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ORIGINAL ARTICLE

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THORACIC

Genetic profiles of oligometastatic non-small-cell lung cancer and corresponding brain metastases

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Summary

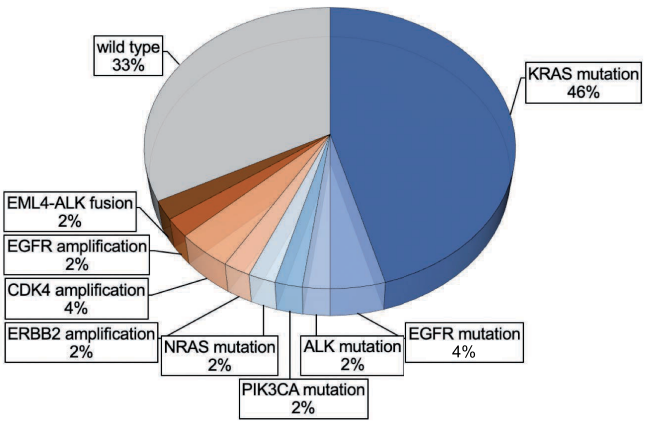
Population: Patients with oligometastatic non-small cell lung cancer with brain metastases.

Intervention: Local ablative treatment including surgical resection of the primary tumor and brain metastases.

Comparison: Targeted sequencing of primary tumors and corresponding brain metastases.

Outcome: Genetic alterations of the primary tumor are often preserved in matched brain metastases. KRAS mutations are common oncogenic drivers.

Genetic alterations of the primary tumor in patients with lung cancer and brain oligometastasis



NSCLC; non-small cell lung cancer; *KRAS:* Kirsten rat sarcoma virus

Abstract

OBJECTIVES: In patients with oligometastatic non-small-cell lung cancer (NSCLC), systemic therapy in combination with local ablative treatment of the primary tumour and all metastatic sites is associated with improved prognosis. For patient selection and treatment allocation, further knowledge about the molecular characteristics of the oligometastatic state is necessary. Here, we performed a genetic characterization of primary NSCLC and corresponding brain metastases (BM).

†These authors are co-senior authors.
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METHODS: We retrospectively identified patients with oligometastatic NSCLC and synchronous (<3 months) or metachronous (>3 months) BM who underwent surgical resection of both primary tumour and BM. Mutation profiling of formalin-fixed paraffin-embedded tumour cell blocks was performed by targeted next-generation sequencing using the Oncomine Focus Assay panel.

RESULTS: Sequencing was successful in 46 paired samples. An oncogenic alteration was present in 31 primary tumours (67.4%) and 40 BM (86.9%). The alteration of the primary tumours was preserved in the corresponding BM in 29 out of 31 cases (93.5%). The most prevalent oncogenic driver in both primary tumours and BM was a KRAS (Kirsten rat sarcoma viral oncogene) mutation ($s = 21$). In 16 patients (34.8%), the BM harboured additional oncogenic alterations. The presence of a private genetic alteration in the BM was an independent predictor of shorter overall survival.

CONCLUSIONS: In oligometastatic NSCLC, BM retain the main genetic alterations of the primary tumours. Patients may profit from targeted inhibition of mutated KRAS. Additional private genetic alterations in the BM are dismal.

Keywords: Non-small-cell lung cancer • Oligometastatic • Brain metastases • Genetic profiling

ABBREVIATIONS

AC	Adenocarcinoma
ALK	Anaplastic lymphoma kinase
BM	Brain metastasis
CI	Confidence interval
EGFR	Epidermal growth factor receptor
FFPE	Formalin fixed paraffin embedded
HR	Hazard ratio
IQR	Interquartile range
KRAS	Kirsten rat sarcoma virus oncogene
LAT	Local ablative treatment
NGS	Next-generation sequencing
NSCLC	Non-small-cell lung cancer
OMD	Oligometastatic disease
OS	Overall survival
SCC	Squamous cell carcinoma
SD	Standard deviation

INTRODUCTION

Lung cancer is the most frequent cause of cancer-related death worldwide and in >60% of all cases, the diagnosis is made in an advanced stage of the disease [1–3]. While the prognosis in metastatic non-small-cell lung cancer (NSCLC) is mostly poor, a subgroup of oligometastatic NSCLC with a limited number of distant metastases and low systemic tumour burden has been associated with a markedly improved survival upon local ablative treatment (LAT) of all metastatic sites in combination with systemic treatment [4, 5]. While there is currently no final consensus on the definition of the oligometastatic state with regard to the number of metastatic lesions or the number of involved organs, many studies and the European Organization for Research and Treatment of Cancer propose to include 5 of fewer distant metastases in 3 or fewer organs [6, 7]. Despite the paradigm shift that occurred with the introduction of the oligometastatic state, patient selection and treatment allocation remain a major challenge.

The brain is the most common metastatic site in lung cancer [8]. Approximately 12–14% of all NSCLC patients present with synchronous brain metastases (BM) at the time of diagnosis and even more may develop metachronous BM over the course of the disease [9]. Both systemic and central nervous disease control have been substantially improved by tyrosine kinase inhibitors for patients harbouring an epidermal growth factor receptor (EGFR) mutation or an anaplastic lymphoma kinase (ALK) translocation [10, 11]. Patients with BM were mostly excluded in these pivotal immune checkpoint inhibitor trials, but limited evidence suggests that checkpoint inhibitors appear to offer comparable intracranial and extracranial efficacy [12].

Overall, the genomic profiles of metastases in oligometastatic disease (OMD) remain vastly unknown and predictive biomarkers that can guide local or systemic treatment in these patients are scarce. We therefore aimed to assess the genomic landscape of oligometastatic NSCLC with its corresponding BM to identify specific somatic alterations with prognostic or predictive impact.

MATERIALS AND METHODS

Ethical statement

The study was performed in compliance with the institutional guidelines and approval by the local ethics committee was obtained (BASEC-reference number: 2020-02720).

Patient cohort, data and tissue collection

We retrospectively identified patients with oligometastatic NSCLC of all histologic subtypes who underwent LAT including surgical resection of the primary tumour and the BM at the University Hospital Zurich between April 2002 and May 2019. OMD was defined as 5 or fewer metastases in 3 or fewer organs. Patients with synchronous BM (occurrence within ≤3 months after initial diagnosis) and metachronous BM (occurrence after >3 months after initial diagnosis) were included. The cohort was retrospectively generated based on systematic search of clinical files and pathology reports. Follow-up data and information on mortality were collected based on clinical reports from general practitioners and specialist clinicians involved in the further treatment and follow-up of the patients who underwent surgery. Patients without recent (<1 year) follow-up reports are regularly contacted within the institutional quality control process. Study follow-up was closed in February 2022.

For a comparable estimation of overall survival (OS) between synchronous and metachronous disease, OS was calculated as the time between the date of BM diagnosis (date of initial diagnosis for synchronous metastases and date of metastases diagnosis for metachronous metastases) and the date of death or censoring. Patients were excluded if no representative formalin-fixed paraffin-embedded (FFPE) tissue block of the primary tumour or the metastases were present. A flowchart of the patient

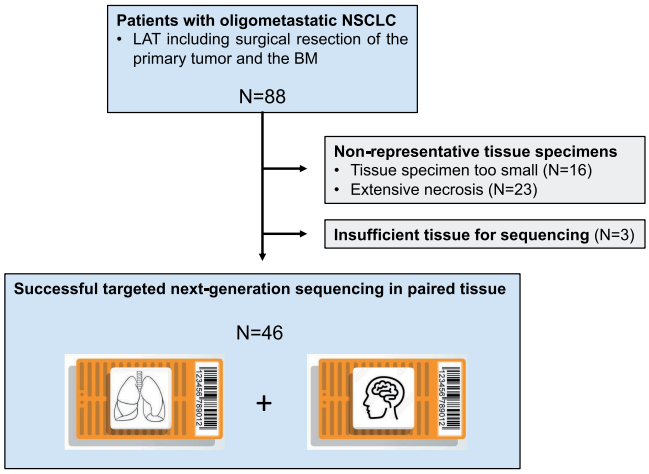

Figure 1: Flowchart depicting the patient selection for the cohort of oligometastatic non-small-cell lung cancer patients with matched tissue specimens of the primary tumour and brain metastases. BM: brain metastasis; LAT: local ablative treatment; NSCLC: non-small-cell lung cancer.

selection is depicted in Fig. 1. All cases were classified based on clinical information, histological morphology and immunohistochemistry by institutional pathologists. Histology was re-evaluated for all patients and the most representative tumour regions were annotated on haematoxylin–eosin-stained sections (Raphael S. Werner and Alex Soltermann) for subsequent analyses. For all patients, a re-staging was performed according to the Union for International Cancer Control 8th edition of the TNM classification.

Study end points

The presence of genetic alterations in the primary tumour and corresponding BM was considered as primary end point. The influence of the genetic profile and other clinico-pathologic variables such as age, sex, syn-/metachronous disease, histology, vascular invasion and number of metastases on OS were defined as secondary end points.

Next-generation sequencing

Next-generation sequencing (NGS) was conducted using the Oncomine Focus Assay panel (Thermo Fisher Scientific, Carlsbad, CA, USA), enabling detection of variants in 52 genes (Supplementary Material, Table S1). Sample analysis and library construction were performed according to the manufacturer's protocol. DNA and RNA were extracted from paraffin-embedded tissue blocks with a Maxwell 16 FFPE Tissue LEV DNA/RNA Purification Kit (Promega, Fitchburg, WI, USA). Sequencing was performed using the Ion S5TM System and the Ion 540 Sequencing Kit (Thermo Fisher Scientific). Ion Reporter software 5.10 (Thermo Fisher Scientific) was used for alignment (hg19/GRChr37), variant calling and annotations.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) if the variables were normally distributed or as median and interquartile range (IQR) if non-normally distributed. The normality of distribution was assessed according to the variable's histogram plot. Comparison of continuous variables was performed using the unpaired t-test for normal distributions and Mann–Whitney *U*-test for non-normal distributions. Categorical variables are expressed as frequencies and percentages and were compared using Chi-squared test. Fisher's exact test was used when frequencies were below 5. Follow-up rates were estimated using the simplified person time method and the proposed person time method by Xue *et al.* [13] Time-to-event analysis was conducted for OS using the Kaplan–Meier method and log-rank tests. With regard to competing risks, the cumulative incidence of death in patients with OMD and BM was calculated using Gray's test. Multivariable Cox proportional regression analysis was performed to estimate the unadjusted and adjusted effects of clinico-pathologic and genetic covariables on OS. The following covariables were used for univariable pre-screening based on background knowledge and clinical reasoning: age at BM diagnosis $\geq$62 years (median split for improved visualization and according to previous publications in this field [14–16]), sex, synchronous versus metachronous BM, number of metastases (1 vs >1), squamoid [squamous cell carcinoma (SCC), adenosquamous carcinoma] versus non-squamoid histology [adenocarcinoma (AC), large-cell lung carcinoma], vascular invasion (primary tumour), Kirsten rat sarcoma viral oncogene (KRAS) mutation (primary tumour), private mutation in BM, MYC amplification in BM, neoadjuvant versus adjuvant systemic treatment, treatment before versus after 2010, smoking history (yes versus no), T-stage and N-stage at initial diagnosis, pneumonectomy. After univariable prescreening was performed, all covariables with a *P*-value of <0.25 in a univariable Cox regression model were incorporated into the multivariable model. The proportional hazards assumption was evaluated by plotting the scaled Schoenfeld residuals over log(time) with a non-zero slope to verify that all models met the proportional hazards assumption.

All statistical analyses were performed using SPSS software (version 29.0, IBM SPSS Inc., Armonk, NY, USA) and R Software (version 4.3.1, R Foundation for Statistical Computing, Institute for Statistics and Mathematics, Vienna, Austria). The reported *P*-values are two-sided and a value of $P < 0.05$ was considered statistically significant.

RESULTS

Cohort description and clinical outcomes after local ablative treatment

Our cohort included 49 patients with oligometastatic NSCLC and BM. All patients underwent LAT including surgical resection of the primary tumour and BM (Table 1). Median age was 62 years and 29 patients (59.2%) were male. Most patients had 1 or 2 distant metastases ($n = 26$ (53.1%) and $n = 14$ (28.6%), respectively) and in 40 patients (81.6%), the brain was the only metastatic site. In 26 patients (53.1%) synchronous BM were present, whereas metachronous BM occurred in 23 patients (46.9%) with a median latency of 15 months. Surgical resection of the primary tumour was most commonly performed by lobectomy ($n = 40$ (81.6%)) and 22 patients (44.9%) had received neoadjuvant systemic treatment. The cohort included AC, SCC, adenosquamous carcinoma and large-cell lung carcinoma in 73.5%, 8.2%, 6.1% and 12.2%, respectively. The median OS was 35 months and after 5 years, 38.1% of all patients were alive.

Table 1: Cohort description

Age (years), median [IQR]	62 [54–68]
Sex	
Female	20 (40.8%)
Male	29 (59.2%)
Positive smoking history	45 (91.8%)
Pack years, median [IQR]	40.0 [20.0–60.0]
Histology	
Adenocarcinoma	36 (73.5%)
Squamous cell carcinoma	4 (8.2%)
Adenosquamous carcinoma	3 (6.1%)
Large-cell lung carcinoma	6 (12.2%)
Grading	
G1	0 (0.0%)
G2	12 (24.5%)
G3	37 (75.5%)
UICC staging (8th edition) at initial diagnosis	
IA3	1 (2.0%)
IB	4 (8.2%)
IIB	2 (4.1%)
IIIA	12 (24.5%)
IIIB	4 (8.2%)
IVA	14 (28.6%)
IVB	12 (24.5%)
Synchronous brain metastases	26 (53.1%)
Metachronous brain metastases	23 (46.9%)
Latency (months), median [IQR]	15 [8.0–33.0]
Number of metastases	
1	26 (53.1%)
2	14 (28.6%)
3	3 (6.1%)
4	3 (6.1%)
5	3 (6.1%)
Number of met. organs	
1	40 (81.6%)
2	8 (16.3%)
3	1 (2.0%)
Systemic treatment	41 (83.7%)
Neoadjuvant treatment	22 (44.9%)
Preoperative dexamethasone	43 (87.7%)
Surgery	
Wedge resection	3 (6.1%)
Lobectomy	40 (81.6%)
Bilobctomy	3 (6.1%)
Pneumonectomy	3 (6.1%)
Outcome	
Median OS (months), median [IQR]	35 [12.0–65.5]
2-Year survival	63.0%
5-Year survival	38.1%

IQR: interquartile range; OS: overall survival; UICC: Union for International Cancer Control.

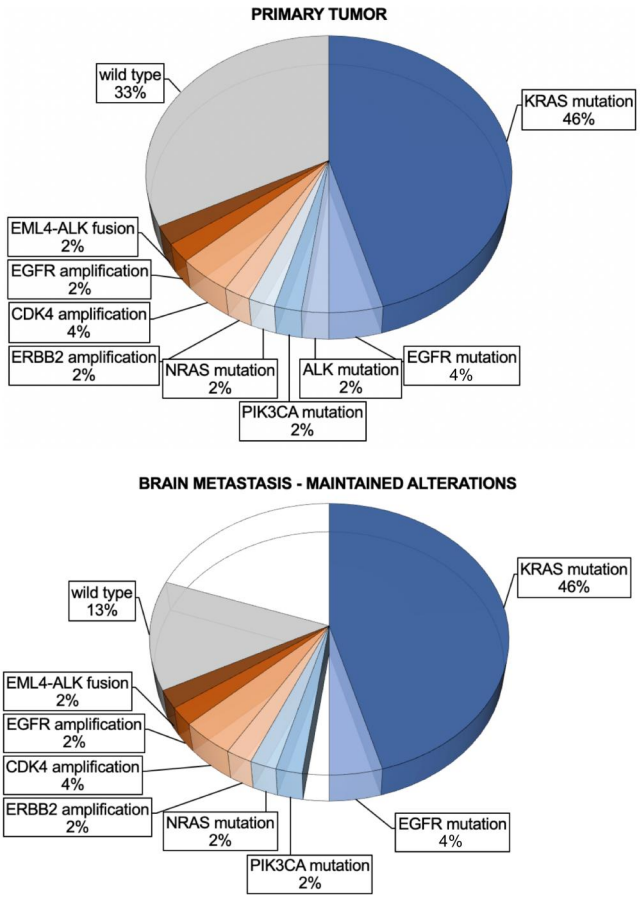

Figure 2: Mutational profiles of primary oligometastatic NSCLC and its corresponding BM with maintained alterations. The depicted mutational profiles of the BM include the maintained alterations only. Private alterations of the brain are shown in Fig. 3. BM: brain metastasis; NSCLC: non-small-cell lung cancer.

KRAS mutations are the most common oncogenic drivers in oligometastatic disease *with* brain metastasis

Targeted NGS using the Oncomine Focus Assay was successfully performed for 46 paired samples including 35 AC, 4 SCC, 3 adenosquamous carcinomas and 4 large-cell lung carcinomas (Fig. 2 and Table 2). An oncogenic alteration was present in 31 primary tumours (67.4%) and 40 BM (86.9%). The most common oncogenic drivers of the primary tumour were KRAS mutations ($n = 21$), followed by EGFR mutations and CDK4 amplifications ($n = 2$ each). The subtypes of KRAS mutations were G12C ($n = 10$), G12V ($n = 4$), G13C ($n = 3$), G12A ($n = 2$) and Q61H ($n = 2$). Primary tumours furthermore harboured 1 ALK mutation, 1 NRAS mutation, 1 EGFR amplification, 1 ERBB2 amplification, 1 PIK3CA amplification and 1 EML4-ALK fusion. Secondary genetic alterations and corresponding variant allele frequencies are shown in Table 2. The oncogenic driver alteration of the primary tumour was most commonly preserved in the corresponding BM (29 out of 31 cases, 93.5%). KRAS mutations were equally distributed in patients with synchronous BM ($n = 12$, 50.0%) and metachronous BM ($n = 10$, 45.5%, $p = 0.85$). The mean number of metastases was not significantly different between KRAS-mutated and non-KRAS-mutated cases [1.9 (SD: 1.3) and 1.9 (SD 1.1), $P = 0.95$]. No targeted therapies towards KRAS mutations were administered.

Private alterations of the brain metastasis

While driver alterations were most commonly preserved, BM harboured 19 private oncogenic alterations in 16 patients (34.8%, Fig. 3 and Table 2). These alterations included KRAS mutations ($n = 2$, G12C and G12V), EGFR mutations ($n = 2$, L858R and T790M), RET mutation ($n = 1$), EML4-ALK fusion ($n = 1$), MYC amplifications ($n = 5$), MYCN amplification ($n = 1$), EGFR amplification ($n = 1$), MET amplification ($n = 1$), FGFR amplification ($n = 1$), ERBB2 amplification ($n = 1$), CCND1 amplification ($n = 1$), PDGFRA amplification ($n = 1$) and KIT amplification ($n = 1$). Private alterations of the BM were more common in

Table 2: Genetic profiles of the primary tumours and corresponding BM including variant allele frequencies

	Primary tumour profile				Brain metastasis profile			
Patient ID	Oncogenic driver	Secondary mutations	Amplifications	Fusions	Oncogenic driver	Secondary mutations	Amplifications	Fusions
1	KRAS p. Gly12Val *(VAF 54%)*		CDK4 (6.2), AR (4.93)	wt	KRAS p. Gly12Val *(VAF 51%)*		CDK4 (8.21), AR (5.68)	wt
2	KRAS p. Gly12Ala *(VAF 5.8%)*		wt	wt	KRAS p. Gly12Ala *(VAF 35%)*		wt	wt
3	KRAS p. Gly13Cys *(VAF 33%)*		wt	wt	KRAS p. Gly13Cys *(VAF 62%)*		wt	wt
4	wt		wt	wt	wt		PDGFRA (5.9), KIT (4.91)	wt
5	EGFR p. Gly719Ala *(VAF 22%)*		wt	wt	n/a	n/a	n/a	n/a
6	wt		PIK3CA (5.19), EGFR (16.44)	wt	n/a	n/a	n/a	n/a
7	KRAS p. Gly12Cys *(VAF 42%)*	IDH1 p. Arg132His *(VAF 12%)*	wt	wt	KRAS p. Gly12Cys *(VAF 89%)*	IDH1 p. Arg132His *(VAF 39%)* RET p. Ala883Thr *(VAF 4.2%)*	wt	wt
8	KRAS p. Gly12Cys *(VAF 26%)*	PIK3CA p. Glu542Lys *(VAF 12%)*	wt	wt	n/a	n/a	n/a	n/a
9	PIK3CA p. Thr1025Asn *(VAF 7.2%)*		wt	wt	PIK3CA p. Thr1025Asn *(VAF 12.7%)*		wt	wt
10	KRAS p. Gln61His *(VAF 9.2%)*		wt	wt	KRAS p. Gln61His *(VAF 38%)*		wt	wt
11	NRAS p. Gln61Arg *(VAF 49%)*		wt	wt	NRAS p. Gln61Arg *(VAF 41%)*		wt	wt
12	EGFR p. Glu746_Ala750del *(VAF 74%)*		EGFR (5.15)	wt	EGFR p. Glu746_Ala750del *(VAF 75%)*	EGFR p. Thr790Met *(VAF 16.6%)*	EGFR (6.1)	wt
13	wt		ERBB2 (38.41)	wt	wt		ERBB2 (28.1)	wt
14	wt		wt	wt	wt		wt	EML4-ALK *(VAF 19.3%)*
15	wt		wt	wt	wt		MYC (5.63)	wt
16	wt		wt	wt	wt		wt	wt
17	KRAS p. Gly12Cys *(VAF 33%)*		wt	wt	KRAS p. Gly12Cys *(VAF 51%)*		MYC (5.41)	wt
18	KRAS p. Gly12Val *(VAF 18%)*		wt	wt	KRAS p. Gly12Val *(VAF 55%)*		wt	wt
19	KRAS p. Gln61His *(VAF 33%)*		wt	wt	KRAS p. Gln61His *(VAF 51%)*		wt	wt
20	KRAS p. Gly12Cys *(VAF 41%)*		wt	wt	KRAS p. Gly12Cys *(VAF 60%)*		MYC (5.38)	wt
21	ALK p. Ala1200Val *(VAF 66%)*	RET p. Cys609Tyr *(VAF 25%)*	wt	wt	wt		EGFR (5.04)	wt
22	wt		wt	wt	wt		wt	wt
23	wt		wt	wt	EGFR p. Leu858Arg *(VAF 72%)*		ERBB2 (102)	wt
24	KRAS p. Gly12Cys *(VAF 37%)*		wt	wt	KRAS p. Gly12Cys *(VAF 29%)*		wt	wt

Continued

Table 2: Continued

Patient ID	Primary tumour profile				Brain metastasis profile			
	Oncogenic driver	Secondary mutations	Amplifications	Fusions	Oncogenic driver	Secondary mutations	Amplifications	Fusions
25	wt		wt	EML4-ALK *(VAF 1.54%)*	wt		wt	EML4-ALK *(VAF 2.19%)*
26	wt		wt	wt	KRAS p. Gly12Val *(VAF 35%)*		wt	wt
27	KRAS p. Gly12Cys *(VAF 8.6%)*		wt	wt	KRAS p. Gly12Cys *(VAF 56%)*		wt	wt
28	EGFR p. Ser768_Asp770dup *(VAF 28%)*		wt	wt	EGFR p. Ser768_Asp770dup *(VAF 34%)*		wt	wt
29	wt		wt	wt	wt		wt	wt
30	KRAS p. Gly13Cys *(VAF 40%)*		wt	wt	KRAS p. Gly13Cys *(VAF 40%)*		wt	wt
31	KRAS p. Gly12Cys *(VAF 22%)*		wt	wt	KRAS p. Gly12Cys *(VAF 39%)*		wt	wt
32	wt		CDK4 (41.51)	wt	wt		CDK4 (20.5)	wt
33	KRAS p. Gly13Cys *(VAF 22%)*		wt	wt	KRAS p. Gly13Cys *(VAF 71%)*		wt	wt
34	wt		wt	wt	wt		wt	wt
35	wt		wt	wt	wt		wt	wt
36	KRAS p. Gly12Cys *(VAF 39%)*		wt	wt	KRAS p. Gly12Cys *(VAF 63%)*		MYCN (7.99)	wt
37	wt		CDK4 (9.35)	wt	wt		CDK4 (4.99)	wt
38	KRAS p. Gly12Asp *(VAF 35%)*	ALK p. Gly1123Cys *(VAF 44%)*	wt	wt	KRAS p. Gly12Asp *(VAF 44%)*	ALK p. Gly1123Cys *(VAF 42%)*	wt	wt
39	KRAS p. Gly12Cys *(VAF 40%)*		wt	wt	KRAS p. Gly12Cys *(VAF 35%)*		CCND1 (11.13)	wt
40	wt		wt	wt	wt		wt	wt
41	wt		wt	wt	wt		MET (6.79)	wt
42	wt		EGFR (12.76)	wt	wt		EGFR (6.35)	wt
43	wt		wt	wt	KRAS p. Gly12Cys *(VAF 43%)*		wt	wt
44	KRAS p. Gly13Cys *(VAF 31%)*		wt	wt	KRAS p. Gly13Cys *(VAF 34%)*		wt	wt
45	KRAS p. Gly12Val *(VAF 39%)*		wt	wt	KRAS p. Gly12Val *(VAF 52%)*		wt	wt
46	KRAS p. Gly12Val *(VAF 72%)*		wt	wt	KRAS p. Gly12Val *(VAF 56%)*		wt	wt
47	wt		wt	wt	wt		MYC (5.53)	wt
48	KRAS p. Gly12Cys *(VAF 15%)*		wt	wt	KRAS p. Gly12Cys *(VAF 59%)*		wt	wt
49	wt		wt	wt	wt		FGFR1 (5.2), MYC (5.43)	wt

VAF: variant allele frequency; wt: wild type.

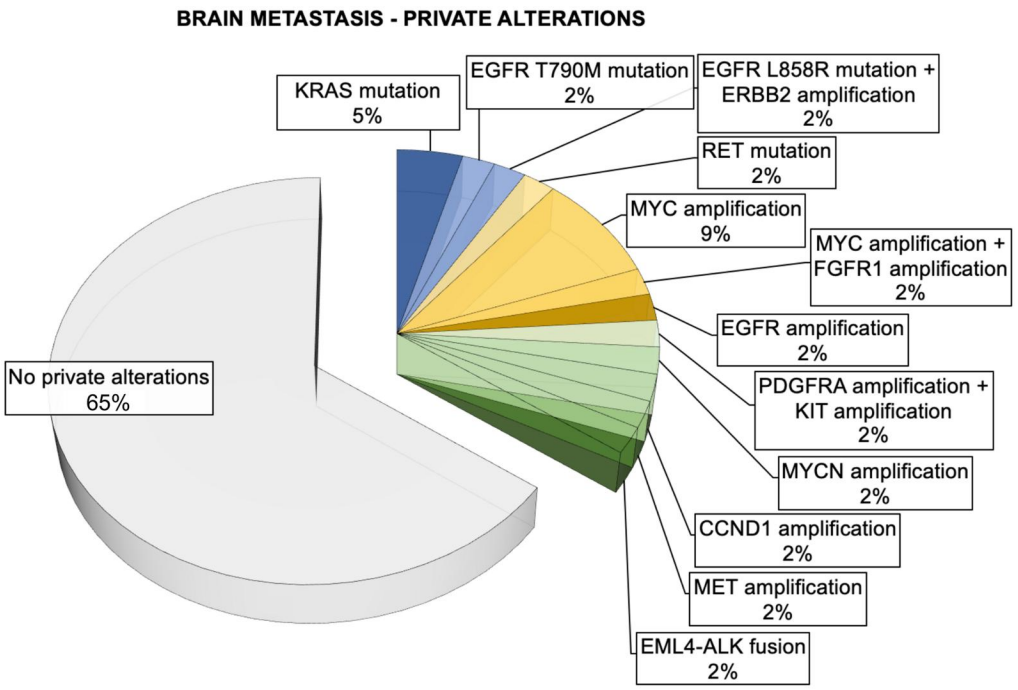

Figure 3: Private genetic alterations of the BM are present in 34.8% of all patients. The most common private alterations are MYC amplifications which were present in 5 patients. BM: brain metastasis.

patients with metachronous metastases ($n = 10$, 45.5%) when compared to patients with synchronous metastases ($n = 6$, 25.0%), although differences were not statistically significant ($P = 0.15$). The 5 private MYC amplifications were found in 4 AC cases and 1 large-cell lung carcinoma case. Two MYC-amplified BM occurred synchronously and 3 MYC-amplified BM occurred metachronously ($P = 0.56$). Metachronous BM furthermore harboured a KRAS G12V mutation, 2 EGFR mutations ($n = 2$, L858R and T790M), EGFR amplification, MET amplification, CCND1 amplification and EML4-ALK fusion. Four MYC amplifications, the EML4-ALK fusion and the MYCN amplification were present after neoadjuvant conventional chemotherapy was performed.

Prognostic clinic-pathologic and mutational parameters in oligometastatic non-small-cell lung cancer

The median follow-up duration for the entire study cohort was 35.0 months (IQR 12.0–65.5). The follow-up rate was 12 months (simplified person time method) and 18.7 months (proposed person time method). Kaplan–Meier survival curves for private alterations in the BM and for MYC amplifications in the BM are shown in Fig. 4. Kaplan–Meier survival curves for age, KRAS status of the primary tumour and syn- or metachronous disease are shown in Fig. 5. Univariable Cox regression analyses were performed and a multivariable Cox regression model was built (Table 3). Median OS was [23.0 (IQR 5.0–34.0)] months in the subgroup of patients with a private alteration in the BM and 56.0 (IQR 16.0–103.0) months in patients without private alterations in the BM. The cumulative incidence of death at 50 months was 75.0% in patients with private alterations in the BM and 43.9% in patients without private alterations in the BM (Gray's test $P = 0.024$). The presence of private alterations in the BM was an independent predictor for shorter OS [hazard ratio (HR), 95% confidence interval (CI): 3.25, 1.22–8.70, $P = 0.019$]. The median OS was [24.0 (IQR 10.0–29.0)] in patients harbouring an MYC amplification in the BM and 53.0 (IQR 14.0–81.0) months in patients with non-MYC mutated BM. The cumulative incidence of death at 50 months was 49.1% in patients without MYC alterations and 100% in patients with MYC alterations in the BM (Gray's test $P = 0.036$). However, MYC alteration in the BM was not significantly associated with OS in the multivariable model (HR, 95% CI: 0.55, 0.12–2.42, $P = 0.43$). The cumulative incidence of death at 50 months was 47.6% in patients with a KRAS mutation in the primary tumour and 61.0% in patients with no KRAS mutation in the primary tumour (Gray's test, $P = 0.43$). The median OS was 68.0 (IQR 32.0—not reached) months in the age group <62 years and 16.0 (IQR 5.0–34.0) months in the age group ≥ 62 years. The cumulative incidence of death at 50 months was 80.9% in patients ≥ 62 years of age and 32.4% in patients <62 years of age (Gray's test, $P < 0.001$). Age <62 years was an independent predictor for increased OS in the multivariable model (HR, 95% CI: 2.87, 1.21–6.78, $P = 0.016$). In the multivariable model, the presence of vascular invasion in the primary tumour was independently associated with shorter OS (HR, 95% CI: 2.71, 1.20–6.13, $P = 0.017$). The median OS was 29.0 (IQR 10.0–68.0) months in patients with vascular invasion and 72.0 (IQR 17.0–103.0) months in patients without vascular invasion. Among the squamoid and non-squamoid groups, age [60.6 (SD: 13.0) vs 59.1 (SD: 13.1) years, $P = 0.79$], male sex (71.4% vs 57.1%, $P = 0.48$), synchronous disease (42.9% vs 47.6%, $P = 1.0$), histological grading (G3 in 71.4% vs 64.3%, $P = 0.32$) and rates of neoadjuvant treatment (50.0% vs 45.7%, $P = 1.0$) were equally distributed. In the multivariate regression model, no significant association between histology and OS was present (HR, 95% CI: 1.66, 0.61–4.51, $P = 0.32$). The cumulative incidence of death at

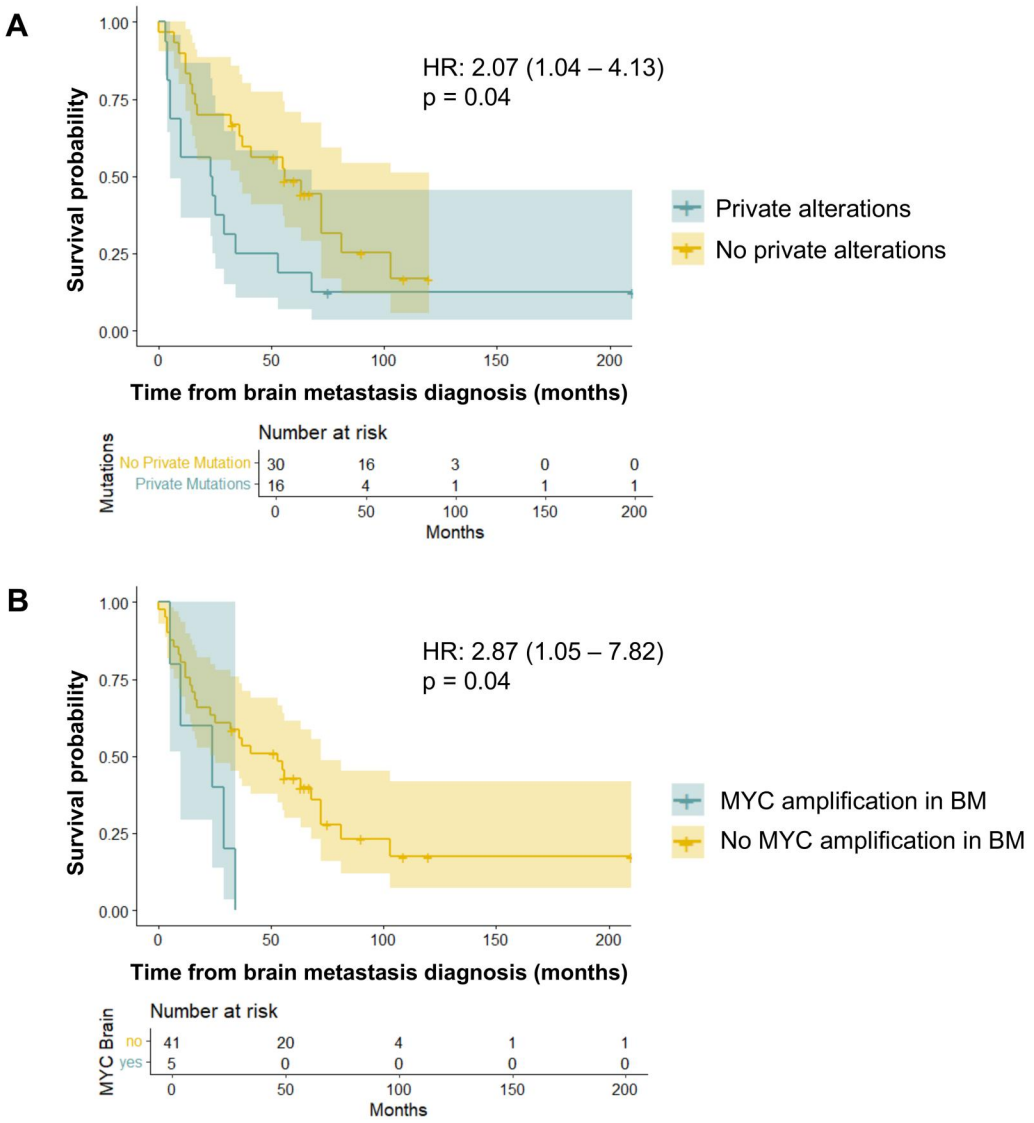

Figure 4: (**A**) The presence of private alterations in BM was significantly associated with overall survival in oligometastatic disease. (**B**) In the subgroup of patients harbouring private MYC amplifications of the BM ($n = 5$), a reduced overall survival was seen compared to patients without MYC overexpression in BM. BM: brain metastasis; HR: hazard ratio.

50 months was 71.4% in the squamoid group and 51.7% in the non-squamoid group (Gray's test, $P < 0.041$).

DISCUSSION

Metastatic lung cancer is a highly heterogeneous disease with a vast histological, genetic and immunological diversity that requires a personalized treatment approach [17, 18]. In this study, we performed a genotyping of oligometastatic NSCLC with matched primary tumours and BM using NGS on FFPE tissue specimens. In our study cohort, all histotypes were included and patients with synchronous and metachronous BM were equally represented. In 67.4% of all primary tumours and in 86.9% of all BM, oncogenic genetic alterations were present. In the majority (93.5%) of all cases, oncogenic alterations of the primary tumour were preserved in the matched BM. While a previous study by Vassella *et al.* [19] on BM in lung AC showed a higher incidence of mutations that were private to BM, the genetic aberrations that were present in the primary site were as well maintained in the majority of cases. In contrast, Paik *et al.* [20] found a low proportion of shared events between primary lung SCC and 9 matched BM upon whole-exome sequencing. The authors deduced that the presence of subclonal mutations indicates a clonally divergent cancer evolution [20]. Despite the high proportion of shared primary oncogenic drivers in our cohort, additional private genetic aberrations of the BM were revealed in 34.8% of all cases. This suggests that while trunk mutations are commonly preserved, a branching, subclonal cancer evolution is simultaneously present and contributes to the metastatic process in the brain. Knowing that biopsies from metastatic lesions, especially from BM, are often difficult and burdensome to take, the findings of our study may give certain reassurance that treatments targeting the primary tumour's oncogenic driver are often appropriate for BM as well.

Our results show that private alterations were more common in metachronous BM. In the multivariable regression model, the presence of private genetic alterations in BM was independently

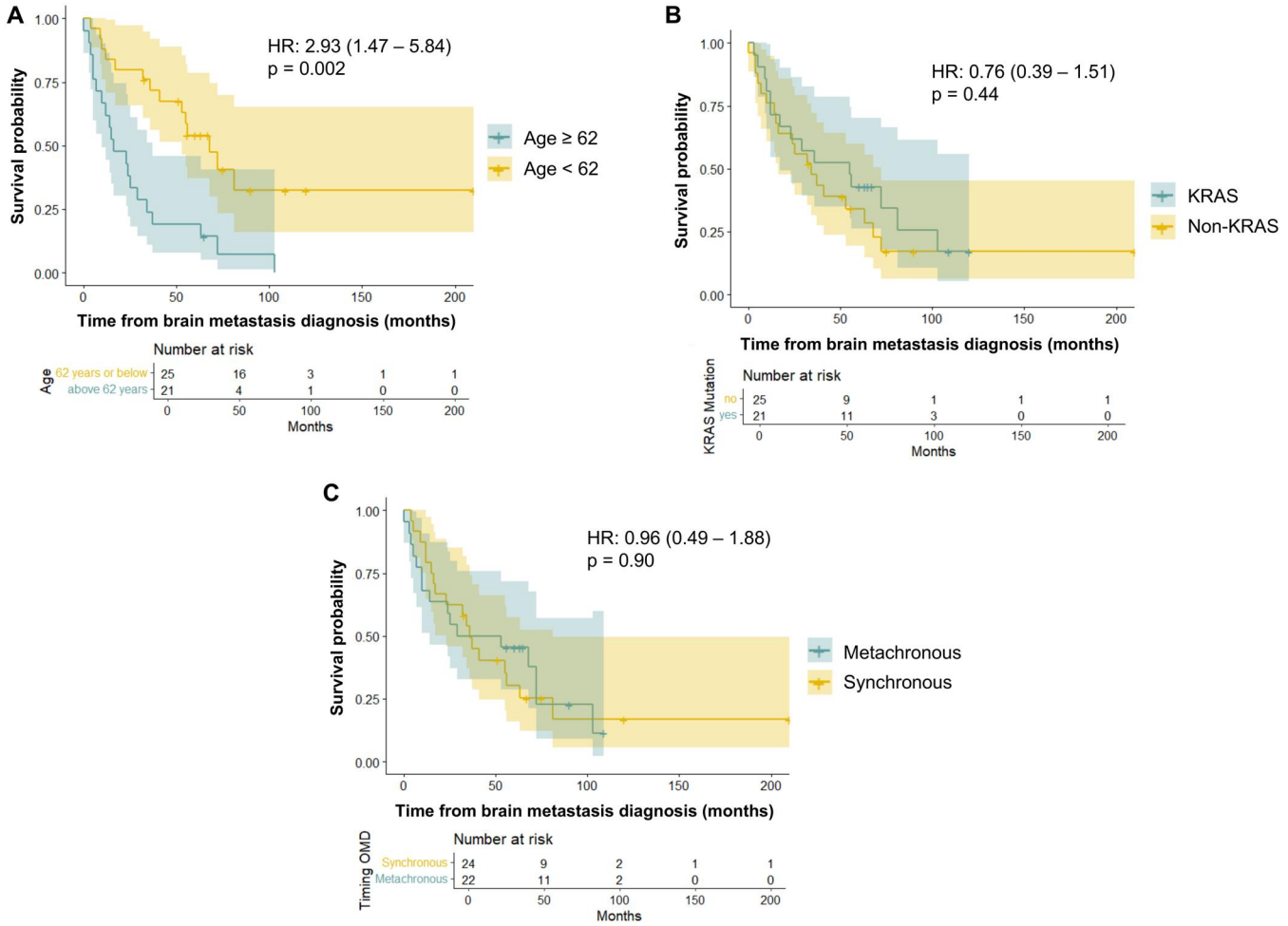

Figure 5: (**A**) Among patients aged <62 years, overall survival was significantly longer after local ablative treatment for oligometastatic non-small-cell lung cancer with BM compared to patients aged ≥62 years. (**B**) OS is comparable in patients with KRAS-mutated and non-KRAS-mutated primary tumours. (**C**) In patients with synchronous and metachronous BM, no significant differences in OS were found. BM: brain metastasis; OS: overall survival.

related to shorter OS. The association between an accumulation of genetic alterations in the process of tumour evolution and disease progression has been well described within the concept of the hallmarks of cancer [21]. Genomic instability is a hallmark of cancer and results in an accumulation of DNA damage and increased cancer cell proliferation, which confers to a shorter OS [21]. Regarding the private alterations found in the BM, targeted treatment options are limited. Out of the 16 patients with private alterations in BM, a targeted treatment beyond clinical trials is currently only available for 3 cases (2 EGFR mutations and 1 RET mutation) [22].

Among NSCLC, the incidence of BM is higher in AC when compared to SCC, and oncogene-addicted NSCLC are particularly prone to develop BM [9, 10, 23, 24]. In our OMD cohort, KRAS mutations were the most common oncogenic driver, occurring in 46% of all primary tumours and in 50% of all BM. These findings are in line with previous studies: Vassella *et al.* [19] demonstrated a significant increase in KRAS mutations among brain metastatic NSCLC when compared to other reported Union for International Cancer Control stage IV NSCLC cohorts. In a different study, KRAS was among the most frequently mutated genes among 76 next-generation sequenced lung AC BM [25]. In the past, a variety of studies have shown that OS is adversely affected by KRAS mutations [26]. However, in the multivariable regression model of our cohort, no significant association was found between KRAS mutation status and OS. The KRAS G12C mutation was the variant with the highest prevalence in our cohort [$n = 10/21$ KRAS mutations (47.6%)]. With novel KRAS G12C inhibitors currently being investigated in clinical trails, this high proportion of targetable KRAS G12C mutations among oligometastatic NSCLC becomes increasingly significant [27]. With sotorasib and adagrasib, the limited data suggest a promising intracranial activity [28].

A major difference between the primary tumour and the corresponding BM was the appearance of private MYC amplifications in BM. While MYC amplifications were not present in the primary tumour, 5 BM (10.9%) harboured an MYC amplification. For patients that harboured an MYC amplification in the BM, the univariate analysis showed a reduced OS with an HR of 2.87. While the multivariate regression model showed no significant association between the presence of MYC amplifications and OS, these findings may have been limited by the sample size. MYC aberrations and an upregulation of MYC-related pathways are found in many cancers and lead to acquisition of hallmarks of cancer or dysregulation of the tumour microenvironment [29]. A previous study of lung AC BM compared with the Cancer Genome Atlas Program (TGCA)-matched primary tumours has revealed higher frequencies of MYC amplifications in BM (12%

Table 3: Univariable and multivariable Cox regression analyses of parameters associated with overall survival

Factor	Univariate HR	95% CI	*P*-value	Multivariate HR	95% CI	*P*-value
Age (≥62 vs <62 years)	2.93	1.47–5.84	0.002	2.87	1.21–6.78	0.016
Sex (male versus female)	1.32	0.66–2.64	0.43			
Metachronous versus synchronous BM	0.96	0.49–1.88	0.90			
No. of metastases (1 vs >1)	2.05	1.02–4.10	0.44			
Squamoid versus non-squamoid histology	2.20	0.95–5.13	0.07	1.66	0.61–4.51	0.32
Vascular invasion	1.70	0.81–3.56	0.16	2.71	1.20–6.13	0.017
KRAS mutation	0.76	0.39–1.51	0.44			
Private mutation in BM	2.07	1.04–4.13	0.04	3.25	1.22–8.70	0.019
MYC amplification in BM	2.87	1.05–7.82	0.04	0.55	0.12–2.42	0.43
Systemic treatment (adjuvant versus neoadjuvant treatment)	1.78	0.90–3.50	0.10	1.83	0.78–4.29	0.16
Treatment date (before 2010 versus after 2010)	0.75	0.33–1.75	0.51			
Smoking history (yes/no)	0.91	0.27–3.01	0.88			
T-stage (at initial diagnosis)	0.67	0.34–1.32	0.26			
N-stage (at initial diagnosis)	0.96	0.66–1.40	0.82			
Pneumonectomy	0.53	0.07–3.87	0.53			

BM: brain metastasis; CI: confidence interval; HR: hazard ratio.

vs 6%) [30]. In addition, a functional assessment of MYC overexpression in patient-derived xenograft models confirmed an increased incidence of BM [30]. Similarly, Vassella *et al.* [19] also report a higher incidence of MYC amplifications among lung AC BM. The association of MYC alterations with an aggressive clinical behaviour has been previously shown in non-Hodgkin lymphomas, where especially the subgroup of B-cell lymphomas with a complex karyotype show poor response to conventional chemotherapy [31]. As a master regulator of various cellular programs involved in cancer growth and host immune response evasion, the MYC pathways may thus also be a promising target in oligometastatic NSCLC with BM. Although causation is unclear and needs to be assessed in larger cohorts, it is notable that 4 out of 5 MYC amplifications in our cohort occurred after a neoadjuvant conventional chemotherapy. Similarly, MYC alterations as a mutational imprint after chemotherapy are known from other cancer entities: in glioma, MYC amplifications are often encountered after progression post-temozolomide treatment [32].

In our cohort, age 62 years and the presence of vascular invasion in the primary tumour were 2 further independent predictors of shorter OS. The association of younger age with improved OS was previously reported in a Swiss multicentre study with a 5-year OS of 45% in the age group <60 years [14]. Similarly, the large meta-analysis by Ashworth *et al.* [33] that describes a 5-year OS of 29.4% included a young population with a median age of 61.1 years, notably almost 10 years younger than the general age of an NSCLC population. The association of vascular invasion with reduced survival is well documented in patients with resected NSCLC and it is not surprising that this hallmark of cancer also confers to poor outcome in OMD [34]. The good long-term outcome in our cohort with a 5-year OS of 43.5% can be put down to the large proportion of AC cases with isolated BM and encourages the use of LAT in oligometastatic NSCLC.

Limitations

This study has certain limitations. Our retrospective cohort of OMD patients with BM embraces varying treatment approaches including conventional chemotherapy, immunotherapy and targeted therapy that may affect survival. Since our study covers the niche of OMD patients treated with an aggressive approach, the inclusion period is long and certain FFPE specimens have been stored for >10 years. While our fixation methods and storage conditions were strictly standardized and our DNA extraction approach allowed to detect genetic alterations in older specimens, a certain age-related DNA degradation cannot be excluded. Furthermore, a subgroup of patients with early-stage or locally advanced NSCLC and potential metachronous OMD but previous death of other causes remains excluded from our cohort.

A further limitation is the medical treatment-related selection of mutational profiles under neoadjuvant treatment. In our cohort, 44.9% of all patients had undergone neoadjuvant treatment and especially in metachronous disease, a systemic treatment-related genetic imprint such as the abovementioned MYC amplifications is possible. Further studies are therefore required for a detailed assessment of tumour evolution in non-chemotherapy-naive patients. Last but not least, the tumour immune microenvironment and spatial transcriptomic landscape are known to play a major role in the mechanism of cancer progression and have not been investigated in this study [35]. Further immunological and digital spatial analyses among primary tumours and paired BM are therefore required to better understand the role of the immune response in oligometastatic NSCLC.

CONCLUSION

In summary, our study shows that oncogenic alterations of the primary tumour are maintained in the majority of matched BM. KRAS mutations were the most common oncogenic drivers in our cohort and in particular the KRAS G12C variant plays an important role in OMD. Novel KRAS inhibitors may therefore offer a valuable treatment option and clinical trials combining KRAS inhibitors with LAT could affect a large proportion of OMD patients. We observed that private genetic alterations were an independent predictor of poor OS. MYC amplifications were the most frequent private genetic aberrations in BM and were associated with poor OS. These findings are in line with recent results and corresponding data in non-Hodgkin lymphomas and

suggest that treatments targeting MYC-related pathways should be further investigated in patients with BM.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Raphael S. Werner: Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **Markus Rechsteiner:** Data curation; Formal analysis; Investigation; Methodology; Validation; Writing—review & editing. **Holger Moch:** Methodology; Validation; Writing—review & editing. **Alessandra Curioni-Fontecedro:** Investigation; Methodology; Validation; Writing—review & editing. **Michael Weller:** Methodology; Validation; Writing—review & editing. Tobias Weiss: Methodology; Validation; Writing—review & editing. **Luca Regli:** Methodology; Validation; Writing—review & editing. **Emilie Le Rhun:** Methodology; Validation; Writing—review & editing. **Fabian Mairinger:** Validation; Writing—review & editing. **Isabelle Opitz:** Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing. **Alex Soltermann:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing.

Reviewer information

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