



P3.271. Osimertinib with or without Bevacizumab as first-line treatment in metastatic NSCLC with EGFR L858R Mutation (CTONG2002/FLAIR)



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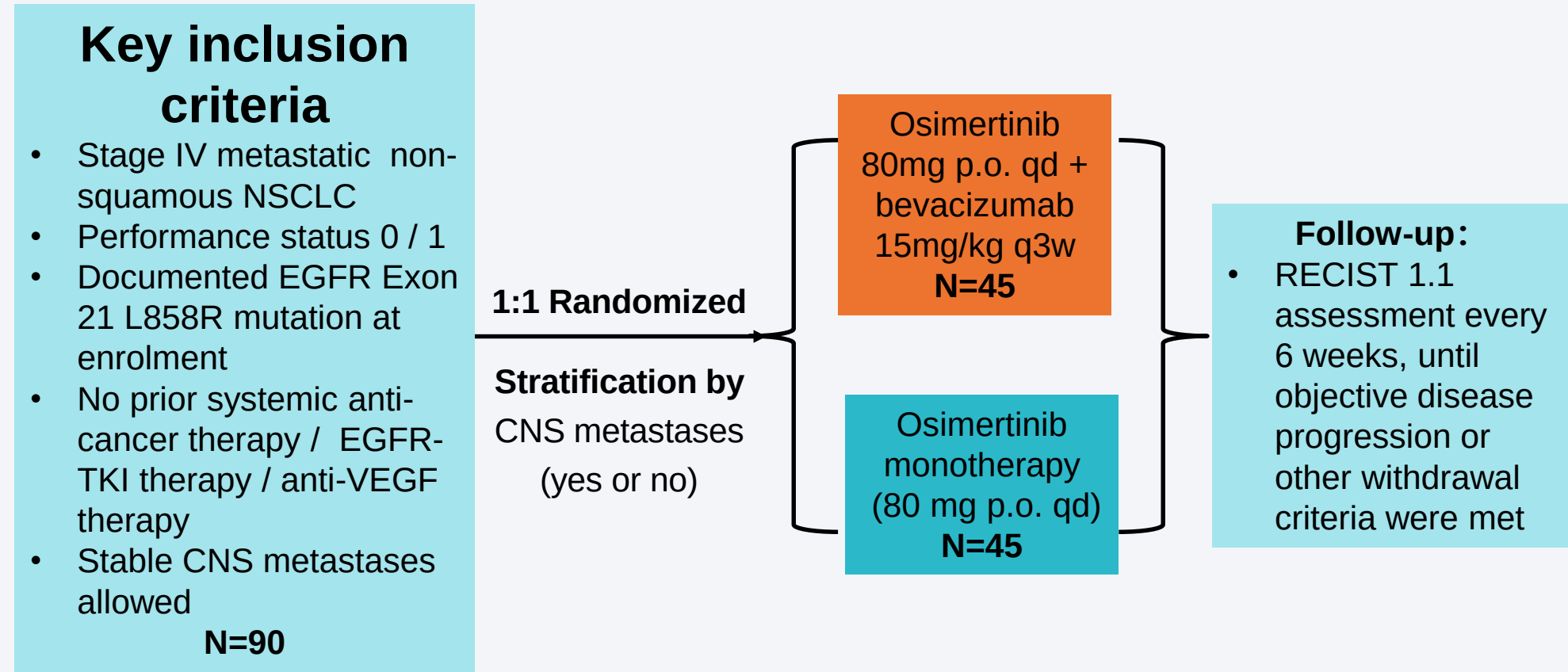
INTRODUCTION

- Osimertinib has emerged as standard first-line treatment for patients with advanced EGFR mutated non-small cell lung cancer (NSCLC).¹⁻²
- However, patients with EGFR L858R mutation had suboptimal treatment outcomes with Osimertinib monotherapy compared with those with EGFR 19 deletion.
- Prior studies³⁻⁷ suggest that adding bevacizumab to EGFR-TKI improve efficacy in first-line setting. Nevertheless, subgroup analyses focusing on patients harboring EGFR L858R mutation from prior studies were exploratory in nature. The clinical benefit conferred by combining an Osimertinib with bevacizumab in this specific population remains to be further investigated and validated.
- The prospective, multi-center, randomized, phase II study (NCT04988607, CTONG2002, FLAIR), aiming to evaluate the efficacy and safety of Osimertinib plus bevacizumab versus Osimertinib monotherapy as first-line treatment in patients with metastatic NSCLC harboring EGFR L858R mutation.

METHODS

- Patients with EGFR L858R-mutant, stage IVA/IVB or recurrent non-squamous NSCLC, ECOG PS 0-1, were stratified by CNS metastases and randomized 1:1 to first-line osimertinib plus bevacizumab or osimertinib monotherapy until progression or discontinuation.
- The primary endpoint was PFS; secondary endpoints included 24-month OS rate, TTF, ORR, DCR, DoR, CNS-PFS, CNS-ORR, and safety. Data cutoff: 06 January 2026.

Figure 1. Study design



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
- **Secondary endpoints:** ORR, DCR, DoR, CNS PFS & ORR & DCR & DoR, 24m OS rate, TTF, Safety profile

The intention-to-treat (ITT) population included all randomized patients and was analyzed according to the treatment group assigned at randomization. The full analysis set (FAS) included all patients who have taken at least one dose of protocol-assigned treatment and had adequate baseline and/or post-baseline efficacy assessment, according to the treatment assigned at randomization. Efficacy analyses were based on the full analysis set (FAS; n=88). Safety analyses included all treated patients (n=88). For primary endpoints, we determined that approximately 68 events of progression or death in a total of 90 randomly assigned participants would provide at approximately 68% power to detect a hazard ratio (HR) of 0.6 at a two-sided alpha level of 0.1. All analyses were performed using SAS 9.4.

CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; qd, once daily; TKI, tyrosine kinase inhibitor; ORR, objective response rate; DoR, duration of response; DCR, disease control rate; PD, progression disease; TTF, time to treatment failure; OS, overall survival.

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RESULTS

Baseline characteristics

- Between September 2021 to August 2023, 90 patients were randomized (45 per arm). 88 patients received at least one dose of protocol-assigned treatment, including 43 in the Osimertinib plus bevacizumab group and 45 in the Osimertinib monotherapy group.
- Baseline characteristics were generally balanced across arms (Table 1).

Table 1. Baseline characteristics

Characteristic, n (%)	Osimertinib plus bevacizumab (N=43)	Osimertinib monotherapy (N=45)
Age , median(range), years	59.0(31.0–92.0)	59.0(41.0–82.0)
Sex		
Female	21 (48.8%)	28 (62.2%)
Male	22 (51.2%)	17 (37.8%)
Smoking status		
Never	30 (69.8%)	33 (73.3 %)
Current/Stop	13 (30.2%)	12 (26.7%)
ECOG PS		
0	8 (18.6%)	13 (28.9 %)
1	35 (81.4%)	32 (71.1 %)
Pathological diagnosis		
Adenocarcinoma	43 (100.0%)	45 (100.0%)
Squamous cell carcinoma	0	0
Large cell carcinoma	0	0
Clinical stage at screening		
IV	42 (97.7 %)	45 (100.0%)
Recurrence ^a	1 (2.3 %)	0
Baseline brain metastases		
Yes	19 (44.2%)	19 (42.2 %)
No	24 (55.8 %)	26 (57.8 %)
Baseline bone metastases		
Yes	27 (62.8%)	25 (55.6 %)
No	16 (37.2 %)	20 (44.4 %)

^a Patients with relapse in clinical stage IV are classified as "recurrence"

Efficacy

- Median PFS was significantly longer with Osimertinib plus bevacizumab versus Osimertinib monotherapy (19.8 vs 12.6 months; HR 0.53 [90% CI, 0.35-0.80]) (Figure 2).
- PFS benefit was consistent across pre-defined subgroups (Figure 3).
- The objective response rate was 69.8% (95%CI: 53.9–82.8) in the Osimertinib plus bevacizumab group and 60.0% (95%CI: 44.3–74.3) in the Osimertinib monotherapy group (Table 2).

Figure 2. Kaplan–Meier analysis of progression-free survival

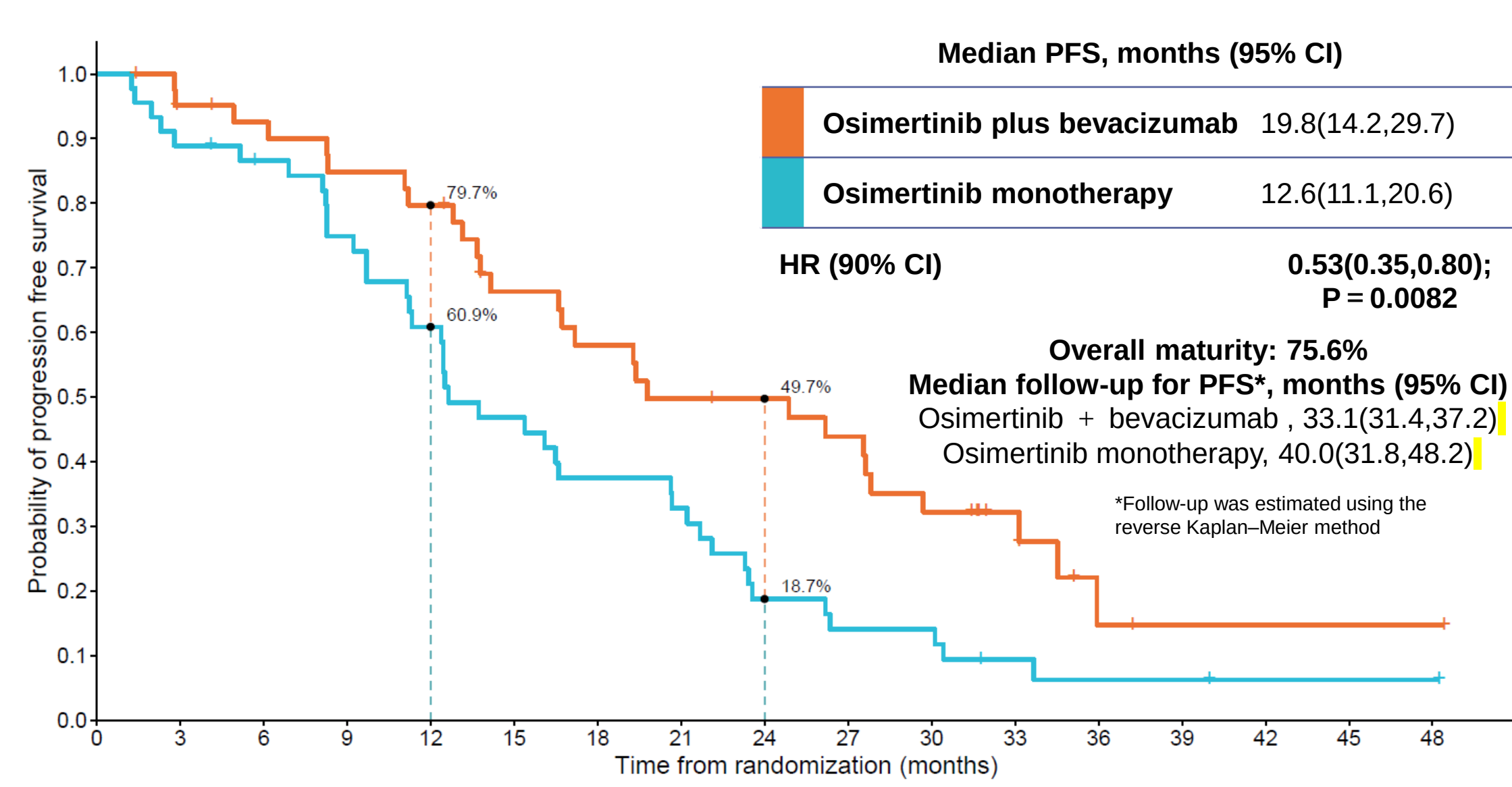


Figure 3. Subgroup analysis of progression-free survival

Subgroup	Osimertinib+Bevacizumab (Event/Total)	Osimertinib monotherapy (Event/Total)	HR (95% CI)
Gender			
Male	16/22	13/17	0.753 (0.361 - 1.570)
Female	12/21	27/28	0.345 (0.171 - 0.693)
Age			
<65 yrs	18/28	25/28	0.468 (0.253 - 0.865)
≥65 yrs	10/15	15/17	0.701 (0.310 - 1.582)
Smoke			
Never	18/30	31/33	0.406 (0.225 - 0.735)
Current or stop	10/13	9/12	0.953 (0.383 - 2.371)
ECOG			
0	6/8	11/13	0.977 (0.352 - 2.708)
1	22/35	29/32	0.433 (0.245 - 0.764)
Brain metastasis			
Yes	12/19	18/19	0.478 (0.225 - 1.015)
No	16/24	22/26	0.569 (0.298 - 1.087)
Bone metastasis			
Yes	18/27	25/25	0.493 (0.263 - 0.924)
No	10/16	15/20	0.569 (0.254 - 1.277)
Overall	28/43	40/45	0.528 (0.323 - 0.863)

NE, not estimable.

Table 2. Summary of tumor response

	Osimertinib plus bevacizumab (N=43)	Osimertinib monotherapy (N=45)
Type of response, n (%)		
Complete response	0	0
Partial response	30 (69.8 %)	27 (60.0 %)
Stable disease	13 (30.2 %)	16 (35.6 %)
Progression Disease	0	2 (4.4%)
Objective response rate, % of patients (95% CI)	69.8% (53.9–82.8)	60.0% (44.3–74.3)
Disease control rate, % of patients (95% CI)	100% (91.2–100.0)	95.6% (84.9–99.5)
Median duration of response, months (95% CI)	19.4 (12.4–28.3)	11.2 (10.0–19.4)

CONCLUSION

- FLAIR study demonstrated Osimertinib plus bevacizumab as first-line treatment significantly improved progression-free survival vs. Osimertinib monotherapy in metastatic NSCLC patients with EGFR L858R mutation.
 - Median PFS: 19.8 vs. 12.6 months; HR 0.53; 90% CI, 0.35-0.80; P = 0.0082
 - PFS benefit was consistent across all prespecified subgroups
- The safety profile of Osimertinib plus bevacizumab was consistent with the established profiles of each agent and no new safety signals were identified.
- Osimertinib plus bevacizumab offers a potential treatment option as first-line treatment in metastatic NSCLC harboring EGFR L858R mutation.

Safety summary

- The median duration of total Osimertinib exposure was 19.0 (range, 2.1–39.3) months in the Osimertinib plus bevacizumab and 14.9 (range, 1.2–48.8) months in the Osimertinib monotherapy. The median duration of bevacizumab exposure in the Osimertinib plus bevacizumab group was 12.4 (range 0.7–39.3) months.
- The most common TRAEs were proteinuria in osimertinib plus bevacizumab, and platelet count decreased and rash in osimertinib monotherapy. No new safety signals were identified (Figure 4).

Table 3. Safety summary

Patients with Adverse events, n (%)	Osimertinib plus bevacizumab (N=43)	Osimertinib monotherapy (N=45)
Treatment-emergent adverse events	43 (100 %)	42 (93.3 %)
Grade ≥ 3	23 (53.5 %)	16 (35.6 %)
Serious	11 (25.6 %)	13 (28.9 %)
leading to discontinuation	15 (34.9 %)	2 (4.4 %)
leading to interruption	26 (60.5 %)	9 (20.0 %)
Leading to Death*	2 (4.7%)	1 (2.2%)
Treatment-related adverse events	42 (97.7 %)	39 (86.7 %)
Grade ≥ 3	15 (34.9 %)	8 (17.8 %)
Serious	4 (9.3 %)	3 (6.7 %)
leading to discontinuation	15 (34.9 %)	1 (2.2 %)
leading to interruption	18 (41.9 %)	4 (8.9 %)
Leading to Death	0	0

*Two deaths (4.7%) occurred in the Osimertinib plus bevacizumab group, both attributed to COVID-19 pneumonia, while one death occurred in the osimertinib group with an unknown cause.

Figure 4. Treatment-related adverse events with Frequency ≥ 10%

