

INTRODUCTION

Single-agent checkpoint inhibitor therapy achieves suboptimal outcomes in patients with advanced *RET* fusion-positive lung cancer. Prospective data on the role of adding checkpoint inhibitor therapy to platinum doublet chemotherapy has not previously been available.

METHODS

In the global, registrational, phase 3 LIBRETTO-431 study, patients with *RET* fusion-positive lung cancer were randomized to receive selpercatinib or platinum-doublet chemotherapy (carboplatin/cisplatin and pemetrexed) with or without pembrolizumab. An analysis of outcomes including progression-free survival (PFS) and overall survival (OS) in patients treated with chemoimmunotherapy and chemotherapy alone was performed. The decision to include pembrolizumab was left to provider discretion.

Statistics. Baseline characteristics were compared by treatment arm utilizing Fisher’s exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Blinded independent central review (BICR) progression-free survival (PFS) was defined as time from randomization to BICR-assessed disease progression (RECIST v1.1) or death from any cause in the absence of BICR-documented progressive disease, with patients censored at the last adequate tumor assessment. Overall survival (OS) was defined as time from randomization to death from any cause. Duration of response (DOR) was defined as time from first documented complete/partial response (CR/PR, RECIST v1.1) to first occurrence of disease recurrence, progression or death. OS and DOR were calculated using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. Overall response rate (ORR) was defined as the proportion of patients achieving a best overall response (BOR) of CR/PR. PD-L1 status was categorized by TPS as negative, 1-49%, ≥50%, or positive when the exact value was unspecified.

DISCUSSION AND CONCLUSION

- In patients with advanced *RET* fusion-positive lung cancer treated in global, multicenter, phase 3 LIBRETTO-431 trial, PFS, OS and DOR outcomes were not significantly different in this secondary analysis.
- In the chemoimmunotherapy-treated group, PFS was not significantly different by PD-L1 status.
- Chemotherapy alone is a reasonable strategy for *RET* fusion-positive tumors.
- Based on the overall findings from LIBRETTO-431, selective RET inhibitors remain the preferred first-line therapy for patients with advanced *RET* fusion-positive NSCLC.

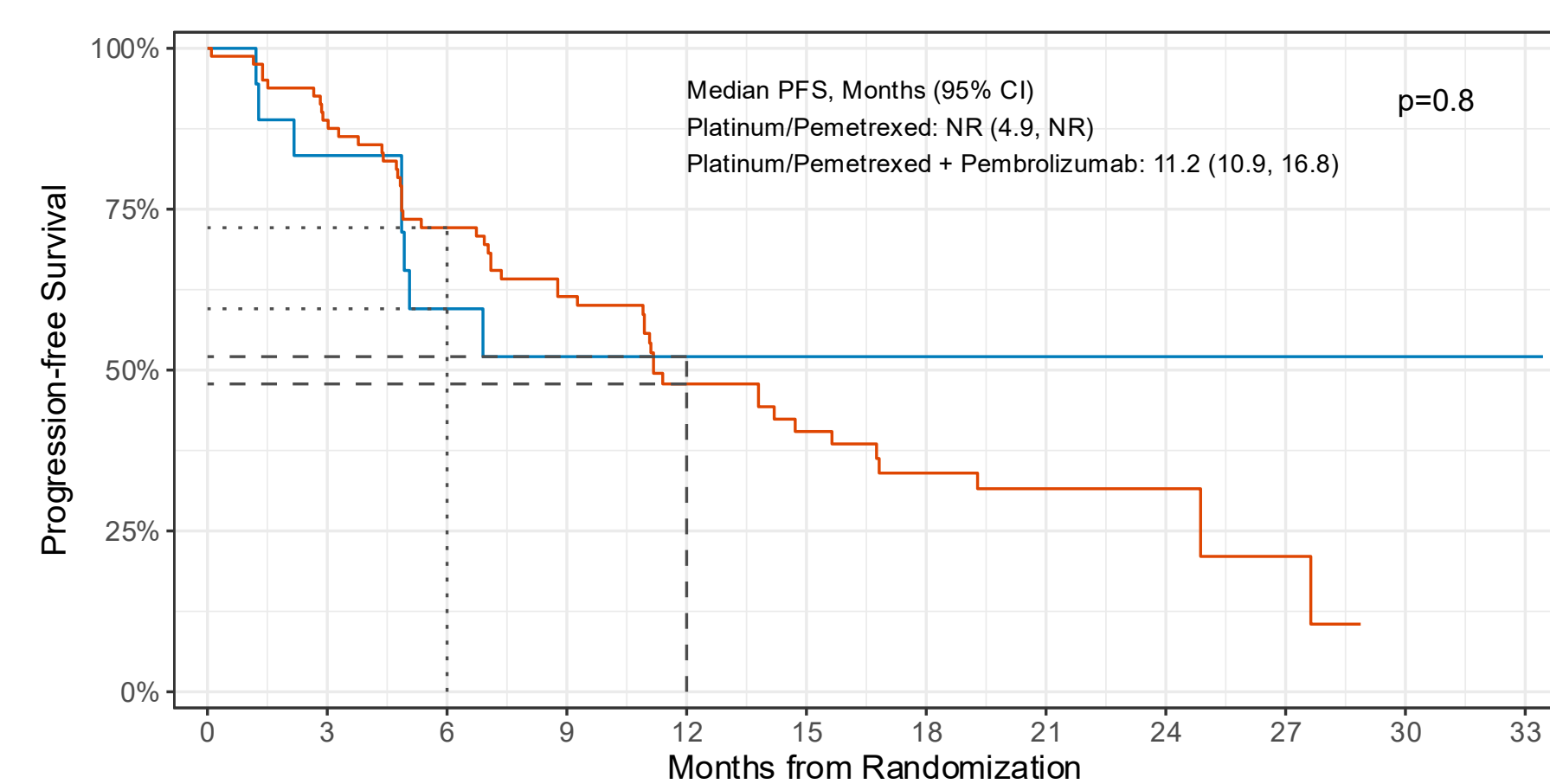
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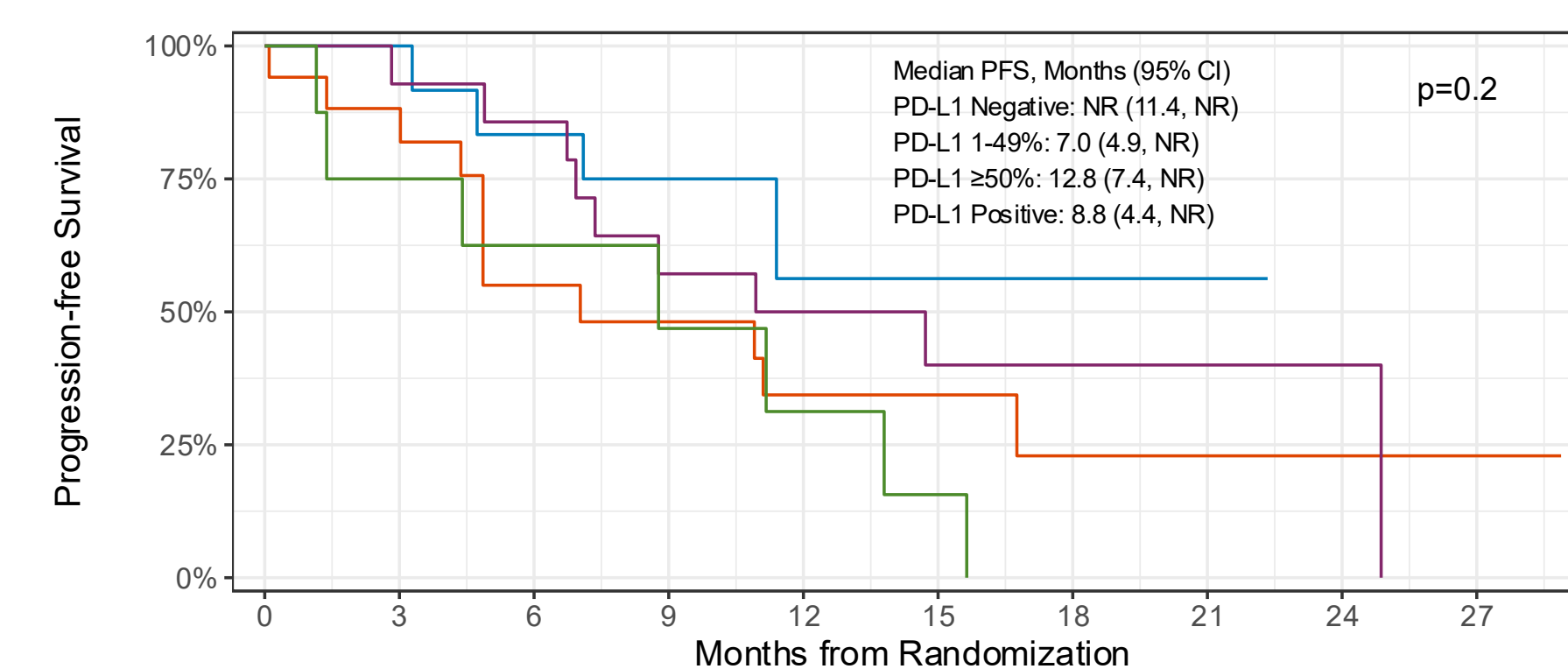
This work was supported by the National Cancer Institute/National Institutes of Health P30CA008748, 1R01CA25917701, 1R01CA251591 grants, and The Happy Lungs Project. This abstract is based on research using data from data contributor Eli Lilly that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and Vivli and Eli Lilly are not in any way responsible for, the contents of this publication.

RESULTS

1A



1B



1C

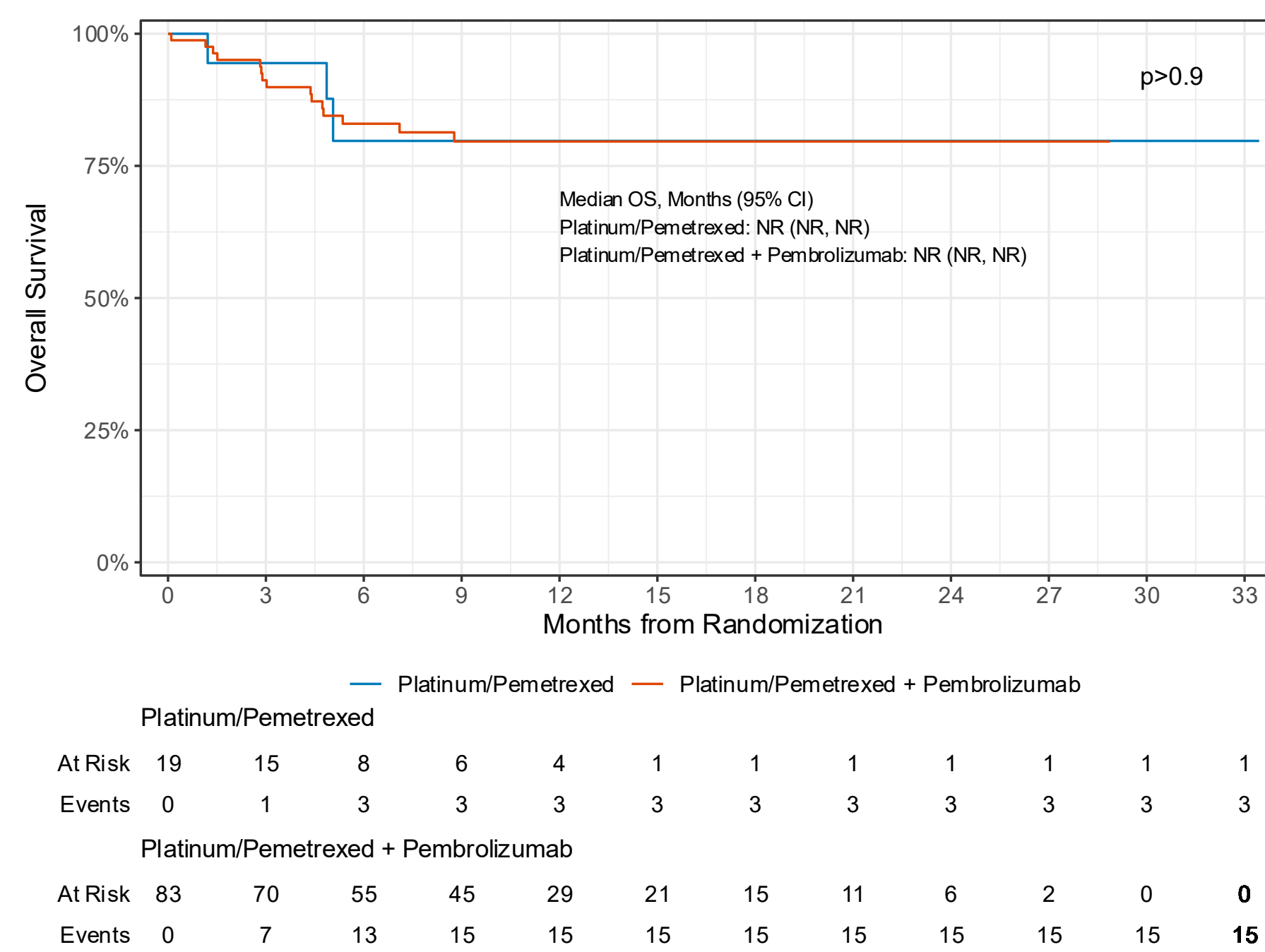


Figure 1. Survival. (A) Kaplan-Meier curves of PFS in chemotherapy (blue) and chemoimmunotherapy (red) groups are shown. (B) Kaplan-Meier curves of PFS by PD-L1 status in the chemoimmunotherapy group are shown. (C) Kaplan-Meier curves of OS in chemotherapy (blue) and chemoimmunotherapy (red) groups are shown. CI, confidence interval; NR, not reached.

Characteristic	Overall N = 102 ²	Platinum/Pemetrexed N = 19 ²	Platinum/Pemetrexed + Pembrolizumab N = 83 ²	p-value ²
Age	63 (53.0, 69)	65 (55.0, 70)	62 (51.0, 69)	0.4
Sex				0.5
Female	57 (55.9%)	9 (47.4%)	48 (57.8%)	
Male	45 (44.1%)	10 (52.6%)	35 (42.2%)	
Region of Enrollment				0.4
East Asia	51 (50.0%)	10 (52.6%)	41 (49.4%)	
Europe	42 (41.2%)	6 (31.6%)	36 (43.4%)	
North America	2 (2.0%)	1 (5.3%)	1 (1.2%)	
Other	7 (6.9%)	2 (10.5%)	5 (6.0%)	
Smoking Status				0.10
Never	68 (66.7%)	9 (47.4%)	59 (71.1%)	
Former	32 (31.4%)	10 (52.6%)	22 (26.5%)	
Current	2 (2.0%)	0 (0.0%)	2 (2.4%)	
ECOG Performance Status Score				0.014
0	40 (39.2%)	13 (68.4%)	27 (32.5%)	
1	58 (56.9%)	6 (31.6%)	52 (62.7%)	
2	4 (3.9%)	0 (0.0%)	4 (4.8%)	
Stage of Disease				0.8
III	8 (7.8%)	1 (5.3%)	7 (8.4%)	
IVA	45 (44.1%)	10 (52.6%)	35 (42.2%)	
IVB	49 (48.0%)	8 (42.1%)	41 (49.4%)	
PD-L1 Status				0.3
PD-L1 Negative	20 (29.9%)	8 (50.0%)	12 (23.5%)	
PD-L1 1-49%	21 (31.3%)	4 (25.0%)	17 (33.3%)	
PD-L1 ≥50%	17 (25.4%)	3 (18.8%)	14 (27.5%)	
PD-L1 Positive ³	9 (13.4%)	1 (6.3%)	8 (15.7%)	
Unknown	35	3	32	
RET Fusion Result				>0.9
Positive ⁴	39 (38.2%)	8 (42.1%)	31 (37.3%)	
KIF5B::RET	50 (49.0%)	9 (47.4%)	41 (49.4%)	
CCDC6::RET	9 (8.8%)	1 (5.3%)	8 (9.6%)	
Other	4 (3.9%)	1 (5.3%)	3 (3.6%)	

¹Median (Q1, Q3); n (%)

²Wilcoxon rank sum test; Fisher's exact test

³PD-L1 positivity reported; exact expression level unspecified in the original report

⁴RET fusion positive, subtype unspecified

Table 1. Patient Characteristics. The baseline clinical and demographic characteristics of patients treated with chemotherapy, with or without immunotherapy, on LIBRETTO-431 are summarized.

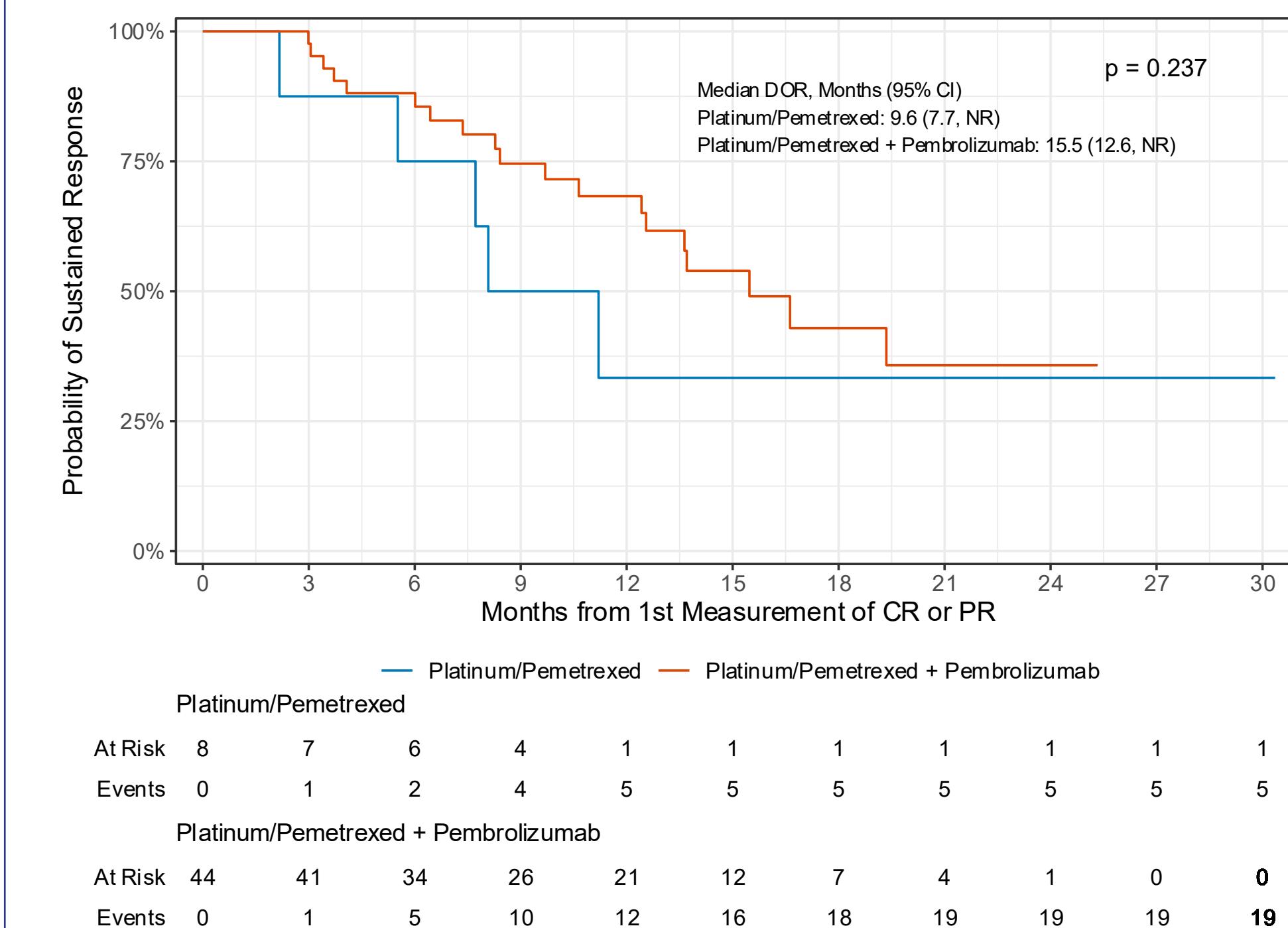


Figure 2. Duration of Response (DOR). Duration of response (DOR) in chemotherapy and chemoimmunotherapy groups. CI, confidence interval; CR, complete response; NR, not reached; PR, partial response.