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Peripheral osimertinib plasma trough concentration as surrogate parameter for development and progression of brain metastases in patients with *EGFR+* advanced non-small cell lung cancer

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Purpose

Progression of existing or development of new brain metastases (BM) often occurs in patients treated with osimertinib for epidermal growth factor receptor (*EGFR)+* non-small cell lung cancer (NSCLC). A possible reason might be pharmacological failure of osimertinib. Therefore, we investigated the relation between steady-state osimertinib plasma trough concentration ($C_{min,SS}$) and BM development or progression in patients with advanced *EGFR+* NSCLC.

Methods

Study sites: Maastricht University Medical Centre+, Erasmus Medical Centre (Rotterdam), Antoni van Leeuwenhoek Hospital (Amsterdam)

Inclusion criteria:

- ≥ 18 years
- Diagnosed with advanced *EGFR*+ NSCLC
- Use of osimertinib 80 mg, once daily
- Eligible osimertinib plasma $C_{min,SS}$ measurement(s)

Cohort and subgroup definition:

- Cohort; patients with known BM were allocated to the BM cohort. Those without known BM or without brain imaging at start osimertinib were allocated to the no/unknown BM cohort.
- Subgroups: cohorts were subdivided based on osimertinib plasma $C_{min,SS}$.

Osimertinib $C_{min,SS}$	**Subgroup**
<159 ng/mL	Low $C_{min,SS}$
159 – 271 ng/mL	Middle $C_{min,SS}$
>271 ng/mL	High $C_{min,SS}$

Primary outcome: cumulative incidence of progression (BM cohort) or development of BM (no/unknown BM cohort) in osimertinib patients stratified per osimertinib $C_{min,SS}$ subgroup (using competing risk analysis).

Secondary outcome: median overall survival (mOS) in the BM cohort and no/unknown BM cohort (using Kaplan-Meier analysis).

Results

173 patients were included, of which 49 (28%) had BM at start osimertinib (Figure 1 and Table 1). Median $C_{min,SS}$ in the BM cohort was 223.9 ng/mL and 210.0 ng/mL in the no/unknown BM cohort (p = 0.71).

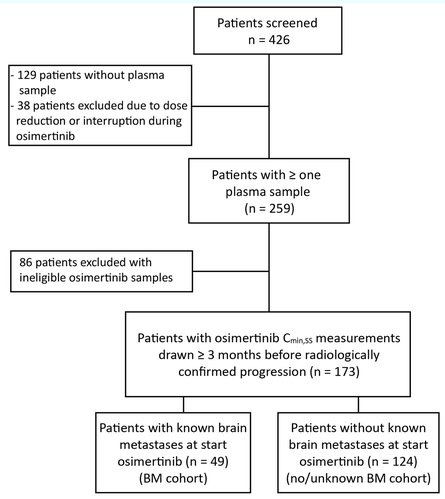

Figure 1. Flow-chart of patient inclusion.

Table 1. Baseline characteristics BM and no/unknown BM cohort.

		BM cohort (n = 49)	**No/unknown BM cohort (n = 124)**
Median age		64 years	65 years
Sex (female)		35 (71%)	85 (69%)
Diagnosis of LM		15 (31%)	NA
Line of treatment	1	16 (33%)	29 (23%)
	2	24 (49%)	63 (51%)
	≥3	9 (18%)	32 (26%)
Prior cranial radiotherapy	WBRT	7 (14%)	NA
	SRT	8 (16%)	NA
	No	34 (69%)	NA
Prior TKI	Erlotinib	17 (52%)	65 (65%)
	Afatinib	4 (12%)	8 (9%)
	Gefitinib	5 (15%)	18 (17%)
Mutation	Exon 19del	27 (55%)	76 (61%)
	L858R	13 (27%)	33 (27%)
	Exon 19del + L858R	3 (6%)	4 (3%)
	Other	6 (12%)	11 (9%)

Abbreviations: BM, brain metastases; LM, leptomeningeal metastases; WBRT, whole brain radiotherapy; SRT, stereotactic radiotherapy; NA, not applicable; TKI, tyrosine kinase inhibitor

Progression and development of BM

Median follow-up was 24.9 months (95% CI 3.2 – 35.8) in the BM cohort. In total 18 patients (36.7%) had progression of BM. After 6 months the cumulative incidence was 0%, 0.6% and 0.6% for the $C_{min,ss,LOW}$, $C_{min,SS,MIDDLE}$ and $C_{min,SS,HIGH}$ subgroups respectively. After 12 months this was 17%, 31% and 29% respectively and after 24 months 17%, 50% and 49% (p = 0.250) (Figure 2). Median follow-up in the no/unknown BM cohort was 21.4 months (95% CI 3.9 – 40.5), during which 5 patients (4.0%) developed BM. No differences within the $C_{min,SS}$ subgroups were observed (p = 0.583) (Figure 3).

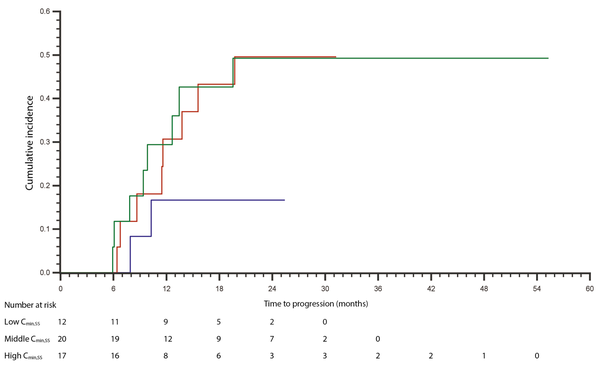

Figure 2. Cumulative incidence progression of BM in BM cohort. Low $C_{min,SS}$ (blue), Middle $C_{min,SS}$ (red), High $C_{min,SS}$ (green).

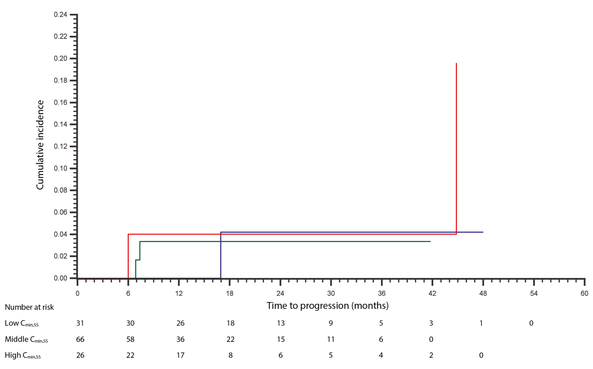

Figure 3. Cumulative incidence development of BM in no/unknown BM cohort. Low $C_{min,SS}$ (blue), Middle $C_{min,SS}$ (red), High $C_{min,SS}$ (green).

Overall survival

During follow-up, 36.7% of patients in the BM cohort died. In the subgroup $C_{min,SS,LOW}$ mOS was not reached (NR) and in the $C_{min,SS,MIDDLE}$ and the $C_{min,SS,HIGH}$ subgroups mOS was 27.3 months (95% CI 15.8 – NR) and 26.2 months (95% CI 11.7 – NR) (Figure 4). In the no/unknown BM cohort, 28.2% died during follow-up. Median OS was 35.4 months (95% CI 27.2 – NR) in the $C_{min,SS,LOW}$ subgroup, NR (95% CI 21.8 – NR) in the $C_{min,SS,MIDDLE}$ subgroup and 19.2 months (95% CI 15.8 – NR) in the $C_{min,SS,HIGH}$ subgroup (Figure 5).

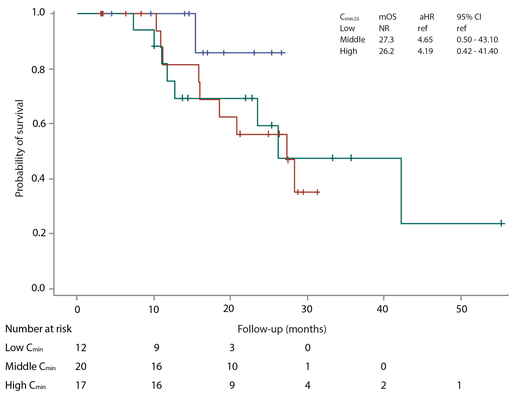

Figure 4. Overall survival BM cohort. Low $C_{min,SS}$ (blue), Middle $C_{min,SS}$ (red), High $C_{min,SS}$ (blue).

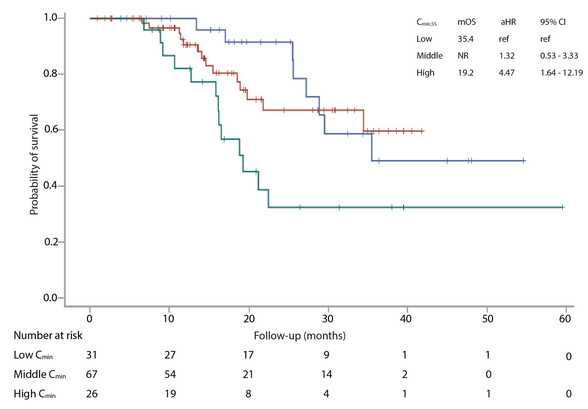

Figure 5. Overall survival no/unknown BM cohort. Low $C_{min,SS}$ (blue), Middle $C_{min,SS}$ (red), High $C_{min,SS}$ (green).

Conclusion

No relation was observed between osimertinib exposure, measured as plasma C_{min}, and the development or progression of BM in patients with advanced *EGFR*-mutated NSCLC receiving osimertinib.