with advanced NSCLC and are typically associated with poor overall survival; limited data available for *MET* exon 14 skipping NSCLC suggest a similar proportion of cases involve brain metastases[1-4]
- Tepotinib is an oral, once daily, highly selective MET tyrosine kinase inhibitor that blocks MET-mediated signaling pathways involved in tumorigenesis[5,6]
- In the Phase II VISION study (NCT02864992), tepotinib had robust and durable efficacy in patients with advanced NSCLC (data cut-off January 1, 2020)[7]
  - Overall ORR (95% CI) was 44.5% (36.3, 53.0) by IRC and 54.8% (46.4, 63.0) by INV
  - Median PFS (95% CI) was 8.6 months (8.0, 11.0) by IRC, and 9.7 months (7.0, 12.2) by INV
- Here, we present data supporting tepotinib brain penetration, activity of tepotinib in brain metastases from preclinical models, and clinical data from patients enrolled in VISION (data cut-off January 1, 2020)
  - Updated overall efficacy analysis from VISION Cohort A (data cut-off July 1, 2020) is presented in Poster 1283P[7]

METHODS

Brain penetration

- *In vivo* penetration of the blood–brain barrier was assessed in Wistar rats (n=3), at tepotinib dose 3.66 mg/kg/h iv by determining the unbound brain-to-plasma concentration/exposure ratio using liquid chromatography with tandem mass spectrometry
- Brain tissue binding in humans is considered to be highly similar to that in rats[8]

Preclinical efficacy in brain metastases

- *In vivo* efficacy was assessed in two PDXs obtained from human lung cancer brain metastases harboring high *MET* gene amplification (*MET* gain in copy number: 11 for LU5349 and 24 for LU5406) grown in NOD-SCID mice
- Subcutaneous PDX (n=5/group) or PDX orthotopically implanted into the brain (n=10/group) were treated with tepotinib 125 mg/kg or vehicle control orally once daily
- Intracranial tumor growth was monitored by T2-weighted MRI

Clinical efficacy in brain metastases

- In the VISION study, patients with *MET* exon 14 skipping NSCLC were treated with tepotinib 500 mg once daily
- Brain metastases-related exclusion criteria: brain metastasis as the only measurable lesions; leptomeningeal disease; neurologically unstable symptomatic brain metastases requiring an increase in steroid dose within 2 weeks and/or have received prior stereotactic radiosurgery/gamma knife within 2 weeks and/or other prior treatment for brain metastases within 4 weeks prior to the start of therapy
- Endpoints included systemic objective response as assessed by IRC per RECIST v1.1 (confirmed by ≥2 post-baseline assessments more than 4 weeks apart), PFS, and safety; analysis in patients with asymptomatic baseline brain lesions identified by IRC (BM-IRC) or investigator (BM-INV) were preplanned subgroup analyses

RESULTS

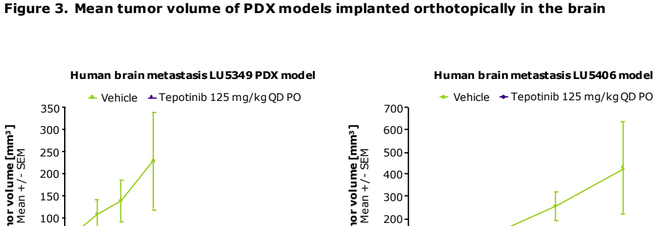
Tepotinib preclinical brain penetration

- Preclinically, relatively high binding of tepotinib in rat brain was observed, resulting in unbound tepotinib in brain tissue lower than in plasma ($f_{u,\ brain}$ = 0.4%, $f_{u,\ plasma}$ = 4%)

Tumor regression in PDX models derived from brain metastases of primary lung tumors

- Tumor volumes of PDX models obtained from NSCLC brain metastases were calculated by multiplying the area of each segmented slice by the slice thickness (**Figure 1**)

Figure 1. Representative tumor region of interest placement (red) on NOD/SCID mouse 27 days after injection of 2 x 10^5 LU5406 cells intracranially



Left: Sagittal view. Middle: Coronal view. Right: Transverse view.

- Upon treatment with tepotinib, both PDX tumors from MET-driven NSCLC brain metastases regressed completely in subcutaneous models (**Figure 2**) and regressed significantly in orthotopic brain models (mean % tumor volume −63% in LU5406 and −84% in LU5349) (**Figure 3**)

Figure 2. Mean tumor volume of PDX models implanted subcutaneously

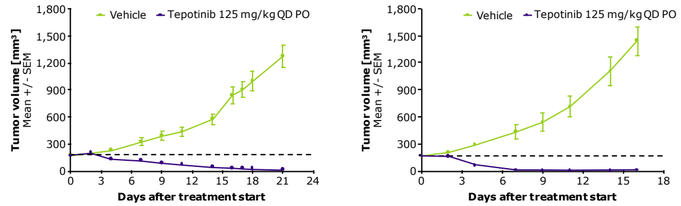


Figure 3. Mean tumor volume of PDX models implanted orthotopically in the brain

Activity of tepotinib in patients with brain metastases

- By January 1, 2020, VISION had enrolled 22 patients with baseline brain metastases (identified by IRC or by INV)
- Demographic characteristics in patients with brain metastases at baseline (n=22) were similar to the overall *MET* exon 14 skipping population enrolled in VISION (n=152)
  - There were 15 patients in the BM-IRC subgroup and 15 patients in the BM-INV subgroup; 8 patients were identified by both IRC and INV as having brain metastases at baseline
- Patients evaluable for OR had ≥2 post-baseline assessments or discontinuation for any reason
  - In the OR-evaluable population, there were 14 patients in the BM-IRC subgroup and 13 in the BM-INV subgroup (**Table 2**)
- Confirmed systemic best overall response in the BM-IRC subgroup was partial response in 8 patients and stable disease in 3 patients for ORR (95% CI) 57.1% (28.9, 82.3)

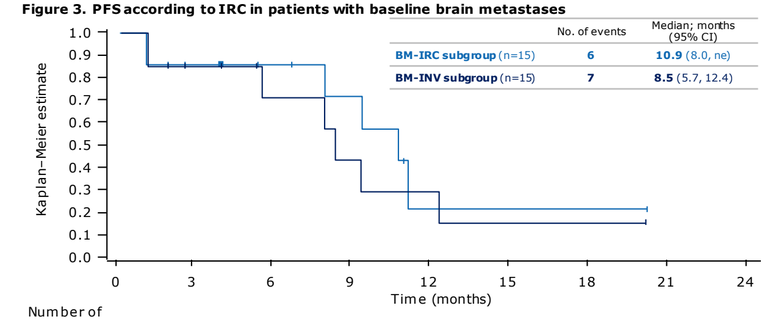
Table 2. Clinical efficacy of tepotinib in patients with baseline brain metastases

		BM-IRC	BM-INV
Patients with brain metastases; n	Non-target lesions*	14	12
	Target lesions†	0	1
Objective response rate; % (95% CI)		57.1% (28.9, 82.3)	53.8% (25.1, 80.8)
Best overall response; n	Partial response	8	7
	Stable disease	3	3

*Target lesions were measured and recorded at baseline and comprise measurable lesions up to a maximum of 2 per organ and 5 in total. Target lesions were selected on the basis of their size (lesions with the longest diameter), representativeness of all involved organs, and amenability to repeat measurements. The sum of diameters for all target lesions at baseline were used as a reference to characterise objective tumor regression. †Non-target lesions include all lesions not selected as target lesions. Measurement of non-target lesions at baseline was not required.

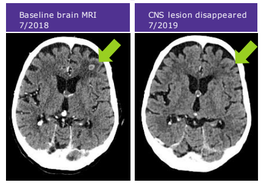
- PFS (95% CI) was 10.9 months (8.0, ne) for the BM-IRC subgroup and 8.5 months (5.7, 12.4) for the BM-INV subgroup (**Figure 3**)

Figure 3. PFS according to IRC in patients with baseline brain metastases



	No. of events	Median; months (95% CI)
BM-IRC subgroup (n=15)	**6**	**10.9** (8.0, ne)
BM-INV subgroup (n=15)	**7**	**8.5** (5.7, 12.4)

A case report from the VISION study



Images courtesy of Dr Remi Veillon.

- 72-year-old female former smoker, diagnosed with metastatic adenocarcinoma of the lung cT3N2M1a (pleura)
- No radiotherapy received
- 6/2017 to 11/2017: treated with first-line carboplatin/pemetrexed, in combination for 2 months followed by pemetrexed alone, with partial response
- 12/2017: disease progression (lung and bones) treated with second-line pembrolizumab with partial response
- 6/2018: disease progression (lung, adenopathy, and CNS frontal lesion)
- 8/2018 to 7/2019: on-treatment with third-line tepotinib. Disappearance of brain metastasis with systemic partial response
- Disease progression in the liver (no CNS progression)

Safety

- CNS-related adverse events (any cause) were observed in 36.4% (n=8/22) of patients with brain metastases, comparable to the 30.3% (n=46/152) of patients in the overall population
  - CNS-related adverse events reported in patients with brain metastases were headache (n=3), aphasia, ataxia, cognitive disorder, dizziness, intracranial hemorrhage, paresthesia, syncope, and tremor (all n=1)
  - Most (90.9%) CNS-related adverse events were grades 1-2 and not considered related to tepotinib
  - One patient had grade 3 aphasia and grade 2 intracranial haemorrhage, both of which required hospitalisation, but these were not considered related to tepotinib

Abbreviations: BM, brain metastases; CI, confidence interval; CNS, central nervous system; f_u, brain, unbound brain fraction; f_u, plasma, unbound plasma fraction; INV, investigator assessed; IRC, independent review committee; iv, intravenous; $K_{p,uu}$, ratio of free brain vs plasma concentration; MET, mesenchymal-epithelial transition factor; MRI, magnetic resonance imaging; ne, not estimable; NOD/SCID, Nonobese diabetic/severe combined immunodeficiency; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; PDX, patient-derived xenograft; PO, by mouth; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; SEM, standard error of mean.

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