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MANAGEMENT OF PARESTHESIA IN PATIENTS TREATED WITH LAZERTINIB: INTEGRATED ANALYSIS OF LASER201 AND LASER301 STUDIES

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1. INTRODUCTION

- Lazertinib, a third-generation tyrosine kinase inhibitor (TKI), has shown efficacy as a front-line and later line treatment for locally advanced or metastatic epidermal growth factor receptor (*EGFR)*-mutated non-small cell lung cancer (NSCLC)[1,2].
- Despite a manageable safety profile, paresthesia was reported in 33–39% of patients receiving lazertinib in the LASER201 (NCT03046992) and LASER301 (NCT04248829) studies[1,2].
- We performed an integrated analysis to characterize the clinical features of paresthesia and related adverse events (AEs) and examined the impact of lazertinib dose reduction (DR) on its exposure duration, safety, and clinical efficacy.

2. METHODS

- **Patients**: 332 patients who received lazertinib (240 mg/day) in the LASER201 (N=136) or LASER301 (N=196) studies were analyzed.
- **AE in the scope of analysis**: Paresthesia and related AEs (including hypoesthesia, peripheral sensory neuropathy, and polyneuropathy) were included.
- **Lazertinib exposure duration**: Duration from the first dosing date to the last dosing date was calculated.
- **AE severity**: The severity of paresthesia and related AEs before DR and after DR was summarized.
- **Efficacy**: Progression-free survival (PFS) was calculated for patients with and without DR within the first 12 months of treatment initiation.

3. RESULTS

Table 1. Frequency and severity of paresthesia and related AEs

Treatment-emergent paresthesia or related AEs, n (%) of patients	Received ≥1 dose of lazertinib 240 mg (332 patients)			
	Any grade†	Grade 1	Grade 2	Grade 3
All AEs	160 (48.2)	86 (25.9)	64 (19.3)	10 (3.0)
Treatment-related AEs	143 (43.1)	77 (23.2)	56 (16.9)	10 (3.0)
Events leading to:				
Dose adjustment	24 (7.2)	1 (0.3)	15 (4.5)	8 (2.4)
Dose interruption	11 (3.3)	1 (0.3)	4 (1.5)	6 (1.8)
Dose reduction	22 (6.6)	6 (1.8)	14 (4.2)	2 (0.6)
Drug discontinuation	5 (1.5)	0	2 (0.6)	3 (0.9)

†AE severity was graded using CTCAE version 4.3 (LASER201) or 5.0 (LASER301). The highest AE severity recorded for each category was used for the analysis.

- 48% had paresthesia or related AEs. Of which, most were grade 1/2 and none were serious. DR due to paresthesia or related AEs was infrequent (7%) **(Table 1)**.
- Median time to onset of paresthesia was 105 days (Q1: 65; Q3: 188). However, there was a substantial lag time between the onset of paresthesia and the first DR (median 164 days, Q1: 85; Q3: 515).
- No notable difference in patient characteristics were observed in those with or without paresthesia and related AEs except for race (**Table 2**).

Table 2. Patient characteristics

	With paresthesia or related AEs (N=160)	Without paresthesia or related AEs (N=172)	Total (N=332)
Age, years, median (Q1, Q3)	64.5 (56.5, 71.0)	64.5 (55.0, 72.0)	64.5 (56.0, 71.0)
Male, n (%)	58 (36.3)	72 (41.9)	130 (39.2)
Asian, n (%)	134 (83.8)	119 (69.2)	253 (76.2)
WHO performance status, n (%)			
0	35 (21.9)	47 (27.3)	82 (24.7)
1	125 (78.1)	125 (72.7)	250 (75.3)
†*EGFR* mutation status			
TKI-naïve, N	118	120	238
Exon 19 deletion, n (%)	78 (66.1)	68 (56.7)	146 (61.3)
L858R, n (%)	40 (33.9)	52 (43.3)	92 (38.7)
TKI 2nd or later line, N	41	52	93
T790M(+), n (%)	37 (90.2)	43 (82.7)	80 (86.0)
T790M(-) or unknown, n (%)	4 (9.8)	9 (17.3)	13 (14.0)
Brain metastases at baseline, n (%)	63 (39.4)	56 (32.6)	119 (35.8)
Weight, kg, mean (SD)	61.2 (11.99)	61.9 (12.69)	61.6 (12.34)

†G719X mutation for one patient.

Table 3. Lazertinib exposure duration

LASER201	
Lazertinib 240 mg (N=76)	†Exposure duration (months), median (Q1, Q3)
DR (N=12)	21.7 (13.6, 26.3)
No DR (N=64)	12.6 (5.5, 20.6)
‖Time to dose reduction (months), median (Q1, Q3): 4.8 (1.5, 13.8)	
LASER301	
Lazertinib 240 mg (N=196)	†Exposure duration (months), median (Q1, Q3)
DR (N=42)	13.7 (10.2, 20.7)
No DR (N=154)	15.2 (10.0, 20.7)
‖Time to dose reduction (months), median (Q1, Q3): 5.3 (2.3, 7.6)	

†Duration from the first lazertinib dosing date to the last dosing date.
‖ Duration from initiation of lazertinib treatment to first DR.

- Lazertinib exposure duration in patients with DR was not shorter than those without DR **(Table 3)**, suggesting AEs were well managed in the dose reduced group.
- In LASER201, the median exposure duration was 22 months in patients with DR and 13 months in those without DR.
- In LASER301, exposure duration in patients with DR and without DR was similar (median 14 vs. 15 months).
- For 13 patients in LASER301 with DR due to paresthesia or related AEs, AE severity decreased in 8 patients (62%) and 1 patient had complete AE resolution after DR **(Figure 1)**.

Figure 1. Paresthesia & related AEs decreased in severity after DR

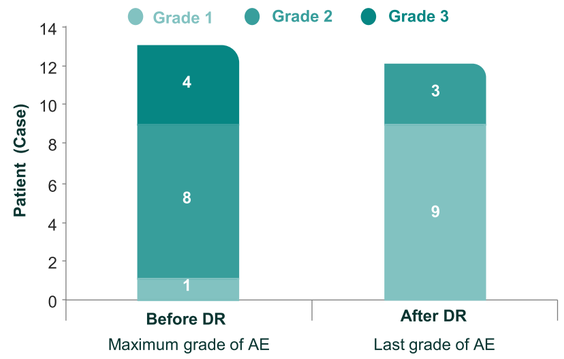
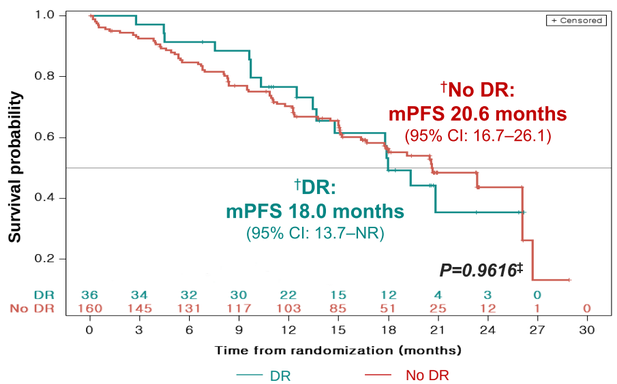


Figure 2. PFS for patients with and without DR within the first 12 months of treatment initiation (LASER301)



Hazard ratio for patients with no DR (Ref: DR): 0.99 (95% CI 0.58–1.67)
PFS was evaluated based on investigator assessment in LASER301.
Median PFS (mPFS) and 95% CI were calculated using the Kaplan-Meier estimate.
†DR: Patients with DR within the first 12 months of lazertinib initiation; No DR: Patients without DR within the first 12 months of lazertinib initiation.
‡ P-value from log-rank test.

- In patients with DR due to any AEs, clinical efficacy was not compromised by DR of lazertinib to 160 mg.
- PFS in patients with and without DR within the first 12 months of treatment initiation was similar (mPFS 18 vs 21 months; log-rank *P=0.9616*) (**Figure 1**).

4. CONCLUSIONS

- In this pooled analysis, paresthesia and related AEs occurred in 48% of the patients who received lazertinib. These AEs were mostly **mild or moderate** in severity (grade 1 or 2) **rarely leading to dose discontinuation** and were manageable with pharmacological interventions and/or dose adjustment.
- Nature of paresthesia and related AEs **appeared reversible**, consistent with recent data suggesting that paresthesia induced by EGFR TKI treatment is mechanistically distinct from chemotherapy-induced peripheral neuropathy.[3]
- Prompt dose adjustment upon onset of paresthesia may improve tolerability of lazertinib treatment **without compromising clinical efficacy.**
- Further studies are required to understand and manage risk factors for paresthesia induced by EGFR TKI treatment.

REFERENCES

1. Cho, B.C., et al., Lazertinib versus gefitinib as first-line treatment in patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC): Results From LASER301. J Clin Oncol, 2023:101200jco2300515.
2. Ahn, M.J., et al., Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, Phase 1-2 study. Lancet Oncol, 2019. 20(12):1681-1690
3. Kim, H., et al. EGFR inhibitor lazertinib activates a subset of 1 sensory neurons via TRPA1 in mice. Poster presented at: The 26th Annual Meeting of the Korean Society for Brain and Neural Sciences; Sep 2023; Korea.

DISCLOSURES & CONTACT

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