Treatment sequencing in the VISION study of tepotinib in patients with *MET* exon 14 (*MET*ex14) skipping NSCLC

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CONCLUSIONS

- **Tepotinib demonstrated robust and durable efficacy in VISION – the largest study of a MET inhibitor in patients with *MET*ex14 skipping NSCLC**
  - **The outcomes were notable in the 1L setting, which further support its early use in the treatment sequence**
  - **Outcomes in patients with smoking history support the use of 1L tepotinib rather than IO-based regimens**
  - **Efficacy was also observed in the +2L patients regardless of prior therapies, including IO and/or platinum-based CT**
- **Almost half of this elderly population in the VISION study received subsequent treatment which was higher than the 20–30% reported for 1L CT or IO in the IPSOS trial in elderly patients (median age 75 years)**
- **Shorter DOR and PFS outcomes with platinum-based CT and/or IO-containing regimens, both pre and post VISION, further support the use of tepotinib in patients with *MET*ex14 skipping NSCLC**
- **Use of MET inhibitors post tepotinib was high, with encouraging clinical benefit reported when the rechallenge occurred following a break in MET inhibitor use**

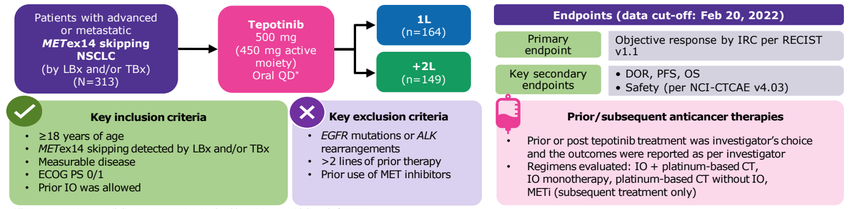
INTRODUCTION

- *MET*ex14 skipping is reported in 3–4% of patients with NSCLC and is sensitive to MET inhibition[1–4]
- Tepotinib is an oral, once daily, highly selective, potent MET inhibitor that has shown clinical activity in MET-driven tumors[5,6] and is approved in many countries in North America, Europe, South America and Asia, for treating advanced/metastatic *MET*ex14 skipping NSCLC
- In *MET*ex14 skipping NSCLC, there is a scarcity of data on post METi treatments and their outcomes
- Apart from METi, there are no other treatments specifically approved for *MET*ex14 skipping NSCLC, thus SOC (IO, CT, and METi) is used to treat these patients if a clinical trial is not available
- Albeit low reported efficacy in *MET*ex14 skipping NSCLC, IO is sometimes administered as ~50% of patients with *MET*ex14 have a smoking history and PD-L1 >50%[7]
- **We report treatment sequencing prior/post tepotinib of IO, CT, and METi (post only) considering smoking history**

METHODS

- VISION is a single-arm, Phase II trial of tepotinib administered as 500 mg (450 mg active moiety) QD to patients with advanced NSCLC harboring *MET*ex14 skipping (**Figure 1**)

Figure 1. Study design, endpoints, and eligibility criteria of VISION



*Treatment continues until disease progression, intolerable toxicity, or withdrawal of consent.

RESULTS

Baseline characteristics

VISION enrolled (**Table 1**):

- 164 treatment-naïve patients (median age 74.0 years)
- 149 previously treated patients (median age 70.8 years)
  - 92 (61.7%) received tepotinib as 2L
  - 57 (38.3%) received tepotinib as +3L (n=54 as 3L, n=3 as 4L)
  - 1L regimens prior to enrolling in VISION were:
    - Platinum-CT without IO (n=87, 58.4%)
    - IO monotherapy (n=34, 22.8%)
    - IO + platinum-CT (n=19, 12.8%)

Table 1. Baseline characteristics

Baseline characteristics		1L (n=164)	+2L		
			All +2L (n=149)	2L (n=92)	+3L (n=57)
Median age, years (range)		74.0 (47–94)	70.8 (41–89)	70.4 (41-89)	71.9 (52-88)
Sex, %	Male	50.6	47.7	50.0	43.9
	Female	49.4	52.3	50.0	56.1
Race*, %	White	68.3	55.7	55.4	56.1
	Asian	30.5	37.6	39.1	35.1
ECOG PS†, %	0	27.4	24.2	25.0	22.8
	1	72.0	75.8	75.0	77.2
Smoking history†, %	Yes	53.7	40.9	39.2	43.9
	Former smoker	49.4	39.6	37.0	43.9
	Current smoker	4.3	1.3	2.2	0
	No	45.7	53.0	54.3	50.9

*Race was missing/not collected at the study site for eight patients, three patients were Black/African American, and one patient was recorded as 'other'. †One 1L patient was ECOG PS 2. ‡Smoking history was missing in ten patients.

Efficacy outcomes prior to tepotinib

- Across all prior 1L regimens, median duration of treatment was 4 months (IQR 1.8, 7.3), with an ORR of 24.8%, median longest DOR of 6.0 months (IQR 4.0, 12.0), and median longest PFS of 4.0 months (IQR 2.0, 8.5)

Efficacy outcomes with tepotinib

- In contrast, 1L outcomes to tepotinib were greatly improved with an ORR of 56.1%, mDOR of 46.4 months, and mPFS of 12.6 months (**Table 2**)

Table 2. Treatment sequencing outcomes with tepotinib

Efficacy outcomes	Patients, n	ORR, % (95% CI)*	mDOR†, months (IQR or 95% CI)*	mPFS‡, months (IQR or 95% CI)*
1L treatment§ prior to tepotinib by investigator assessment				
Prior 1L IO + platinum-CT	19	26.3	5.0 (1.0, 8.0)	5.0 (2.0, 6.5)
Prior 1L IO mono	34	23.5	7.5 (5.5, 13.5)	5.0 (3.0, 9.0)
Prior 1L platinum-CT without IO	87	27.6	5.0 (4.0, 12.0)	4.0 (2.0, 11.0)
Tepotinib by IRC§				
1L	164	56.1 (48.1, 63.8)	46.4 (13.8, ne)	12.6 (9.6, 17.7)
2L	92	45.7 (35.2, 56.4)	12.6 (8.3, 20.8)	10.9 (8.2, 13.8)
2L+	149	45.0 (36.8, 53.3)	12.4 (9.5, 18.5)	11.0 (8.2, 13.7)
3L+	57	43.9 (30.7, 57.6)	10.8 (8.3, ne)	11.0 (5.7, 14.7)

*95% confidence intervals for efficacy outcomes with tepotinib and IQR for other treatments. †In the case of prior tepotinib treatment by investigator, mDOR and mPFS as well as corresponding IQRs were based on a descriptive analysis and not on a survival analysis. ‡Nine patients received other 1L treatment.

Efficacy outcomes by smoking history

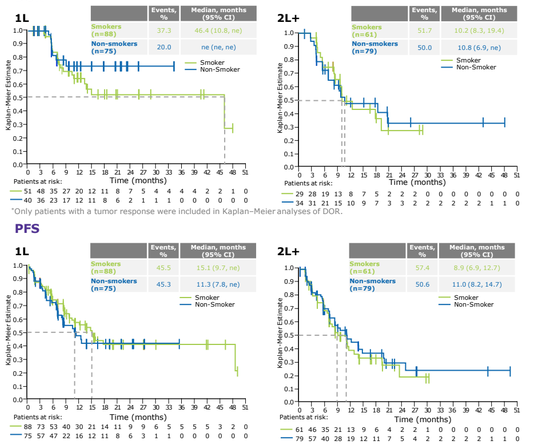
- Among patients with smoking history, outcomes were poor to 1L treatments prior to enrolling in VISION, including IO-containing regimens (**Table 3**)
- 1L outcomes with tepotinib in patients with smoking history were ORR of 58.0% (95% CI: 47.0, 68.4), with a mDOR of 46.4 months (95% CI: 10.8, ne), and a mPFS of 15.1 months (95% CI: 9.7, ne)
- Outcomes in patients who never smoked were comparable (**Table 3, Figure 2**)

Table 3. Efficacy outcomes by smoking history

Efficacy outcomes	Smoking history (n)*	ORR, % (95% CI)†	mDOR‡, months (IQR or 95% CI)†	mPFS‡, months (IQR or 95% CI)†
1L treatment§ prior to tepotinib by investigator assessment				
IO + platinum-CT	Yes (6)	33.3	8.0‖	5.5 (5.0, 6.5)
	No (12)	25.0	3.0 (1.0, 5.0)	5.0 (2.0, 7.0)
IO mono	Yes (21)	14.3	8.0 (6.0, 27.0)	5.0 (2.5, 9.0)
	No (13)	38.5	7.0 (5.0, 13.0)	5.5 (3.0, 9.0)
Platinum-CT without IO	Yes (32)	25.0	4.0 (4.0, 4.0)	4.0 (1.0, 13.0)
	No (48)	25.0	11.0 (4.0, 13.0)	4.0 (2.0, 11.0)
Tepotinib by IRC				
1L	Yes (88)	58.0 (47.0, 68.4)	46.4 (10.8, ne)	15.1 (9.7, ne)
	No (75)	53.3 (41.4, 64.9)	ne (ne, ne)	11.3 (7.8, ne)
2L+	Yes (61)	47.5 (34.6, 60.7)	10.2 (8.3, 19.4)	8.9 (6.9, 12.7)
	No (79)	43.0 (31.9, 54.7)	10.8 (6.9, ne)	11.0 (8.2, 14.7)

*Smoking history was missing in ten patients. †95% confidence intervals for efficacy outcomes with tepotinib and IQR for other treatments. ‡In the case of prior tepotinib treatment by investigator, mDOR and mPFS as well as corresponding IQR were based on a descriptive analysis and not on a survival analysis. §Nine patients received other 1L treatment. ‖No IQR is reported as data was only available from one patient.

Figure 2. Efficacy outcomes with tepotinib according to smoking history in treatment-naïve patients and previously treated patients

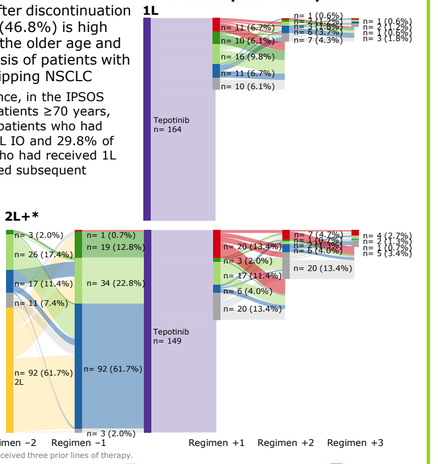


†Only patients with a tumor response were included in Kaplan–Meier analyses of DOR.

Efficacy outcomes post tepotinib

- Overall, 265 patients (84.7%) discontinued tepotinib and of these, 124 patients (46.8%) received subsequent treatment (**Figure 3**)
- The proportion of VISION patients who received treatment after discontinuation of tepotinib (46.8%) is high considering the older age and poor prognosis of patients with *MET*ex14 skipping NSCLC
  - For reference, in the IPSOS study in patients ≥70 years, 20.2% of patients who had received 1L IO and 29.8% of patients who had received 1L CT, received subsequent therapy[9]

Figure 3. Sankey plots for prior and subsequent therapies



*Three patients had received three prior lines of therapy.

- Outcomes to platinum-based CT and IO-containing regimens received after discontinuing tepotinib were also lower than those obtained with tepotinib (**Table 4**)

Table 4. Post tepotinib treatment outcomes

Efficacy outcomes	Patients, n	ORR, %	mPFS*, months (IQR)
Post tepotinib treatment by investigator assessment			
Any subsequent platinum-CT	46	10.9	2.0 (2.0, 7.0)
Platinum-CT without IO	31	6.5	2.0 (2.0, 2.0)
Any subsequent IO	56	16.1	3.0 (2.0, 7.0)
IO mono	43	14.0	3.0 (2.0, 7.0)
IO + platinum-CT	15	20.0	5.5 (3.5, 7.5)

*In the case of post tepotinib treatment by investigator, mPFS was based on a descriptive analysis (using the longest PFS per patient in any regimen post tepotinib) and not on a survival analysis.

METi rechallenge

- 48 patients received subsequent METi (20 crizotinib, 15 capmatinib, 4 bozitinib, 3 tepotinib [**Table 5**], 3 amivantamab, 3 cabozantinib, 4 other [2 SYM 015, 1 savolitinib, 1 TPX0022]; 4 patients received different METi in subsequent lines)
- 31 patients received METi as next subsequent treatment after tepotinib (11 patients after 1L tepotinib and 20 patients after 2L+ tepotinib)
- Best overall response across all subsequent METi was PR in three patients and SD in 11 patients, and the median longest DOR and PFS were 4.0 and 2.5 months, respectively
  - Of the three patients with PRs, one patient discontinued tepotinib due to an AE and following a break of 1.8 months received METi as next subsequent treatment, and two patients received CT/IO regimens followed by METi

Table 5. Tepotinib post VISION

	VISION	Post VISION	
Patient	**Tepotinib DOT (BOR)**	**Subsequent treatment**	**Subsequent tepotinib DOT**
1	6.1 months (PR)	Atezolizumab → Docetaxel → Tepotinib	10.1 months
2	8.5 months (PR)	Docetaxel/ramucirumab → Tepotinib	2.7 months
3	9.7 months (PR)	Nephrectomy for a single new lesion in kidney → Tepotinib	5.6 months

Abbreviations: 1L, first line; 2L, second line; 2L+, second or later line; 3L+, third or later line; 4L, fourth line; AE, adverse event; ALK, anaplastic lymphoma kinase; BOR, best objective response; CT, chemotherapy; DOR, duration of response; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IO, immunotherapy; IPSOS, a Phase III, global, multicenter, open-label, randomized, controlled study examining the efficacy, safety and patient-reported outcomes with atezolizumab versus single agent chemotherapy in patients who were considered unsuitable for 1L platinum-doublet chemotherapy; IQR, interquartile range; IRC, independent review committee; LBx, liquid biopsy; m, median; MET, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14; METi, MET inhibitors; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ne, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, disease progression; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response, QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOC, standard of care; TBx, tissue biopsy.

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