

Multi-regional sequencing reveals mono- and polyclonal seeding patterns in oligometastatic non-small cell lung cancer

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INTRODUCTION

Background

In oligometastatic non-small cell lung cancer (NSCLC), local ablative treatments (LAT), such as surgery and radiotherapy, have been shown to improve survival when combined with systemic therapy alone.

However, molecular features underlying “true” oligometastatic disease (OMD) remain poorly defined, and selecting appropriate patients for LAT continues to be a major challenge.

Aim

To characterize the genetic landscape of OMD through comprehensive next-generation sequencing (NGS) of primary tumors and matched metastatic lesions.

METHODS

Design: Single-center cohort; patients identified from a prospectively maintained REDCap database.

OMD definition: ≤5 metastases across ≤3 organs.

Surgery: Primary tumor resection between January 2015 and December 2024.

Next-generation Sequencing: Oncomine Comprehensive Assay Plus (517 genes, ThermoFisher)

Prospectively maintained REDCap database, single centre

Oligometastatic NSCLC (≤5 metastases, ≤3 organs)
resected 2015–2024

34 primary tumors + 40 matched metastases

Oncomine Comprehensive Assay Plus (517 genes)

Monoclonal vs. polyclonal seeding
RFS and OS analysis

RESULTS

100%

of primary-tumor truncal mutations retained in
matched metastases (34/34)

26.5%

polyclonal seeding with private metastatic
mutations (9/34 patients)

KRAS

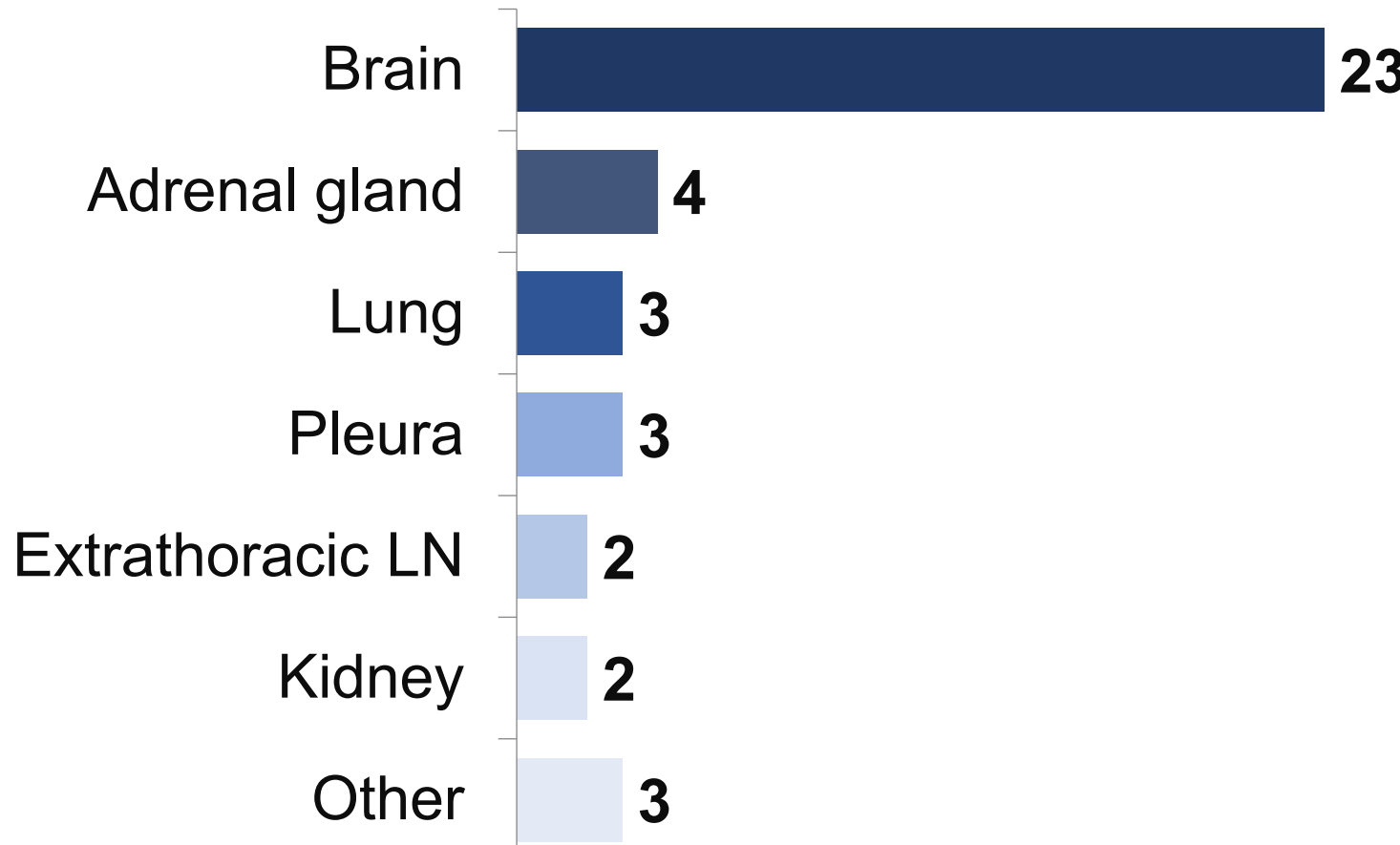
most frequent truncal alteration (50.0%)

Cohort and metastatic sites

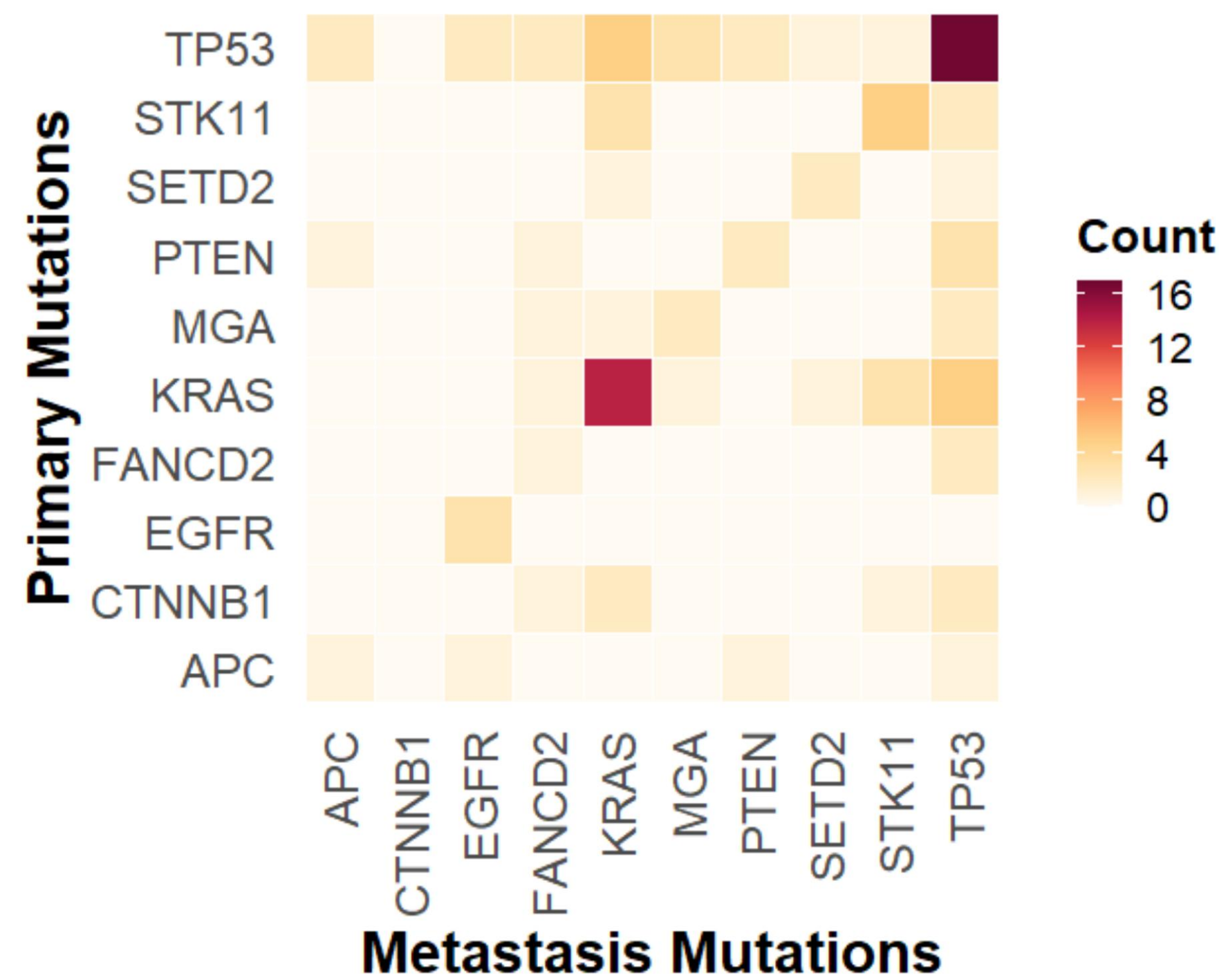
34 patients with oligometastatic NSCLC. NGS was successful on all 74 specimens (34 primary tumors and 40 matched metastases).

Timing: Synchronous OMD at initial diagnosis in 14 patients (41.2%); metachronous OMD in 20 patients (58.8%).

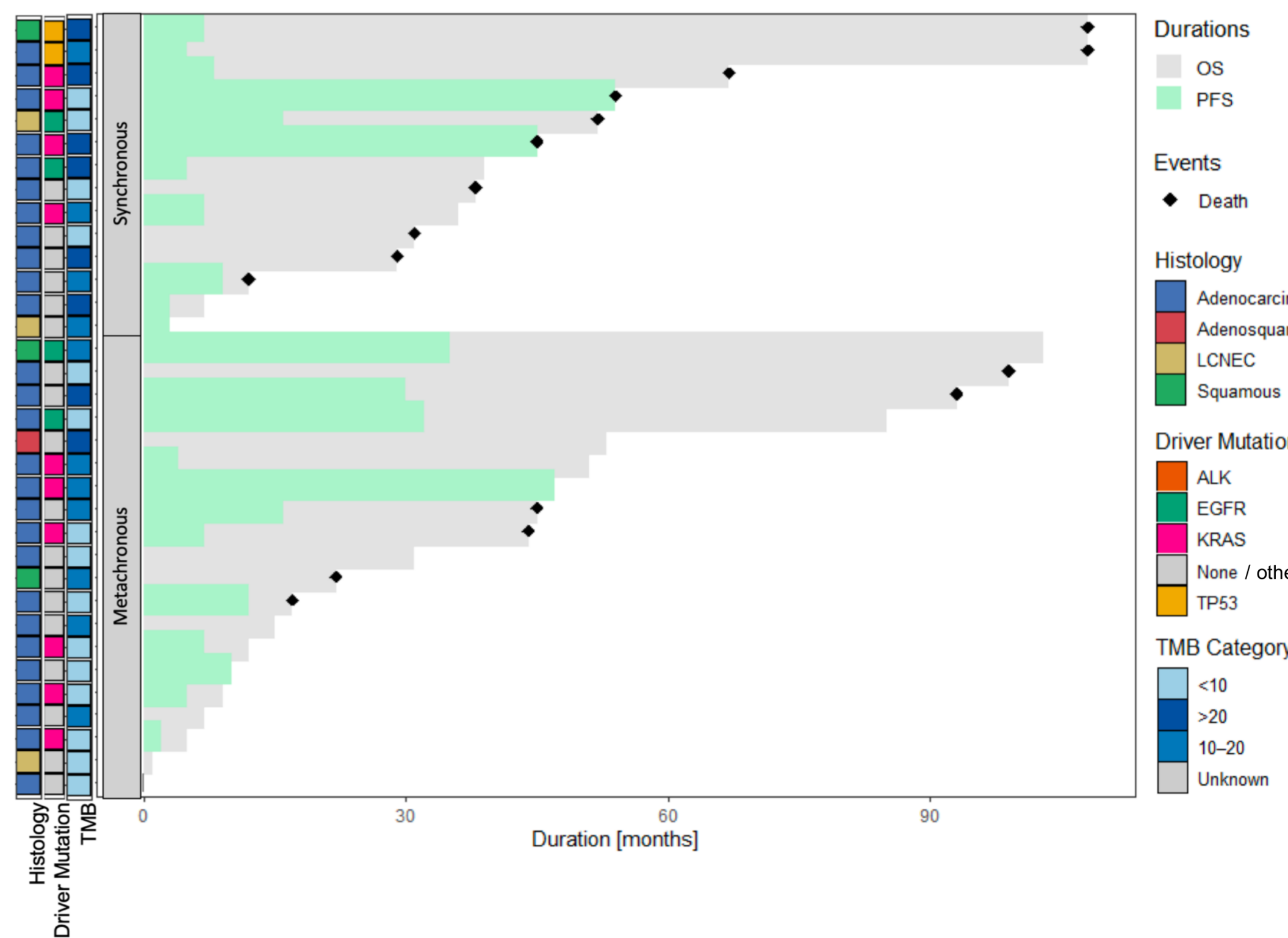
Histology: Adenocarcinoma 27, squamous-cell carcinoma 3, adenosquamous carcinoma 1, large-cell neuroendocrine carcinoma 3, undifferentiated carcinoma 1.



A Shared (co-)mutations, primary vs. metastasis



B Overall and recurrence-free survival by OMD timing

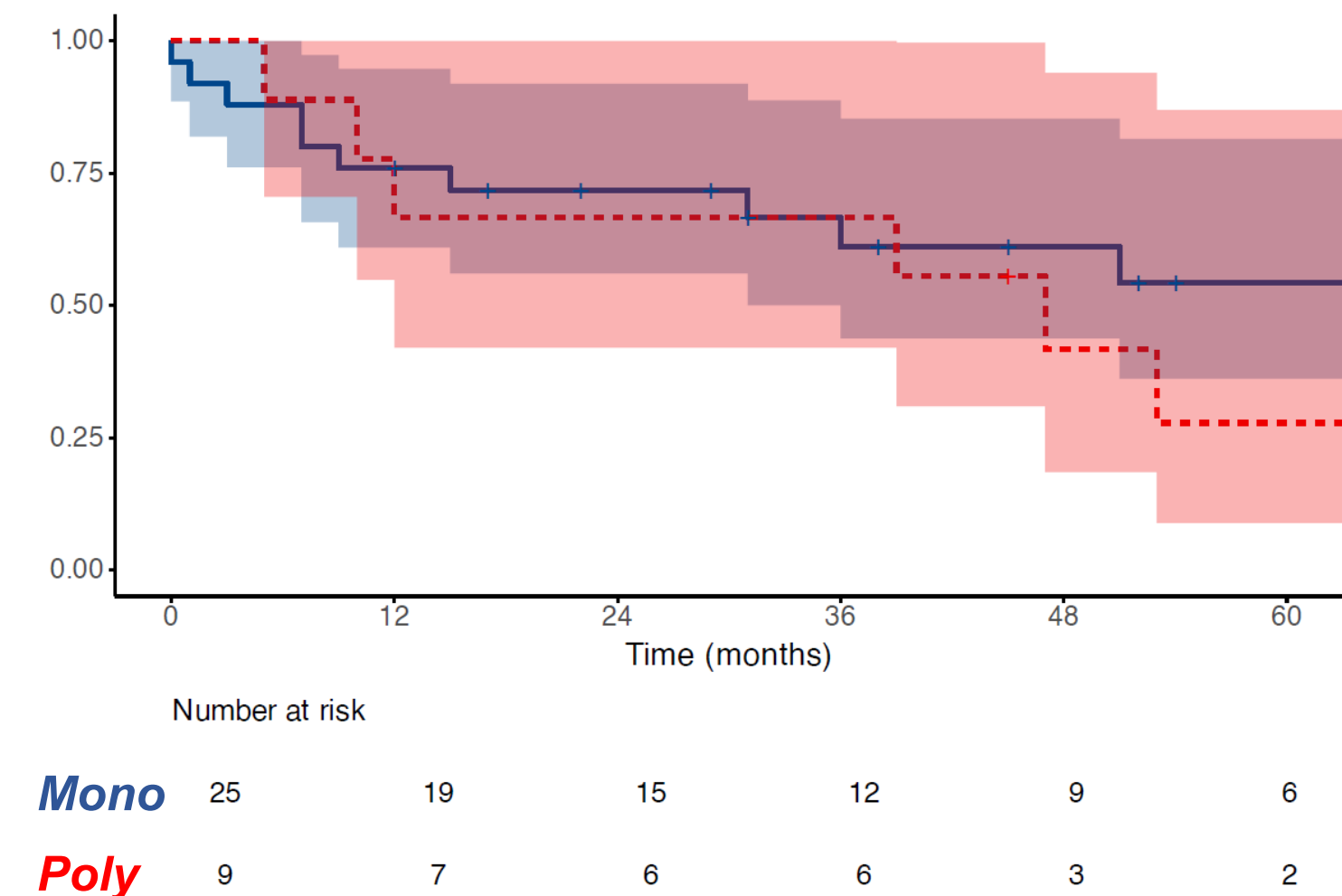


Survival by seeding pattern

Polyclonal seeding by additional private mutations in the metastasis, was present in 9 patients (26.5%): brain (n=3), adrenal gland (n=2), pleura, kidney and skin (n=1 each).

	Monoclonal (n=25)	Polyclonal (n=9)	P
Median OS, months (IQR)	50.0 (17.3–81.8)	31.0 (11.3–52.5)	0.36
Median PFS, months (IQR)	19.5 (5.0–43.0)	8.5 (4.0–27.5)	0.75

Recurrence-free and overall survival were comparable between monoclonal and polyclonal seeding.



DISCUSSION AND CONCLUSION

Key Message

Based on multiregional next-generation sequencing of this single-center cohort, this study demonstrates that monoclonal seeding is a common form of tumor dissemination in synchronous and metachronous oligometastatic non-small cell lung cancer.

Despite the high degree of clonality, polyclonal seeding was present in one fourth (26.5%) of all metastases, including subclonal somatic changes even in prognostic genes such as KEAP1 and STK11.

This supports the indication of repeat biopsy or resection of metastatic sites whenever a change in systemic treatment is being considered, since private alterations may not be captured by the primary tumor alone.

Future Directions

Survival did not differ between seeding patterns in this cohort, but statistical significance was limited due to the cohort's size. Larger, prospective series are needed to assess whether the mutational profile can predict metastatic trajectories and whether clonal architecture can refine patient selection for local ablative treatment.

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