

Clinical outcomes of neoadjuvant therapy in early-stage NSCLC harboring ALK, ROS1, or RET fusions

Jaime Rubio-Perez¹, Sameh Daher^{1,2}, Matteo Repetto¹, Alessandro Di Federico¹, M. Lomibao¹, Ling Feng Yi¹, Alexander Drilon^{1,3}

¹Memorial Sloan Kettering Cancer Center, New York, USA 1, ²Affiliatin Ramban HealthCare Campus, Technion, Haifa, Israel, ³Weil Cornell Medical College, New York, USA

Correspondence: jrubioperez05@gmail.com / rubiopj@mskcc.org



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INTRODUCTION

- Oncogenic fusions involving *ALK/ROS1/RET* define a distinct subset of non-small cell lung cancer (NSCLC) characterized by sensitivity to tyrosine kinase inhibitors (TKIs)¹.
- While targeted therapies have improved outcomes in advanced disease, the optimal perioperative management of early-stage fusion-positive NSCLC remains undefined.
- PD-L1 expression is the only validated biomarker guiding neoadjuvant treatment; however, oncogenic drivers like EGFR, ALK and recently RET are used to determine standard or investigational perioperative strategies (e.g., considering adjuvant TKI therapy over immunotherapy)²⁻³.
- The NeoADAURA trial⁴ showed that adding osimertinib to neoadjuvant chemotherapy improved major pathological response rates, although no event-free survival (EFS) benefit had been observed at the time of analysis. In the adjuvant setting, only EGFR and ALK and RET fusion-positive NSCLC have demonstrated benefit with targeted therapy. We aimed to characterize treatment patterns and clinical outcomes in patients with resectable ALK-, ROS1-, or RET-rearranged NSCLC treated with neoadjuvant therapy.

METHODS

- We conducted a retrospective, single-institution analysis of patients with early-stage NSCLC (stage II/III) with ALK/ROS1/RET fusion-positive patients who received perioperative treatment between 2012-2025.
- We selected patients who were treated with either neoadjuvant chemotherapy or a TKI, and real-world management was described. Clinical data, treatment patterns, and outcomes were collected.
- EFS was defined as the time from early-stage diagnosis to recurrence, treatment failure, or death. Overall survival (OS) was measured from diagnosis to death from any cause.
- Exploratory analyses included an evaluation of outcomes according to neoadjuvant treatment type and adjuvant TKI exposure. Patterns of recurrence were described.

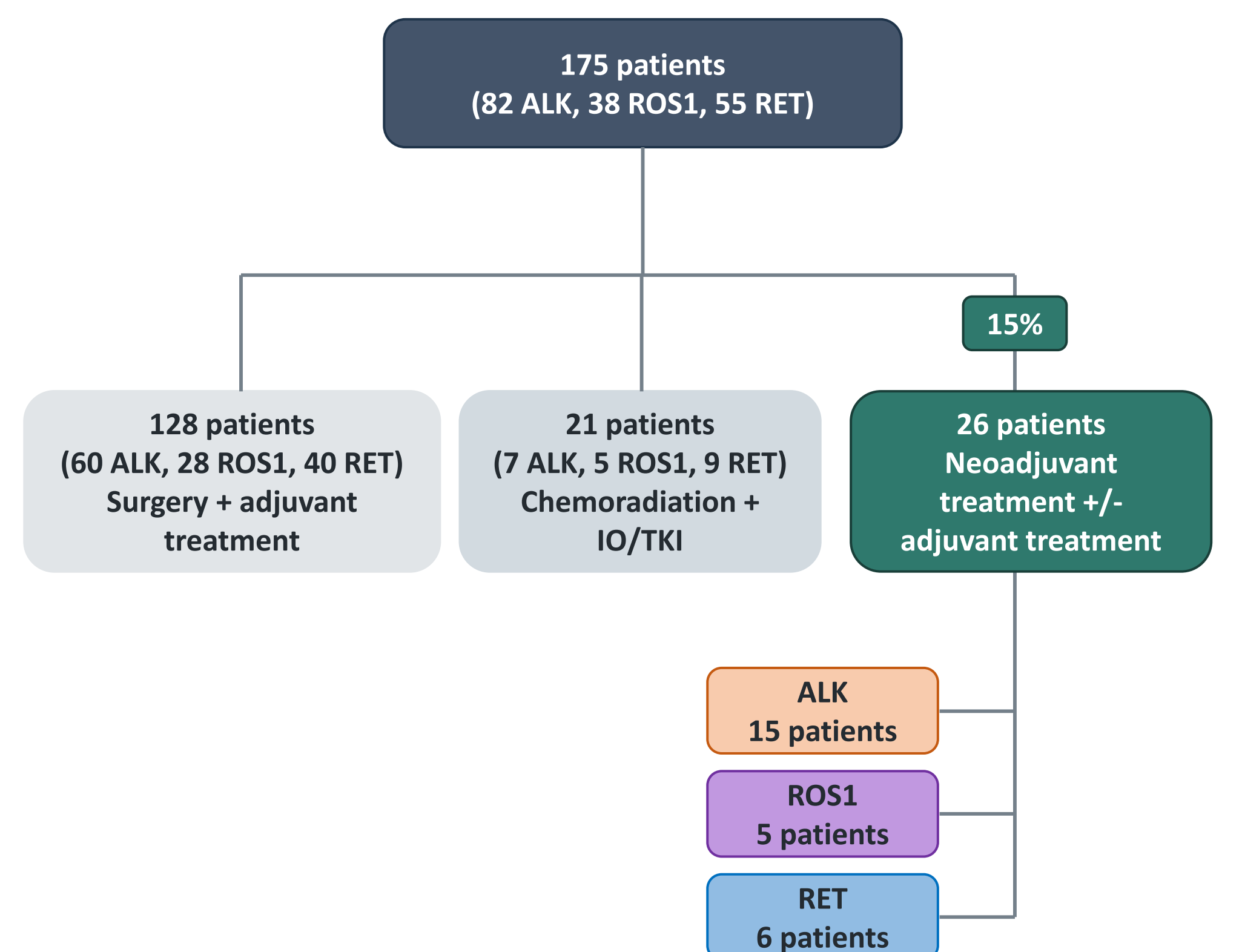


Figure 1. Flow diagram of patient selection for the neoadjuvant treatment analysis in patients with ALK, RET, and ROS1 fusions.

RESULTS

	ALK N = 15 ¹	RET N = 6 ¹	ROS1 N = 5 ¹
Sex			
Female	13 (87%)	2 (33%)	4 (80%)
Male	2 (13%)	4 (67%)	1 (20%)
Age	53 (41-58)	54 (49-70)	51 (45-60)
Smoking status			
Never	9 (60%)	4 (67%)	3 (60%)
Light smoker	6 (40%)	2 (33%)	6 (40%)
Heavy smoker	9 (60%)	4 (67%)	3 (60%)
T			
1	4 (26%)	1 (17%)	2 (40%)
2	6 (40%)	3 (50%)	2 (40%)
3	1 (6.7%)	1 (17%)	0 (0%)
4	4 (27%)	1 (17%)	1 (20%)
N			
0	0 (0%)	1 (17%)	0 (0%)
1	3 (20%)	1 (17%)	1 (20%)
2	10 (67%)	4 (67%)	4 (80%)
3	2 (13%)	0 (0%)	0 (0%)
Stage			
IIA	1(7%)	0 (0%)	0 (0%)
IIB	2 (13%)	1 (17%)	3 (60%)
IIIA	5 (33%)	5 (83%)	1 (20%)
IIIB	7 (47%)	0 (0%)	1 (20%)
Histology			
LUAD	15 (100%)	6 (100%)	5 (100%)

¹ n (%); Median (Q1-Q3); LUAD= Lung Adenocarcinoma

Treatment strategy in individual patients

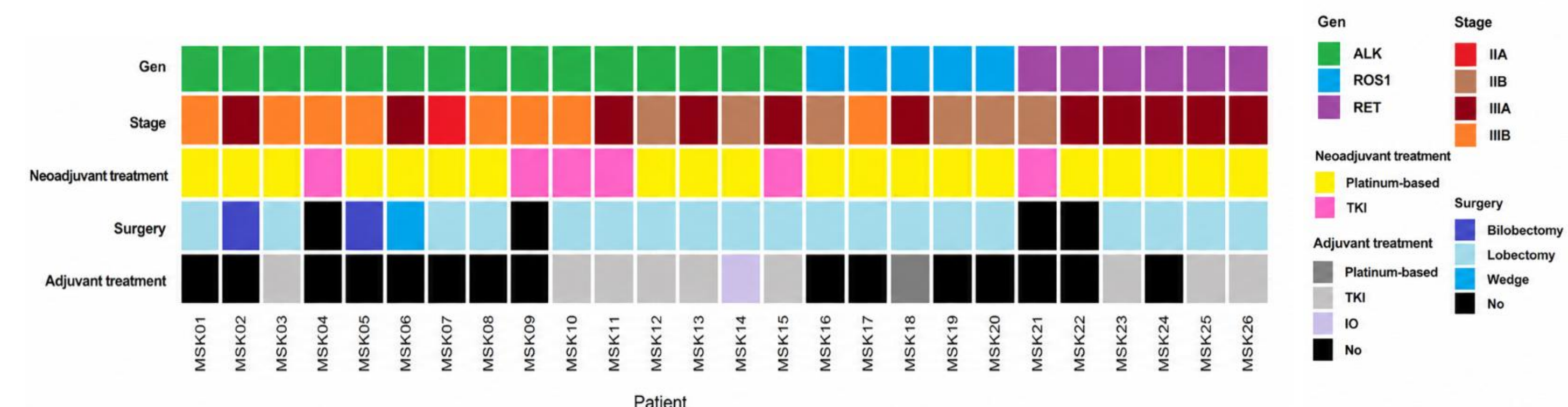


Figure 1. Heatmap summarizing the genotype, disease stage, and perioperative treatment strategies.

****5 ALK patients and 1 RET patient received neoadjuvant targeted therapy with a TKI, three of whom did not subsequently undergo surgery. Among the three patients who underwent surgery, 100% continued TKI therapy after surgery.**

****6 more patients received adjuvant treatment with a TKI (3 ALK and 3 RET patients).**

Treatment pathway

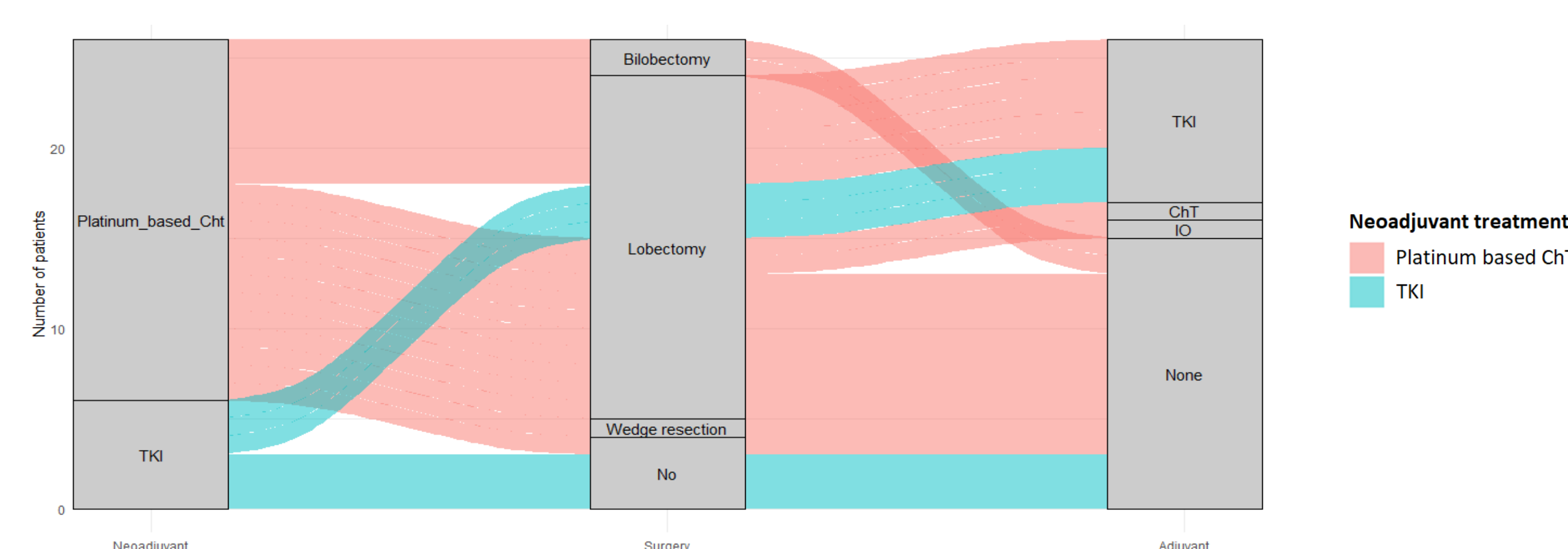
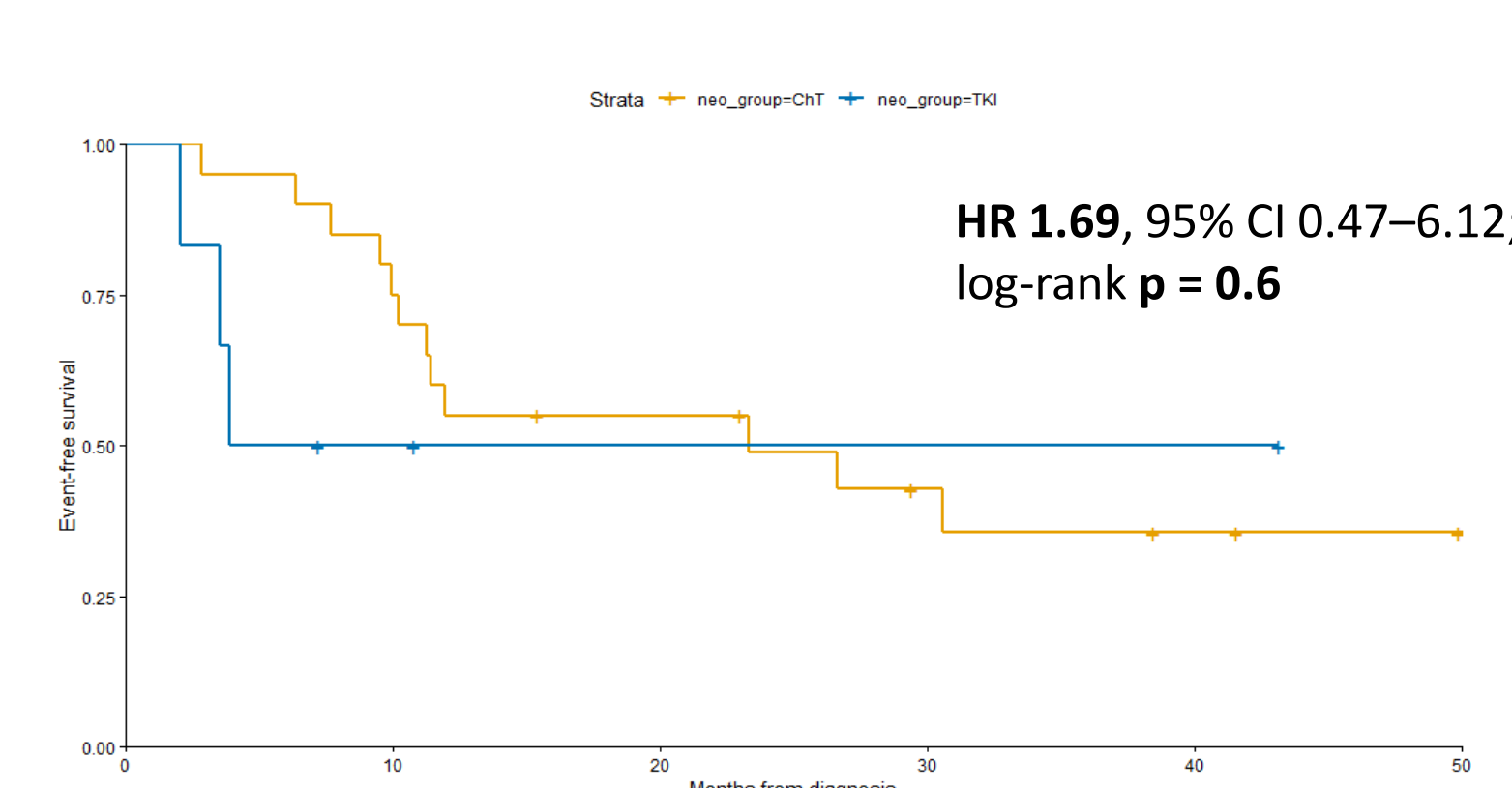


Figure 2. Treatment pathways of the study population from diagnosis onwards.

A. EFS according to neoadjuvant treatment



B. EFS according to adjuvant TKI

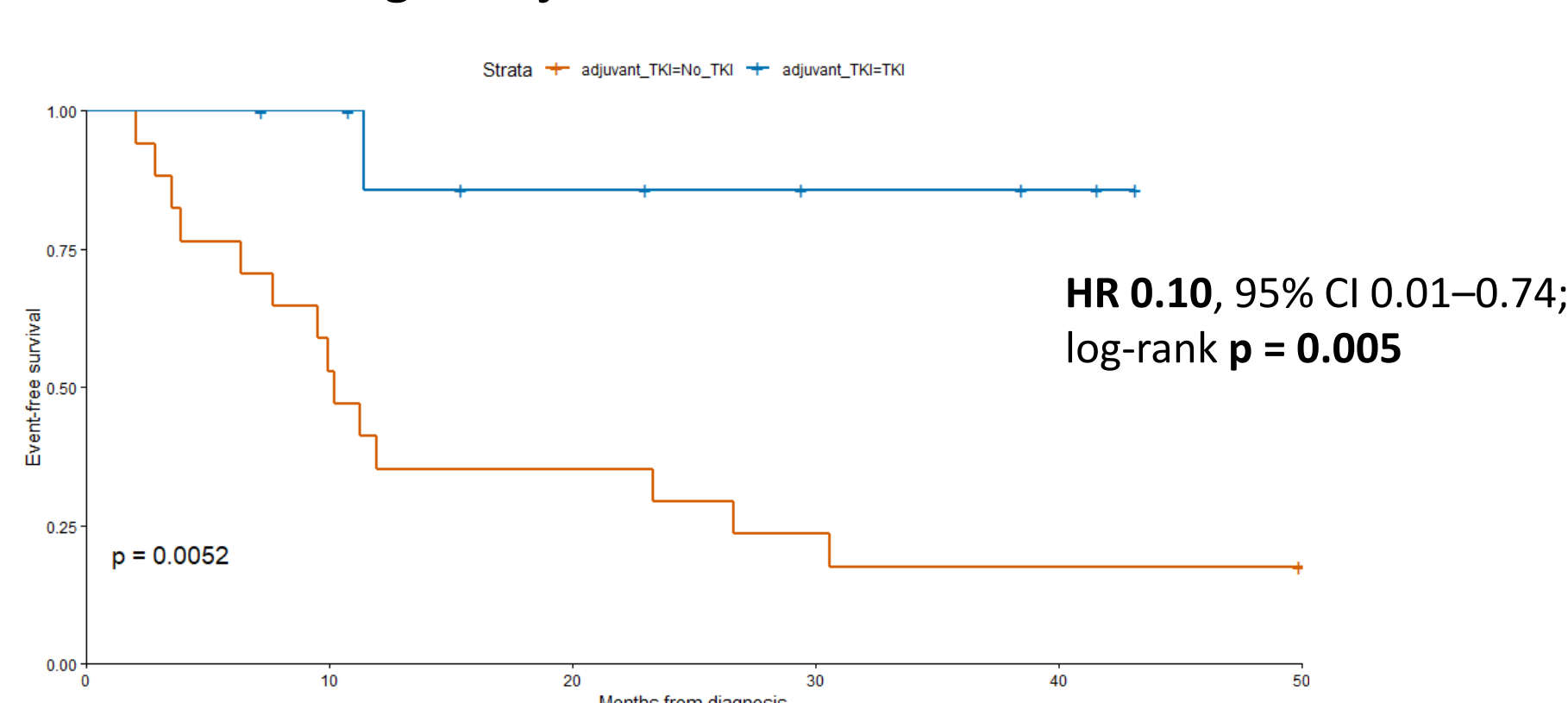
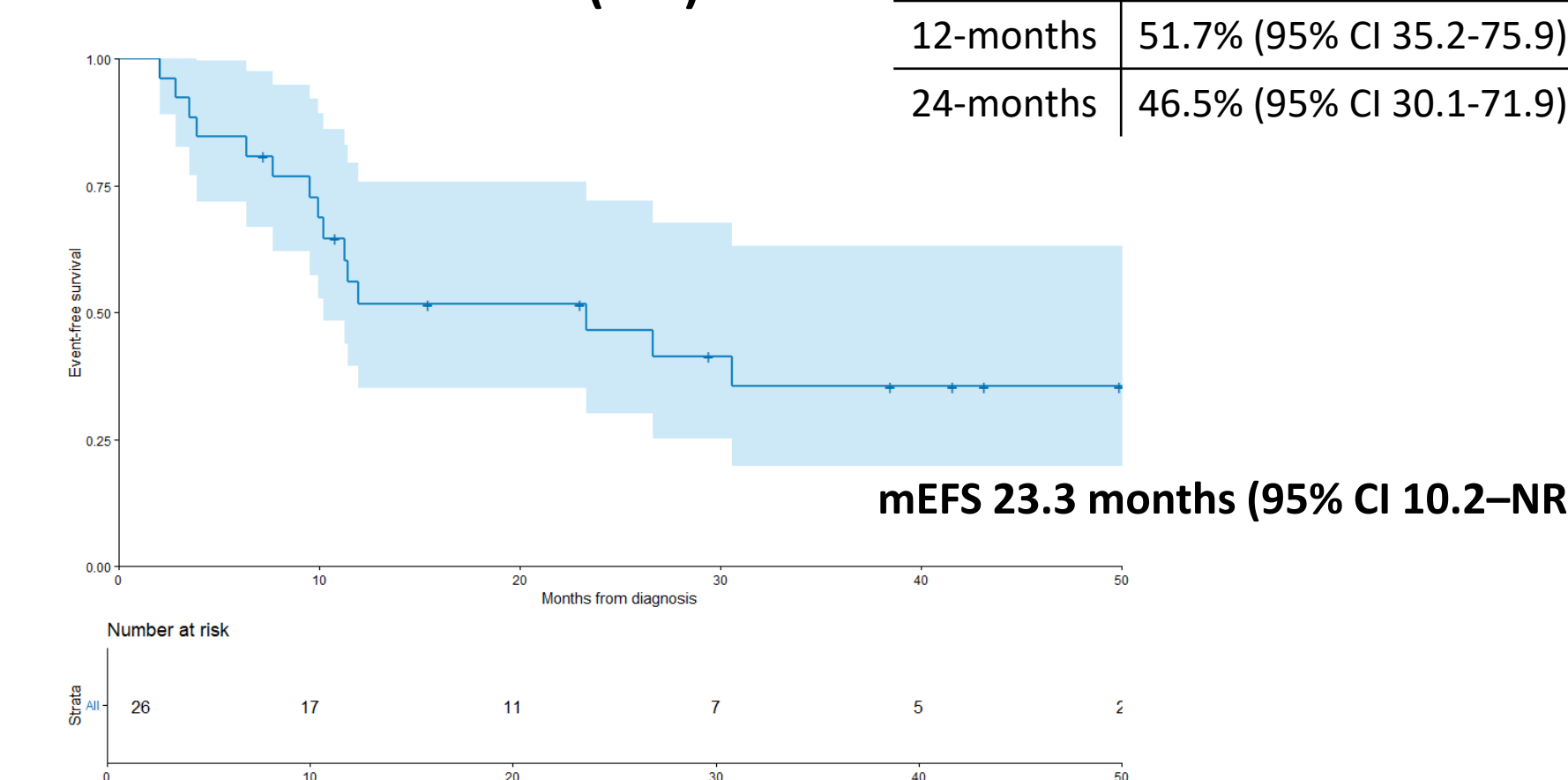


Figure 4. Event-free survival according to treatment strategy. Kaplan-Meier curves showing event-free survival according to (A) neoadjuvant treatment (platinum-based chemotherapy in orange vs TKI therapy in blue) and (B) adjuvant TKI exposure (TKI therapy in blue vs no TKI therapy in red).

A. Event free survival (EFS)



B. Overall survival (OS)

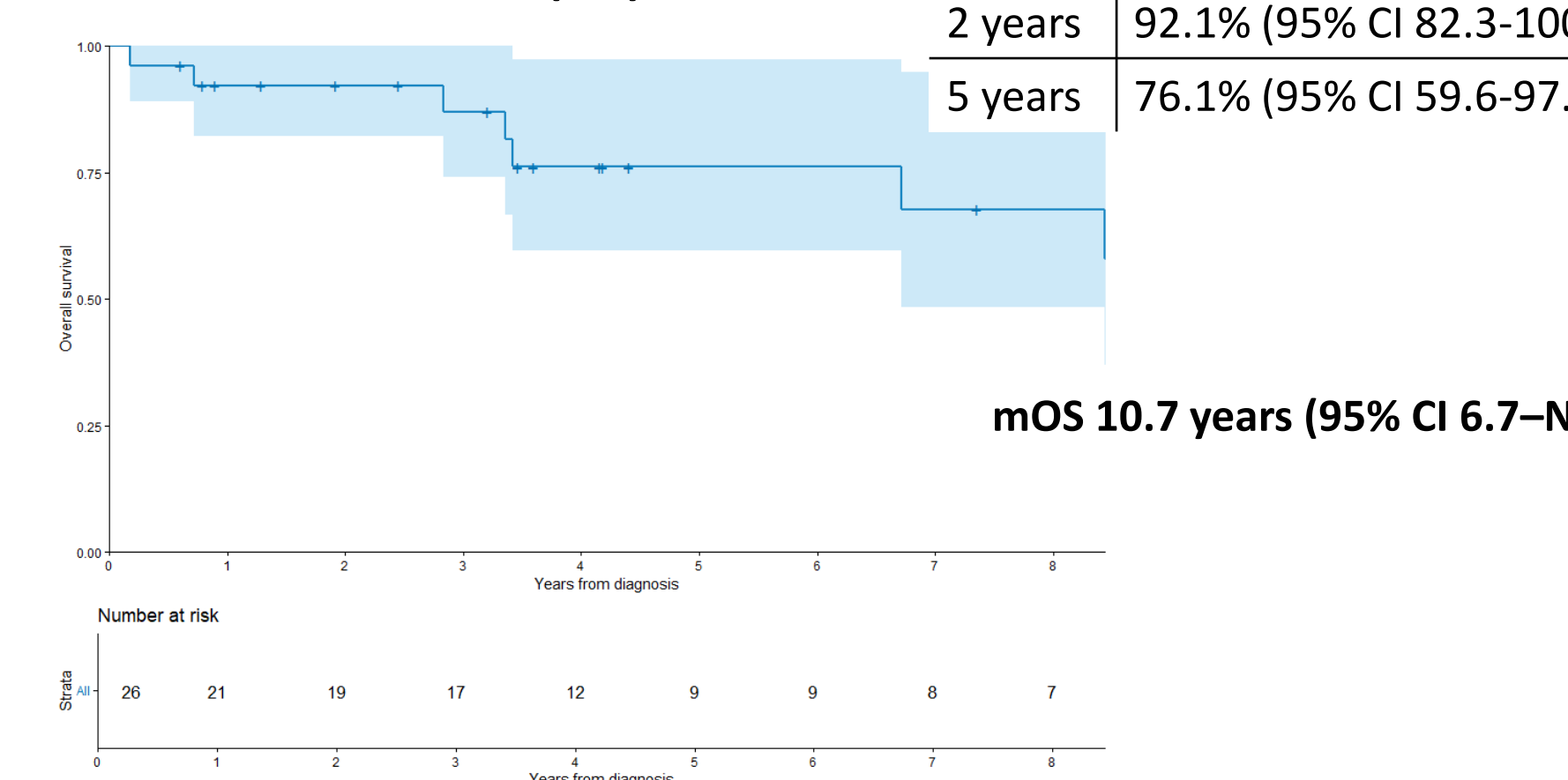


Figure 3. Kaplan-Meier EFS (A) and OS (B) in patients with resectable ALK-, ROS1-, or RET-rearranged NSCLC treated with neoadjuvant therapy.

***Median follow-up was 4.4 years. Sixteen EFS events and nine deaths were observed during follow-up.**

Site of recurrence in individual patients

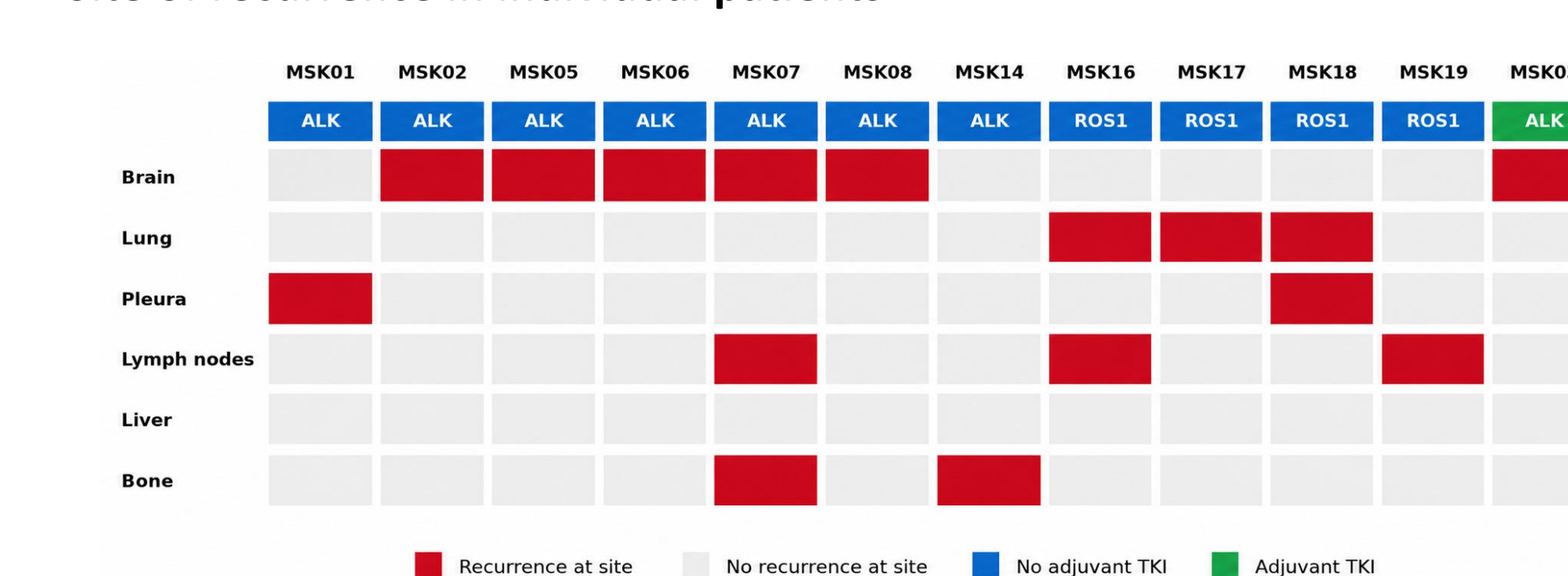


Figure 5. Recurrence Patterns and Sites According to Adjuvant TKI Treatment. Patient 03 was an ALK patient on adjuvant crizotinib.

DISCUSSION AND CONCLUSION

- Whereas EFS was not significantly different between neoadjuvant chemotherapy and TKI therapy, **adjuvant TKI therapy was associated with improved EFS.**
- Benefit may depend more on genotype-directed therapy than treatment timing, supporting the integration of targeted therapies into both the neoadjuvant and adjuvant setting.
- Newer-generation TKIs with improved safety and tolerability profiles have been developed, strengthen the rationale for their use in early-stage disease.
- Prospective clinical trials are needed to validate genotype-directed perioperative strategies across fusion-positive NSCLC.

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****AI wasn't used to elaborate the content or the graphics of this work**