Clinical response to tepotinib according to circulating tumor DNA biomarkers in patients with advanced NSCLC with high-level *MET* amplification detected by liquid biopsy

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CONCLUSIONS

- **Tepotinib provided clinically meaningful activity, with durable responses, in patients with NSCLC with high-level *MET*amp**
- **Efficacy appeared most pronounced in treatment-naïve patients, who had a high ORR of 71.4%, and long median DOR (14.3 months) and PFS (15.6 months)**
- **Baseline focal *MET*amp, *RB1* wild-type status, *MYC* diploidy, and low ctDNA burden were potential predictors of tepotinib benefit**
- **The association between eMR and clinical response to tepotinib supports a role for LBx in serial monitoring of response and resistance**
- **These results further support the NCCN recommendation for tepotinib for NSCLC with high-level *MET*amp[1]**

INTRODUCTION

- High-level *MET*amp occurs in ~1–2% of patients with NSCLC,[2,3] who have a very poor prognosis and a high unmet need for effective treatments[4]
- Promising clinical activity has been reported with MET inhibitors[5,6]
- Tepotinib, a MET inhibitor approved for the treatment of metastatic *MET*ex14 skipping NSCLC,[7–9] has also shown meaningful activity in patients with NSCLC with high-level *MET*amp[10] and is recommended in this setting by NCCN guidelines[1]
- We report updated clinical data and exploratory biomarker analyses from VISION Cohort B, which evaluated tepotinib in patients with NSCLC with high-level *MET*amp detected by an LBx assay

METHODS

- VISION Cohort B enrolled patients with high-level *MET*amp, as detected by an LBx assay (73-gene; Guardant360®; Guardant Health, Redwood City, CA, USA) and defined as *MET* GCN ≥2.5 (**Figure 1**)
- The same LBx assay was used in exploratory biomarker analyses of focal *MET*amp, co-occurring mutations and amplifications, ctDNA burden and early molecular response (eMR) in baseline, Week 6 and/or end-of-treatment blood samples
- Exploratory analyses evaluated OS and biomarkers according to clinical benefit, defined as BOR ≥SD
- The data cut-off was August 20, 2021

Figure 1. VISION Cohort B: Open-label, multicenter, Phase II trial design (NCT02864992)

Key inclusion criteria (Cohort B)

- Advanced NSCLC (*EGFR/ALK* wild-type, all histologies)
- High-level *MET*amp without *MET*ex14 skipping by central LBx assay
- 1L, 2L, or 3L treatment setting
  - Prior immunotherapy allowed
- ECOG PS 0 or 1

Tepotinib 500 mg* once daily

Selected endpoints

Primary:
- ORR† by IRC (RECIST v1.1)

Secondary:
- DOR
- PFS
- OS
- Safety

Exploratory biomarker analyses

- **Focal *MET*amp:** co-amplification of ≤1 of three other chromosome 7 genes (*EGFR*, *BRAF*, *CDK6*)
- **Co-occurring mutations and amplifications**
- **Baseline ctDNA burden:** maxVAF in each patient (used as a surrogate for overall tumor burden)
- **eMR:** undetectable *MET*amp after 6–8 weeks

*Containing 450 mg active moiety. Treatment was administered until disease progression, intolerable toxicity, or withdrawal of consent.
†Objective responses were confirmed ≥4 weeks after response was first observed.

RESULTS

Patients

- Of 3,205 patients prescreened by Guardant360® for enrollment into any VISION cohort, 70 (2.2%) were positive for high-level *MET*amp and negative for *MET*ex14 skipping
- Among 24 patients enrolled into Cohort B, median age was 63.4 years, 88% were male, 88% were smokers, 88% had ECOG PS 1, and 29% were treatment-naïve
- Median baseline tumor load, defined as sum of target lesion diameters, was 95.6 mm

Efficacy

- ORR was 41.7%, mDOR was 14.3 months, mPFS was 4.2 months, and mOS was 7.5 months in the overall population (**Table 1**; **Figure 2**)
- In preplanned subgroup analyses, efficacy appeared most pronounced in treatment-naïve patients (n=7; **Table 1**; **Figure 3**)

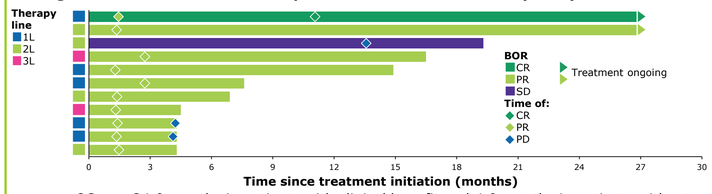
Table 1. Efficacy, overall, and by therapy line

IRC		Overall (N=24)	1L (n=7)	2L (n=11)	3L (n=6)	Scan lower right QR code to view further data
BOR, n (%)	CR	1 (4.2)	1 (14.3)	0	0	Supplementary Figure 1
	PR	9 (37.5)	4 (57.1)	3 (27.3)	2 (33.3)	
	SD	1 (4.2)	0	1 (9.1)	0	
	PD	5 (20.8)	1 (14.3)	3 (27.3)	1 (16.7)	
	NE*	8 (33.3)	1 (14.3)	4 (36.4)	3 (50.0)	
ORR, % (95% CI)		41.7 (22.1, 63.4)	71.4 (29.0, 96.3)	27.3 (6.0, 61.0)	33.3 (4.3, 77.7)	
DCR, % (95% CI)		45.8 (25.6, 67.2)	71.4 (29.0, 96.3)	36.4 (10.9, 69.2)	33.3 (4.3, 77.7)	
mDOR, months (95% CI)		14.3 (2.8, ne)	14.3 (2.8, ne)	ne (ne, ne)	ne (3.2, ne)	Supplementary Figure 2
mPFS, months (95% CI)		4.2 (1.4, 15.6)	15.6 (1.4, ne)	13.6 (1.0, ne)	1.7 (0.6, ne)	Supplementary Figure 3
mOS, months (95% CI)		7.5 (4.0, 15.6)	14.3 (4.0, ne)	7.5 (1.9, 24.0)	2.6 (0.6, ne)	Supplementary Figure 4

*Three patients discontinued before the first tumor assessment due to unrelated AEs (n=2) or consent withdrawal (n=1), and five patients discontinued due to PD by INV before response was confirmed.

- Median treatment duration was 3.6 months (range, 0.1–26.8)
- Treatment duration was ≥1 year in five patients (21%) and ≥2 years in two patients (8%) (**Figure 2**)

Figure 2. Treatment duration in patients with clinical benefit (n=11)



- mOS was 24.0 months in patients with clinical benefit and 4.0 months in patients without clinical benefit (**Figure 4**)

Figure 3. PFS by therapy line

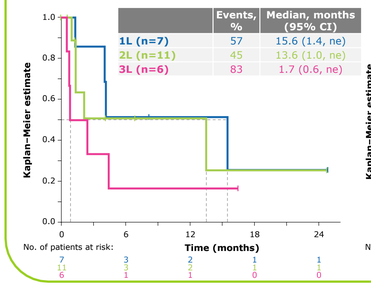
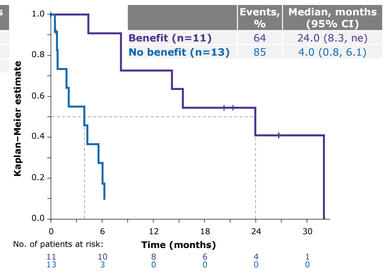


Figure 4. OS according to clinical benefit



Biomarkers

- *MET*amp was focal in 14 patients (58.3%), who had better outcomes than patients with non-focal *MET*amp (**Figure 5**; **Table 2**)
- Baseline *RB1* wild-type and *MYC* diploidy were associated with clinical benefit (**Figure 5**) and improved outcomes (**Table 2**)
- Median baseline ctDNA burden was 10.7% (IQR 7.5, 26.0) and low ctDNA burden (≤median) was associated with greater efficacy (**Figure 5**; **Table 2**)
- eMR was attained by 14/18 evaluable patients (77.8%), who had better outcomes than patients without eMR (**Figure 5**; **Table 2**)
- Of nine patients with available end-of-treatment biomarker profiles, two (22.2%) showed emergence of MET kinase domain mutations (D1228H/N/Y, Y1230C/H and D1231N in one patient, and D1213N, D1228N/H and Y1230H in the other)

Figure 5. Baseline biomarker profiles, eMR, and response to treatment

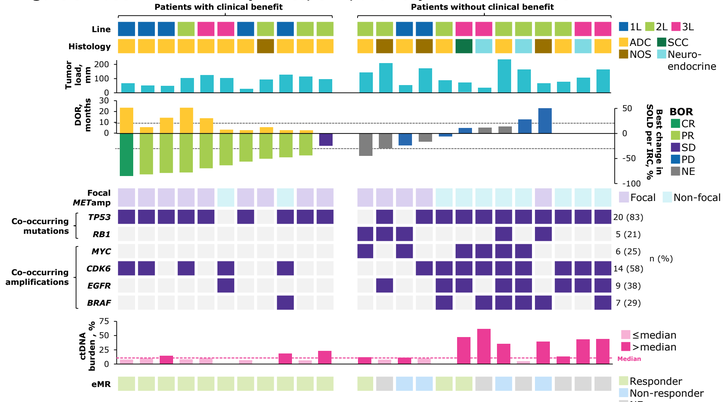


Table 2. Outcomes according to biomarker status

Biomarker	Category	ORR, % (95% CI)	mDOR, months (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
*MET*amp	Focal (n=14)	57.1 (28.9, 82.3)	ne (2.9, ne)	15.6 (1.4, ne)	15.6 (6.4, ne)
	Non-focal (n=10)	20.0 (2.5, 55.6)	3.0 (2.8, ne)	1.4 (0.6, 4.1)	2.2 (0.6, 6.1)
RB1	Wild-type (n=19)	52.6 (28.9, 75.6)	14.3 (2.8, ne)	4.5 (1.4, ne)	8.3 (4.4, 24.1)
	Mutation (n=5)	0 (0, 52.2)	–	1.4 (1.4, ne)	4.9 (2.2, ne)
MYC	Diploidy (n=18)	55.6 (30.8, 78.5)	14.3 (2.8, ne)	13.6 (1.4, ne)	14.3 (5.7, ne)
	Amplification (n=6)	0 (0, 46.0)	–	1.4 (0.8, ne)	3.1 (0.8, ne)
ctDNA burden	≤Median (n=12)	66.7 (34.9, 90.1)	ne (2.9, ne)	ne (1.4, ne)	14.3 (4.5, ne)
	>Median (n=12)	16.7 (2.1, 48.4)	8.6 (2.8, ne)	2.2 (0.8, 4.1)	4.4 (0.8, 8.3)
eMR*	Responder (n=14)	71.4 (41.9, 91.6)	14.3 (2.8, ne)	13.6 (4.1, ne)	14.9 (6.1, ne)
	Non-responder (n=4)	0 (0, 60.2)	–	1.8 (1.4, ne)	4.9 (2.2, ne)

*eMR was evaluable in 18 patients with matched baseline and on-treatment samples at 6–8 weeks.

Safety

- TRAEs were reported at any grade in 17 patients (70.8%) and at Grade 3 in 7 patients (29.2%) (**Table 3**)
- There were no Grade 4 TRAEs, fatal TRAEs, or discontinuations due to TRAEs

Table 3. TRAEs occurring in ≥5% of patients*

TRAEs, n (%)	N=24	
	All grades	Grade 3
Edema (composite event)	11 (45.8)	3 (12.5)
Peripheral edema	10 (41.7)	2 (8.3)
Generalized edema	4 (16.7)	2 (8.3)
Edema (preferred term)	3 (12.5)	1 (4.2)
Constipation	4 (16.7)	0
Transaminases increased	2 (8.3)	1 (4.2)
Diarrhea	2 (8.3)	0
Hypoproteinemia	2 (8.3)	0

*Data shown for individual preferred terms reported in ≥5% of patients, and the composite category 'edema'.

Abbreviations: 1L, first line; 2L, second line; 3L, third line; ADC, adenocarcinoma; AE, adverse event; ALK, anaplastic lymphoma kinase; BOR, best overall response; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; eMR, early molecular response; GCN, gene copy number; INV, investigator; IQR, interquartile range; IRC, independent review committee; LBx, liquid biopsy; m, median; maxVAF, maximum variant allele fraction; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; *MET*ex14, *MET* exon 14; NCCN, National Comprehensive Cancer Network; NE, not evaluable; ne, not estimable; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SCC, squamous cell carcinoma; SD, stable disease; SOLD, sum of target lesion diameters; TRAE, treatment-related adverse event.

References: 1. NCCN. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Non-Small Cell Lung Cancer V.3.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed May 5, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.; 2. Schildhaus HU, et al. *Clin Cancer Res*. 2015;21(4):907–915; 3. Overbeck TR, et al. *Transl Lung Cancer Res*. 2020;9(3):603–616; 4. Kron A, et al. *J Thorac Oncol*. 2020;S1556-0864(20):31091; 5. Camidge DR, et al. *J Thorac Oncol*. 2021;16(6):1017–1029; 6. Wolf J, et al. *N Engl J Med*. 2020;383(10):944–957; 7. Paik PK, et al. *N Engl J Med*. 2020;383(10):931–943; 8. Le X, et al. *Clin Cancer Res*. 2022;28(6):1117–1126; 9. Tepotinib US Prescribing Information, February 2021; 10. Le X, et al. *J Clin Oncol*. 2021;39(suppl 15) [abstract 9021].

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Supplementary materials

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