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Original research

Early years, advanced disease: The unmet need in young adults with non-small cell lung cancer

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ABSTRACT

Introduction: Young adults are a minority of lung cancer (LC) patients, however, clinical presentation and cancer biology can differ. Here, we report the first German cohort study of young adults with LC.
Methods: We included patients diagnosed with LC between 2019 and 2023 at the West German Cancer Centre (University Medicine Essen) in this retrospective cohort study. For analysis of clinicogenomic baseline characteristics and overall survival (OS), patients were stratified by age at diagnosis into a young cohort (YC; n = 56, ≤45 years), an older cohort (OC; n = 2.682, >45 years) and analysed across age decades.
Results: 71 of 2.738 patients with LC (2.59 %) were ≤ 45 years old. 56/71 were diagnosed with NSCLC or SCLC. YC frequently reported no history of smoking (21 % vs. 6 %; p < 0.001). Among YC, adenocarcinoma (59 % vs. 49 %) and NSCLC not-otherwise-specified (NSCLC NOS; 27 % vs. 8.2 %) were the dominant histological subtypes (p < 0.001). Stage IV disease was significantly more common in YC (stage IV: 66 % vs. 44 %; p = 0.005) with more frequent regional lymph node involvement (N1-N3 79 % vs. 56.9 %) and extrathoracic lymph node metastases (38 % vs. 14 %; p < 0.001). Frequent targetable genomic alterations in YC included ALK translocations (21 % vs. 2.2 %; p < 0.001). YC with metastatic NSCLC had similar median OS compared to OC, although OS was improved in those with targetable alterations.
Conclusion: Early-onset LC is characterized by advanced disease stage, adenocarcinoma histopathology and frequent targetable genomic alterations, especially in patients without a history of smoking. Early diagnosis remains a critical unmet medical need in this subgroup of patients.

1. Introduction

Age is the main nonmodifiable risk factor for lung cancer (LC), which is one of the leading contributors to cancer-related mortality worldwide [1,2]. The incidence of LC increases with age, leading to a median age at diagnosis of 69 years in women and 71 years in men [1,3]. Young patients with LC, termed early-onset LC, represent a minority of patients with distinct clinical and genomic characteristics, potentially differing

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tumour biology, and a heterogeneous prognosis.

Young patients with LC are a subgroup of particular interest due to regional differences in genomic profiles and a changing demography, with women having surpassed men in the incidence of LC below 65 years of age in 2024 [2]. A broadly adapted definition of early-onset LC remains elusive. Therefore, age cut-offs ranging from 35 to 50 years of age are employed to study early-onset LC [4–7]. Early-onset LC is commonly associated with adenocarcinoma histology, advanced disease stage at diagnosis, and an increased frequency of targetable genomic alterations. However, smoking history, the patients' ethnic background, and other risk factors vary based on the specific patient population [4–6,8–11]. Whether these studies and current treatment strategies helped to improve early diagnosis and survival outcomes of patients with early-onset LC is unclear, especially in European patients. Considering changing demographics and treatment options as well as geographical differences regarding frequency of genetic alterations, further analysis of early-onset LC is warranted.

Here, we present results of the first German retrospective cohort study on early-onset LC. We set out to assess clinical and genomic characteristics and survival outcomes of patients with early-onset LC, which we diagnosed at our tertiary care centre between 2019 and 2023. To ensure comparability and account for age as a continuous variable, we used both an age cut-off to define young patients with LC (≤45 years of age, young cohort, YC; >45 years of age, older patients; OC) and divided our cohort into age groups using decades.

2. Methods

2.1. Patient selection and ethics

This single centre retrospective cohort study was approved by the Ethics Committee of the Faculty of Medicine of the University of Duisburg-Essen (24–12224-BO). Electronic medical records of all patients diagnosed with LC at the West German Cancer Centre between 2019 and 2023 and available interdisciplinary tumour board documentation were reviewed following data cut-off in July 2024. Patients were stratified by age at diagnosis into YC (≤45 years of age) and OC (>45 years of age). In addition, we divided our cohort into age groups using decades.

We queried our tumour board documentation database for age, sex, performance status by Eastern Cooperative Oncology Group (ECOG), smoking history, date of diagnosis, histological diagnosis, tumour stage, site of metastasis, date of death, and molecular pathology reports. We reviewed medical charts to assess initial symptoms, time to a histological diagnosis, and external molecular pathology results. Histological findings were reported according to the International Classification of Diseases for Oncology (ICD-O) in routine clinical practice and used to match patients to clinical diagnoses. 2.823 patients were matched to a histopathological diagnosis (see Figure S1).

We included patients with a first diagnosis of Non-small cell LC not otherwise specified (NSCLC NOS), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), adenosquamous carcinoma, large cell neuroendocrine carcinoma (LCNEC), Small Cell Lung Cancer (SCLC), typical carcinoid or atypical carcinoid based on available International Classification of Diseases for Oncology (ICD-O 3rd Edition) codes (Table 1, Figure S1) [12]. PD-L1 expression was assessed using immunohistochemistry staining of tumour samples (22C3) and graded by tumour proportion score (TPS) in routine clinical practice. Follow-up data on survival were derived from the West German Cancer Centre Cancer Registry and electronic medical records.

2.2. Molecular testing of tumour samples

Characterization of molecular tumour profiles was performed in routine clinical practice in accordance with local guidelines. Patients receiving next-generation sequencing (NGS) for molecular testing were included in the German National Network Genomic Medicine LC (nNGM). The availability of molecular pathology results depicted in Figure 3D are indicated in the supplementary flowchart (Figure S2). Alterations in genes encoding for the following proteins were derived from DNA-based NGS panels: anaplastic lymphoma kinase (ALK), Kirsten rat sarcoma oncogene (KRAS), TP53 (including variant allelic frequency; VAF), receptor tyrosine-protein kinase erbB-2 (ERBB2), MET proto-oncogene receptor tyrosine kinase (MET), epidermal growth factor receptor (EGFR), serine/threonine kinase 11 (STK11), proto-oncogene tyrosine-protein kinase (ROS1), phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase (PTEN), Kelch-like ECH-associated protein 1 (KEAP1), serine/threonine-protein kinase B-Raf (BRAF), fibroblast growth factor receptor 1, 2, 3, and 4 (FGFR1–4), isocitrate dehydrogenase 1 and 2 (IDH1–2). A TP53 VAF > 25 % was considered high. NGS results were analysed and assessed in routine clinical practice.

Table 1
Clinical Baseline characteristics of patients with Non-Small Cell (NSCLC) and Small Cell Lung Cancer (SCLC) below 45 years (YC) and above 45 years of Age (OC).

Characteristic	OCN = 2682[a]	YCN = 56[a]	p-value	q-value[b]
Age (years)	67.49 (8.99)	38.48 (6.29)	< 0.001[c]	< 0.001
Sex			0.7[c]	0.7
F	1164 (43 %)	26 (46 %)		
M	1518 (57 %)	30 (54 %)		
Never smoked			< 0.001[c]	< 0.001
Yes	162 (6.0 %)	12 (21 %)		
No/Unknown	2520 (94 %)	44 (79 %)		
Packyears	48 (38, 65)	33 (25, 68)	0.029[d]	0.036
ECOG			< 0.001[c]	< 0.001
ECOG0	514 (32 %)	38 (69 %)		
ECOG1	745 (46 %)	9 (16 %)		
ECOG2	272 (17 %)	4 (7.3 %)		
ECOG3	80 (4.9 %)	2 (3.6 %)		
ECOG4	16 (1.0 %)	2 (3.6 %)		
Morphology			< 0.001[c]	< 0.001
NSCLC NOS	220 (8.2 %)	15 (27 %)		
LUAD	1319 (49 %)	33 (59 %)		
LUSC	630 (23 %)	1 (1.8 %)		
Adenosquamous	90 (3.4 %)	1 (1.8 %)		
LCNEC	91 (3.4 %)	1 (1.8 %)		
SCLC	332 (12 %)	5 (8.9 %)		
Stage at Diagnosis			0.005[c]	0.009
IVB	766/2675 (29 %)	29/56 (52 %)		
IVA	396/2675 (15 %)	8/56 (14 %)		
IIIC	88/2675 (3.3 %)	3/56 (5.4 %)		
IIIB	243/2675 (9.1 %)	1/56 (1.8 %)		
IIIA	308/2675 (12 %)	7/56 (13 %)		
II	248/2675 (9.3 %)	5/56 (8.9 %)		
I	622/2675 (23 %)	3/56 (5.4 %)		
0	2/2675 (<0.1 %)	0/56 (0 %)		
NA	2/2675 (<0.1 %)	0/56 (0 %)		
T			0.2[c]	0.2
4	890 (33 %)	25 (45 %)		
3	462 (17 %)	8 (14 %)		
2	508 (19 %)	9 (16 %)		
1	736 (28 %)	10 (18 %)		
0	3 (0.1 %)	0 (0 %)		
NA	76 (2.8 %)	4 (7.1 %)		
N			0.007[c]	0.010
3	598 (22 %)	22 (39 %)		
2	685 (26 %)	15 (27 %)		
1	239 (8.9 %)	7 (13 %)		
0	1079 (40 %)	12 (21 %)		
NA	74 (2.8 %)	0 (0 %)		
M			0.003[c]	0.005
1	1161 (43 %)	37 (66 %)		
0	1485 (55 %)	19 (34 %)		
NA	36 (1.3 %)	0 (0 %)		

[a] Mean (SD); n (%); Median (Q1, Q3); n/N (%)
[b] False discovery rate correction for multiple testing
[c] Pearson's Chi-squared test
[d] Wilcoxon rank sum test

2.3. Graphical and statistical analysis

We applied Pearson's chi-squared test to compare proportions of categorical variables and Wilcoxon rank sum test to compare ordinal nonparametric variables of YC and OC. Log rank test was applied to compare survival outcomes. The association between PY and age was assessed using a linear regression model, with the goodness of fit reported as R-squared. We addressed multiple testing employing a hierarchical approach, given specific comparisons in each table and figure. The unadjusted p-values were initially evaluated for nominal significance at an alpha level of 0.05. In tables 1, 2, and S1, Benjamini-Hochberg adjusted p-values (q-values) were calculated within each table accounting for multiple tests and determined to be significant below a q-value of 0.05 (false discovery rate, FDR).

All statistical tests and graphic design were performed using R v.4.4.2. "Gtsummary" package was used to create tables with the indicated statistical tests [13]. The ggplot2 package was used for graphic design [14]. Kaplan-Meier estimates and a Cox proportional hazards model were employed to analyse overall survival (OS) outcomes and independent outcome variables using the R packages "survival" version 3.8.3 [15] and "survminer" version 0.5.0 [16]. We applied Cox Proportional Hazard Modelling to assess variables contributing to survival outcomes.

3. Results

3.1. Clinical presentation and prior history of young patients with lung cancer

We identified 71 cases of young adults ≤45 years of age with LC. Initial symptoms were heterogeneous with a majority of patients reporting initial respiratory symptoms (dyspnea, persistent cough, haemoptysis) or symptoms related to metastatic spread, e.g. neurological symptoms (including hemihypesthesia, syncope, visual impairment) or pain (thoracic/extremity/back pain) (Figure 1A). Time from symptom onset to a histological diagnosis was not significantly different between young patients with a diagnosis of NSCLC or SCLC (median 42 days; interquartile range (IQR) 28.8–75), and lung carcinoids (median 85 days; IQR 16.2–105) (Figure 1B).

Predisposing medical conditions included a variety of systemic diseases and prior malignancy in a subset of patients (12/71). Five patients had a prior history of cancer including acute lymphatic leukaemia (n = 1), cutaneous melanoma (n = 1), leiomyosarcoma (n = 1), extranodal NK/T cell lymphoma (n = 1), and seminoma (n = 1). Three young patients had a diagnosis of LC after lung transplantation. Beyond lung transplantation, potentially predisposing medical conditions for the development of cancer were infrequent and included Human Immunodeficiency Virus (HIV) infection (n = 1), Cystic Fibrosis (n = 2), Omenn Syndrome (n = 1) and Hypogammaglobulinemia (n = 1). Data on environmental exposure and occupational hazard were limited with one patient reporting to have lived close to a nuclear facility in eastern Europe and one patient had worked in the mining industry. Three patients had a family history of lung cancer. Germline testing was performed in a minority of patients, which detected Lynch Syndrome (n = 1), a retinoblastoma gene (RB1) deletion (n = 1), and a myotonin-protein kinase mutation (DMPK) mutation (n = 1). Eight patients reported prior or current substance abuse: cannabis (n = 5), opioids (n = 2), amphetamines (n = 1), cocaine (n = 1).

3.2. Young patients with lung cancer present with advanced disease at diagnosis

56/71 cases of young adults ≤45 years of age with LC, had a confirmed histopathological diagnosis of NSCLC or SCLC (young cohort; YC). A minority of young patients had typical lung carcinoids (n = 9) or atypical carcinoids (n = 5) (Figure 1C).

For further analysis, we compared YC to an older patient cohort, > 45 years of age (OC; n = 2.682). Sex distribution was comparable between the groups. YC patients had a significantly better performance status at diagnosis compared to OC ($p < 0.001$, $q<0.001$; see Table 1, Figure 1D). NSCLC not otherwise specified (NOS) and adenocarcinoma (LUAD) were the most common morphological subtypes in YC with 15

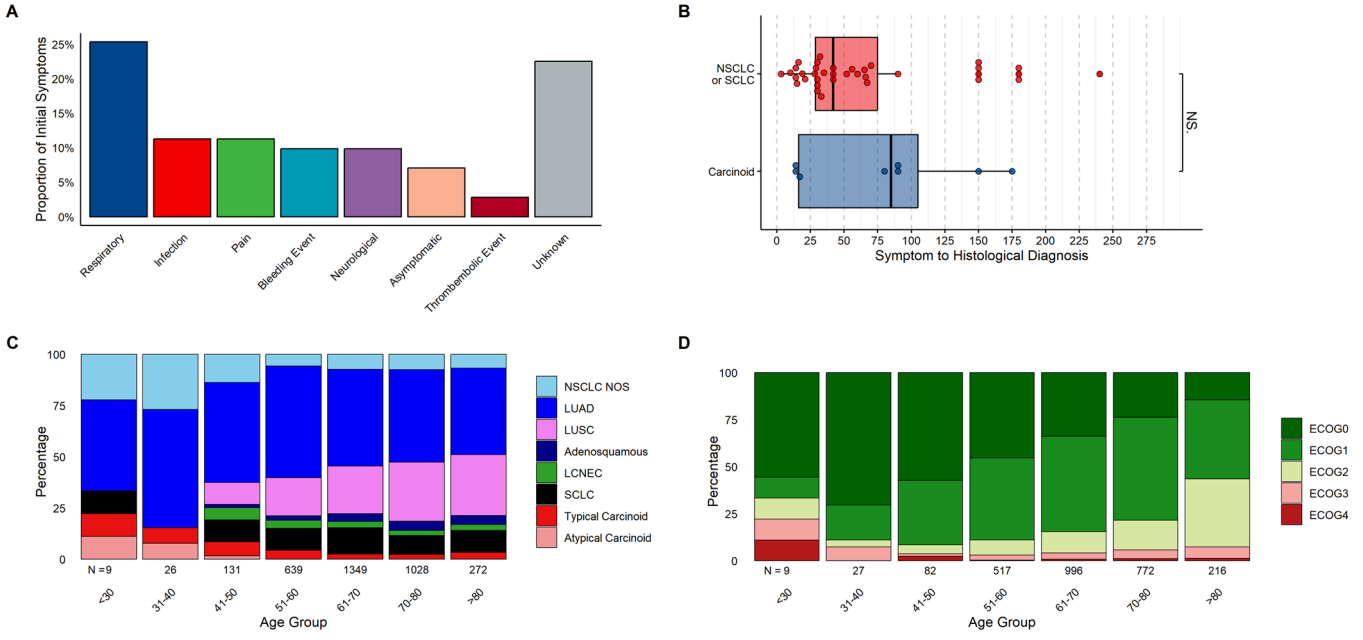

Fig. 1. Clinical presentation and histological diagnosis in patients with lung cancer. Initial symptoms in young patients with lung cancer (A). Time to histological diagnosis in days stratified by histology group in young adults with lung cancer (B). Tumour morphology (C) and ECOG performance status (D) stratified by age group. Abbreviations: NSCLC NOS: Non-Small Cell Lung Cancer not otherwise specified; LUAD: Lung Adenocarcinoma; LUSC: Lung Squamous Cell Carcinoma (LUSC); LCNEC: Large Cell Neuroendocrine Carcinoma; SCLC: Small Cell Lung Cancer; ECOG: Eastern Cooperative Oncology Group performance status; N: number of cases per age group. Statistical test: Wilcoxon rank sum test (NS.: not significant).

(27 %) and 33 cases (59 %), respectively. Only one patient with adenosquamous carcinoma, one patient with squamous cell carcinoma (LUSC) and one patient with large cell neuroendocrine carcinoma (LCNEC) histology were identified in YC. In comparison, adenosquamous, LUSC, and LCNEC grew more common with increasing age and represented 3.4 %, 23 % and 3.4 % of cases in OC, respectively (Figure 1C). SCLC was more frequent in OC compared to YC (n = 332 vs. n = 5; 12 % vs. 8.9 %). YC reported significantly more frequently that they did not have a history of smoking (21 % vs. 6 %; $p < 0.001$, $q<0.001$) and overall fewer pack years (PY; mean 33 vs. 48; $p = 0.029$, $q=0.036$).

YC were staged following a standardised clinical algorithm using positron emission tomography–computed tomography (PET/CT; 45/56, 80 %) and magnetic resonance imaging (MRI) of the brain (37/56; 66 %). In all other cases CT scans of the brain, chest, and abdomen were used for disease staging.

YC commonly presented with more advanced disease stage at diagnosis (Figure 2A) characterized by regional lymph node involvement (N1-N3 79 % vs. 56.9 %; see Table 1, Figure 2C) and metastatic disease (66 % vs. 44 %; Figure 2D). YC with metastatic NSCLC more frequently had extrathoracic lymph node metastases (38 % vs. 14 %; $p = 0.001$, $q=0.006$), while other metastasis sites were equally frequent in YC and OC (see Table S1). In the whole cohort, there was no linear correlation between age at diagnosis and history of smoking measured in PY (Figure 2E; $R^2=0$, $p = 0.5$). However, some young patients reported heavy smoking with PY that exceeded years of age (Figure 2E). Therefore, we explored whether YC with no or a short history of smoking differed in their initial staging. Compared to YC with a history of smoking, YC with no or a short history of smoking often presented with stage IV disease (Figure 2F, G; $p = 0.169$), while OC with no or a short

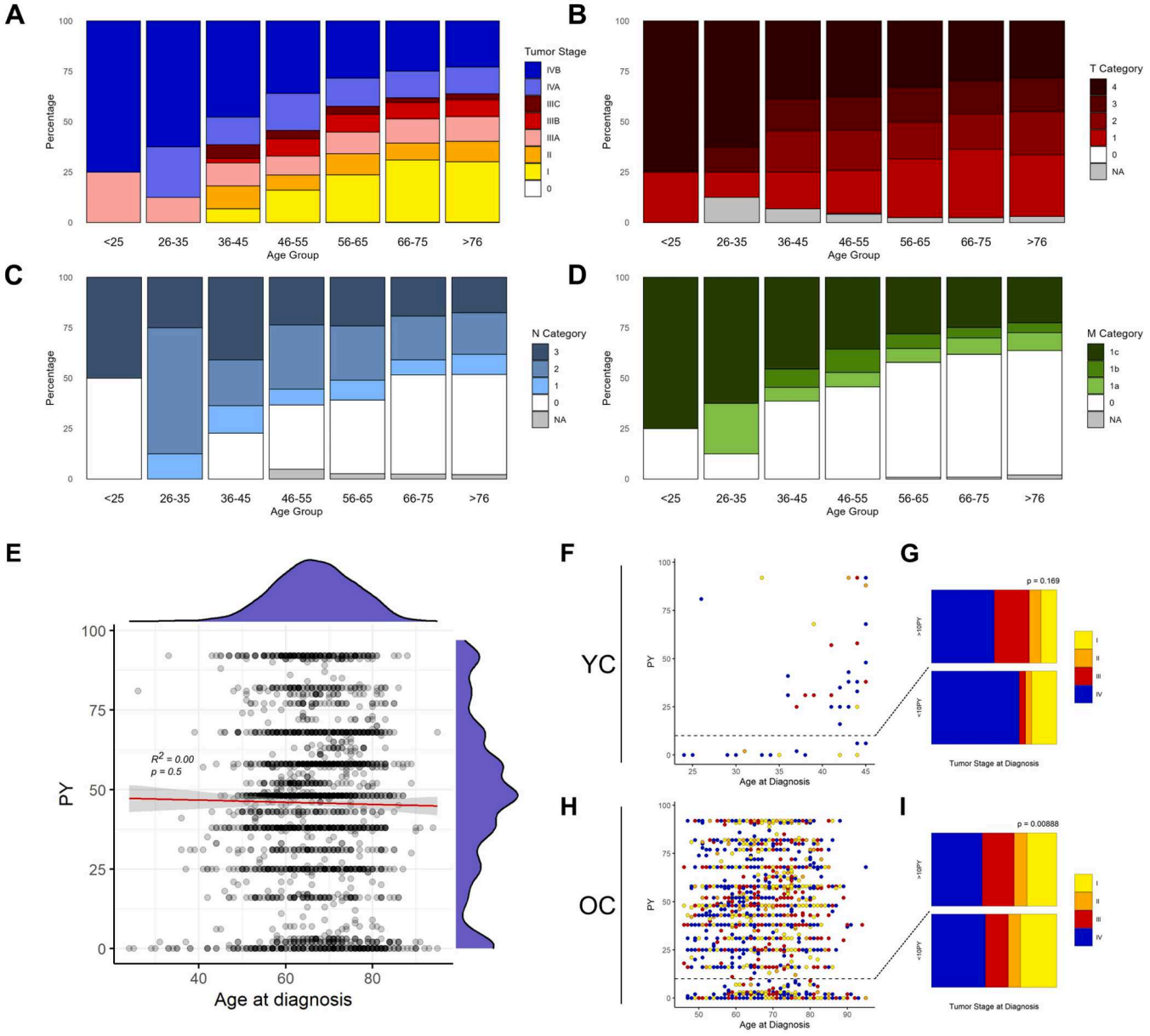

Fig. 2. Initial staging and smoking history of patients with NSCLC and SCLC. Tumour stage according to UICC 8th Edition (A) with detailed tumour size (T; B), lymph node involvement (N; C) and distant metastasis (D) stratified by age at diagnosis. Scatter plot depicting age at diagnosis and smoking history in pack years (PY) in the full cohort, with a linear regression model (PY~age). Distribution of cases are depicted in marginal histograms (E). Tumour stage at diagnosis stratified by age at diagnosis and smoking history as well as patient subgroups according to smoking history (>10PY: top; <10PY: bottom) for patients ≤ 45 years of age (YC; F, G) and > 45 years of age (OC; H, I). Statistical test: Pearson's Chi-squared test (G, I),.

history of smoking were significantly more likely to have lower disease stages compared to OC, who had smoked at least 10PY (Figure 2H, I; p = 0.009).

3.3. Targetable genomic alterations are frequent in young patients with NSCLC

51/71 young patients had a diagnosis of NSCLC of which 39 had available molecular pathology data (Figure S2). A detailed overview of individual patient cases including clinical and molecular pathology data are depicted in Figure 3A-F.

Smoking history was available in 33/39 cases of which 19 patients reported a history of smoking. Frequent alterations included TP53 (OC 62 % vs. YC 56 %; p = 0.6) and KRAS mutations (37 % vs. 20 %; p = 0.3), (see Table 2). A subset of YC had high TP53 VAF (n = 14, 36 %; Figure S4A). ALK rearrangements were detected significantly more frequently in YC (21 % vs 2.2 %; p < 0.001, q<0.001), with ALK-EML4 rearrangements being the most common alteration in YC. Only one patient in YC with a history of heavy smoking had an ALK rearrangement (1/8; Figure 3A, D). MET amplifications were common (6/39; 15 %) with one high-level MET amplification (see Table 2; Figure 3D). BRAF alterations in YC were only detected in patients with a history of smoking, while one ERBB2 copy number variation and one ERBB2 insertion were detected in two female patients without a history of smoking (Figure 3D). Lack of PD-L1 expression was rare among YC (6/39) of which 1/6 an IDH1–2 mutation, 1/6 an ALK translocation, 2/6 patients had an EGFR mutation, and 2/6 TP53 mutations (Figure 3B, C). PD-L1 TPS was not significantly different between YC and OC (Figure S4). Patients with available molecular pathology data had advanced disease (stage III and IV: 35/39; Figure 3D).

Next, we leveraged a large retrospective cohort of NSCLC patients from our centre to explore age-related patterns of genetic alterations in our patient collective. Relative frequency of ALK alterations were highest in age groups < 25, 26–35, and 36–45. ERBB2 alterations were rare overall but detected twice in the age group 26–35. KEAP1 and STK11 alterations were most frequent in patients between the ages of 36 and 65, while TP53 mutations were relatively frequent in patients aged 56–75 (Figure 3E). Additionally, there was a relative increase in MET and EGFR alterations in patients > 76 years of age.

3.4. Therapy and survival of young patients with NSCLC

Due to the limited cohort size, we focused overall survival analysis on patients with stage IV NSCLC. OC had a median follow-up of 42 months and YC of 34 months. Median OS (mOS) was similar in YC and OC with 23.5 months and 29.8 months, respectively (Figure 4A). Overall survival was significantly improved in YC with targetable genomic alteration (mOS not reached vs. 7.7 months; p = 0.03) (Figure 4B).

Data on systemic treatment were available for 31/37 YC patients with metastasized NSCLC of which 14, 9 and 4 patients received second-line, third-line and fourth-line therapy, respectively. Most patients received chemotherapy (Chemo) or chemo-immunotherapy (Chemo-IO) in the first-line setting. Patients, who received first-line targeted therapy, were treated with Osimertinib (n = 2), Brigatinib (n = 1) and Alectinib (n = 5). One patient received targeted first-line therapy as a study participant. Second-line targeted therapies included Alectinib (n = 2) and Crizotinib (n = 1) (Figure 4C).

We included young patients with NSCLC in a cox proportional hazard model to assess variables associated with OS. Albeit limited by small sample size, a late histological diagnosis (>60 days from symptom onset to histological diagnosis; hazard ratio (HR) 1.94, p = 0.441) showed a trend towards worse OS, while the presence of a targetable genomic alteration (HR 0.18, p = 0.158) and low TP53 VAF (HR 0.4, p = 0.366) were non-significantly associated with improved OS. In the full cohort older age, male sex, worse performance status, a histological subtype of NSCLC NOS and advanced tumour stage were independent variables associated with worse OS (Figure S3).

4. Discussion

This study represents the first report on the detailed clinicogenomic characteristics of LC in young adults in Germany. Using tumour board documentation, clinical data, and molecular pathology reports of a large cohort of patients from our tertiary care centre, we provide a current analysis of age-related patterns of LC with a focus on early-onset LC. Based on the known association between smoking status and genomic alterations [10,17], we delineated two distinct subpopulations of young adults with NSCLC in our cohort: a) YC without a history of smoking: stage IV disease at diagnosis, frequent ALK alterations and b) YC with a history of smoking: alterations of TP53, KRAS and BRAF, and lower disease stage at diagnosis.

Furthermore, we contextualised early-onset LC with data from patients with LC of all ages, which is crucial for interpretability since the clinicogenomic characteristics of NSCLC depend on patient-intrinsic factors (e.g. age, ethnicity, socioeconomic background) and patient-extrinsic factors (e.g. screening programmes, environmental exposure, smoking, rate of molecular testing, NGS gene panels) [9,18–20].

4.1. Strengths

Previous European studies on early-onset LC date back to patients followed in 2010–2016, prior to approval of immune checkpoint inhibitor (ICI) treatment for advanced NSCLC [10,11,21]. These European studies highlight advanced disease as a hallmark of early-onset LC. Nonetheless, we still found metastatic disease at diagnosis in a substantial proportion of YC diagnosed in 2019–2023.

Metastatic lung cancer at diagnosis may be related to increased time to a histological diagnosis. As described previously, initial symptoms of YC are heterogeneous, due to often systemic spread of the disease [4]. Median time from symptom onset to a histological diagnosis of NSCLC or SCLC in young patients was 42 days with a majority of patients receiving a diagnosis within the World Health Organisation recommended 90 days [22]. Nonetheless, roughly 1 in 4 YC patients received a histological diagnosis of NSCLC later than 75 days from symptom onset. These findings collectively emphasise that early diagnosis remains a pivotal unmet medical need for young patients with LC.

Early LC detection in young patients is a challenge. Physicians' suspicion of LC in younger patients might be lower and age over 50 years is one inclusion criterion for early LC detection programs using computed tomography (CT) scans [23,24]. Novel imaging techniques, e.g. ultra-low dose photon-counting CT protocols, and non-invasive screening modalities could help to tailor LC screening programs to young adults and enable early LC diagnosis [25,26].

Despite better performance status, mOS was similar in patients with stage IV NSCLC between OC and YC. YC patients with a targetable genomic alteration had significantly improved OS. Albeit limited by small cohort size, we identified low TP53 VAF and presence of a targetable genomic alteration as potential variables associated with improved survival. Meanwhile late histological diagnosis showed a non-significant association with worse OS.

International guidelines recommend molecular testing in stage IV NSCLC to enable biomarker-guided targeted therapy, but real-world molecular testing rates remain insufficient [27]. As thorough molecular testing at our tertiary care centre and other studies highlight, molecular testing is particularly crucial in young patients with NSCLC due to the high incidence of targetable genomic alterations [4,5,10,21,28]. In our cohort, ALK alterations were common in YC, while EGFR mutation frequency was relatively low regardless of age at diagnosis (10 %). This aligns with previous Israeli (19 %), Irish (9 %), and French (8 %) studies on molecular alterations in early-onset LC [4,5,10,11], while other studies with predominantly Asian patients report substantially higher EGFR mutation rates (up to 50 %) [9,29,30].

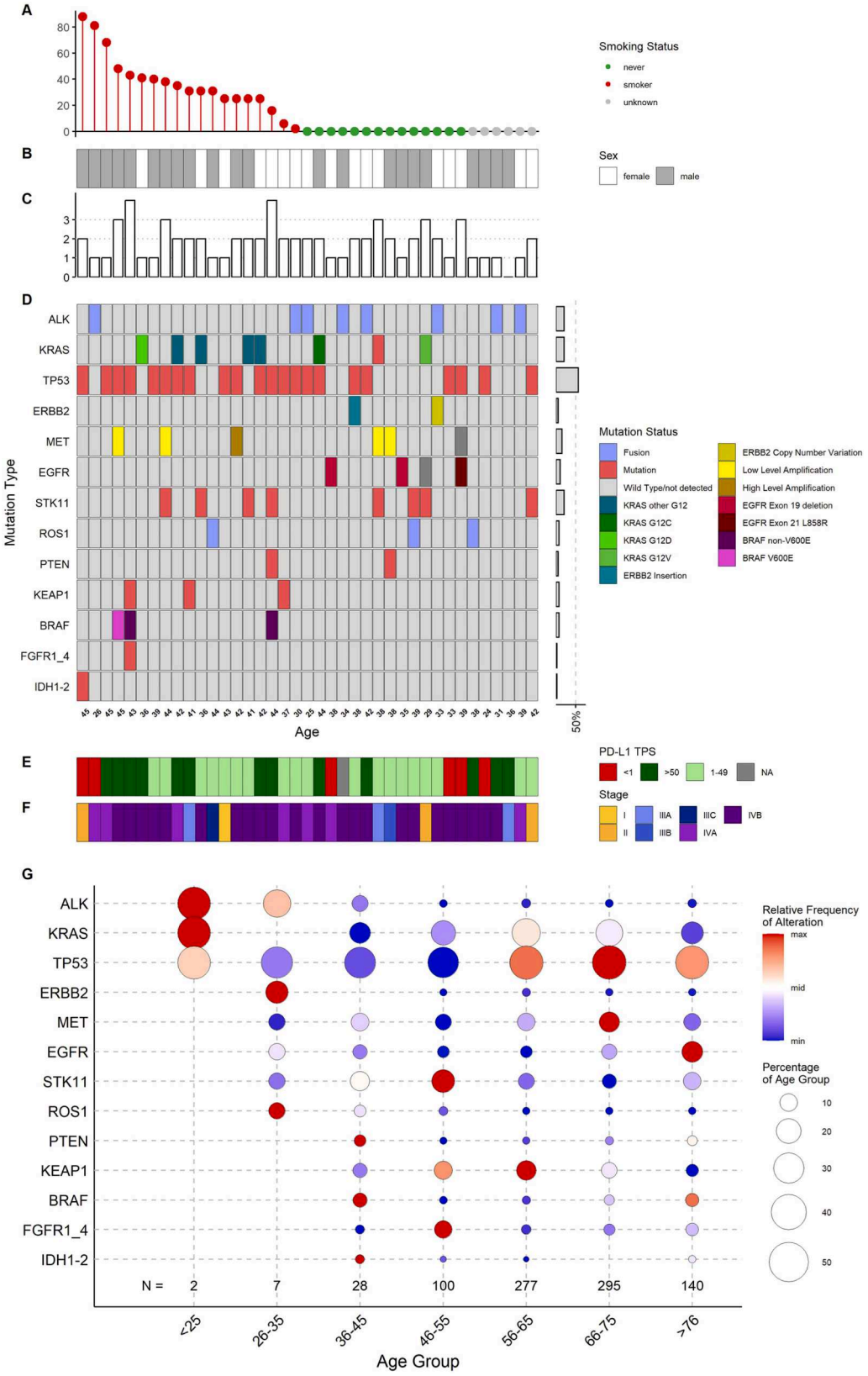

Fig. 3. Clinicogenomic baseline characteristics of YC and OC with NSCLC. Smoking history (A), sex (B), number of mutations detected (C), tile plot of NGS-based genomic testing (D; right: frequency of alteration, bottom: patient age), individual PD-L1 tumour proportion score (PD-L1 TPS) (E), and tumour stage (F) in young adults with NSCLC (n = 39). Each column refers to one patient (A-F). Balloon plot of gene alterations stratified by age groups in patients with NSCLC (G). Relative frequency of gene alterations with age groups as denominator. If the respective alteration was detected in the age group (n > 0), balloon size indicates percentage of cases within the age group. N: number of cases per age group. For abbreviations of molecular markers, please refer to the methods section.

Table 2
Molecular pathology results of patients with Non-Small Cell Lung Cancer (NSCLC) below 45 years of age (YC) and above 45 years of age (OC).

Characteristic	OC N = 825[e]	YCN = 39[e]	p-value[f]	q-value[g]
ALK			< 0.001	< 0.001
Translocation	18 (2.2 %)	8 (21 %)		
Mutation	10 (1.2 %)	0 (0 %)		
WT	795 (96 %)	31 (79 %)		
Other	2 (0.2 %)	0 (0 %)		
KRAS			0.3	0.7
Mutation	31 (3.8 %)	1 (2.6 %)		
G12X	48 (5.8 %)	4 (10 %)		
G12C	114 (14 %)	1 (2.6 %)		
G13X	24 (2.9 %)	0 (0 %)		
G12D	44 (5.3 %)	1 (2.6 %)		
G12V	42 (5.1 %)	1 (2.6 %)		
NA	1 (0.1 %)	0 (0 %)		
WT	521 (63 %)	31 (79 %)		
TP53			0.6	0.8
Mutation	511 (62 %)	22 (56 %)		
WT	314 (38 %)	17 (44 %)		
ERBB2			0.11	0.5
Mutation	14 (1.7 %)	0 (0 %)		
Insertion	2 (0.2 %)	1 (2.6 %)		
Amplification	1 (0.1 %)	0 (0 %)		
Copy Number Variation	3 (0.4 %)	1 (2.6 %)		
Deletion-Insertion	1 (0.1 %)	0 (0 %)		
Other	1 (0.1 %)	0 (0 %)		
WT	803 (97 %)	37 (95 %)		
MET			0.2	0.5
Low Level Amplification	36 (4.4 %)	4 (10 %)		
High Level Amplification	9 (1.1 %)	1 (2.6 %)		
Exon 14 Skipping Mutation	5 (0.6 %)	0 (0 %)		
Mutation	20 (2.4 %)	0 (0 %)		
WT	653 (79 %)	33 (85 %)		
Other	102 (12 %)	1 (2.6 %)		
EGFR			0.9	0.9
Copy Number Variation	2 (0.2 %)	0 (0 %)		
Exon 19 Deletion	40 (4.8 %)	2 (5.1 %)		
Exon 18 Mutation	2 (0.2 %)	0 (0 %)		
Exon 19 Other Mutation	4 (0.5 %)	0 (0 %)		
Exon 20 Insertion	4 (0.5 %)	0 (0 %)		
Exon 20 Other Mutation	5 (0.6 %)	0 (0 %)		
Exon 21 L858R	21 (2.5 %)	1 (2.6 %)		
Exon 21 other	6 (0.7 %)	0 (0 %)		
Compound Mutation	8 (1.0 %)	0 (0 %)		
Other	3 (0.4 %)	1 (2.6 %)		
WT	730 (88 %)	35 (90 %)		
STK11			0.5	0.8
Mutation	116 (14 %)	8 (21 %)		
Other	6 (0.7 %)	0 (0 %)		
WT	703 (85 %)	31 (79 %)		
ROS1			< 0.001	< 0.001
CD74 Translocation	1 (0.1 %)	0 (0 %)		
Translocation	3 (0.4 %)	3 (7.7 %)		
Mutation	15 (1.8 %)	0 (0 %)		
Other	2 (0.2 %)	0 (0 %)		
WT	804 (97 %)	36 (92 %)		
PTEN			0.8	0.9
Mutation	26 (3.2 %)	2 (5.1 %)		
WT	799 (97 %)	37 (95 %)		
KEAP1			0.4	0.8
Mutation	126 (15 %)	3 (7.7 %)		
Other	1 (0.1 %)	0 (0 %)		
WT	698 (85 %)	36 (92 %)		
BRAF			0.7	0.9
Non-V600E Mutation	27 (3.3 %)	2 (5.1 %)		
V600E Mutation	13 (1.6 %)	1 (2.6 %)		
WT	785 (95 %)	36 (92 %)		
FGFR1_4			0.5	0.8
Mutation	63 (7.6 %)	1 (2.6 %)		
NA	1 (0.1 %)	0 (0 %)		
WT	761 (92 %)	38 (97 %)		
IDH1–2			0.7	0.8
Mutation	5 (0.6 %)	1 (2.6 %)		
WT	820 (99 %)	38 (97 %)		

[e] n (%)
[f] Pearson's Chi-squared test
[g] False discovery rate correction for multiple testing

Although we focused our study on early-onset LC, we detected varying frequencies of STK11, KEAP1, MET, and KRAS alterations depending on age at diagnosis. This may point towards age-related changes in tumour biology beyond oncogenic driver mutations, which may be captured insufficiently in current clinical practice. In line with other European patient cohorts with a high prevalence of smoking, the frequency of EGFR mutations was low (11 % of patients with NSCLC) regardless of age at diagnosis [29,30]. This likely reflects the high prevalence of current or former smokers in Germany, affecting approximately 70 % of males and up to 60 % of females [31].

4.2. Limitations

Early-onset LC is increasingly recognized as a distinct clinical subgroup of LC; however, a universally accepted definition of early-onset LC remains elusive [4,32]. We circumvented this by accounting for age as a continuous variable using age groups and ensured comparability by using an age cut-off of 45 years, which aligns with previously identified age cut-offs ranging from 40 to 50 years [5,10,11,33,34]. Nowadays, ageing is increasingly investigated as a non-linear process, with bursts of ageing reported at 45 and 65 years of age. This may strengthen 45 years of age as a potentially meaningful age cut-off [35].

Our study has several limitations inherent to retrospective data collection in a single institution. While our institution is a large super-regional cancer care centre and we were able to build a substantial cohort of young patients, early-onset LC is rare. Hence, statistical interpretability and generalisability of our young cohort remain limited and this study is prone to selection and information bias. Despite initial diagnosis at our centre, some patients may have chosen treatment at other institutions, e.g. after disease relapse, which contributes to incomplete follow-up and molecular pathology results.

While patient-reported smoking history in PY was available as tobacco exposure measure and contextualized molecular findings, PY can be unreliable and do not capture other means of smoking, e.g. second-hand smoking, shisha, or vaping [36]. Data on other risk factors associated with LC were not systematically assessed in tumour board documentation and electronic medical records, hence, only a subset of patients had available data on environmental exposure, or occupational hazards [37,38]. Despite thorough testing of common alterations, not all patients received the same NGS-based genotyping as molecular profiling evolves over time. Since data in our cohort date back to 2019, only some patients in early disease stages were evaluated for molecular alterations, which would be necessary today to enable novel (neo)adjuvant treatment strategies in EGFR-mutant and ALK-rearranged NSCLC [28,39,40].

Despite these limitations, our study's large patient cohort and detailed analysis offer novel insights into early-onset LC in Germany. We provide a contemporary perspective on this distinct subgroup, highlighting the persistent unmet medical need for earlier diagnosis and molecular testing in young patients with LC.

5. Conclusions

In this retrospective German cohort study, the clinicogenomic characteristics of LC in young adults were characterized by adenocarcinoma histology and advanced stage at diagnosis. History of smoking differentiated two subpopulations of patients with early-onset LC: Young patients without a history of smoking often had stage IV disease at diagnosis and frequent ALK alterations. A history of smoking was associated with less frequent targetable genomic alterations and lower disease stage at diagnosis in YC. Early diagnosis remains a pivotal unmet medical need for young patients with LC to improve survival outcomes in this subgroup of patients.

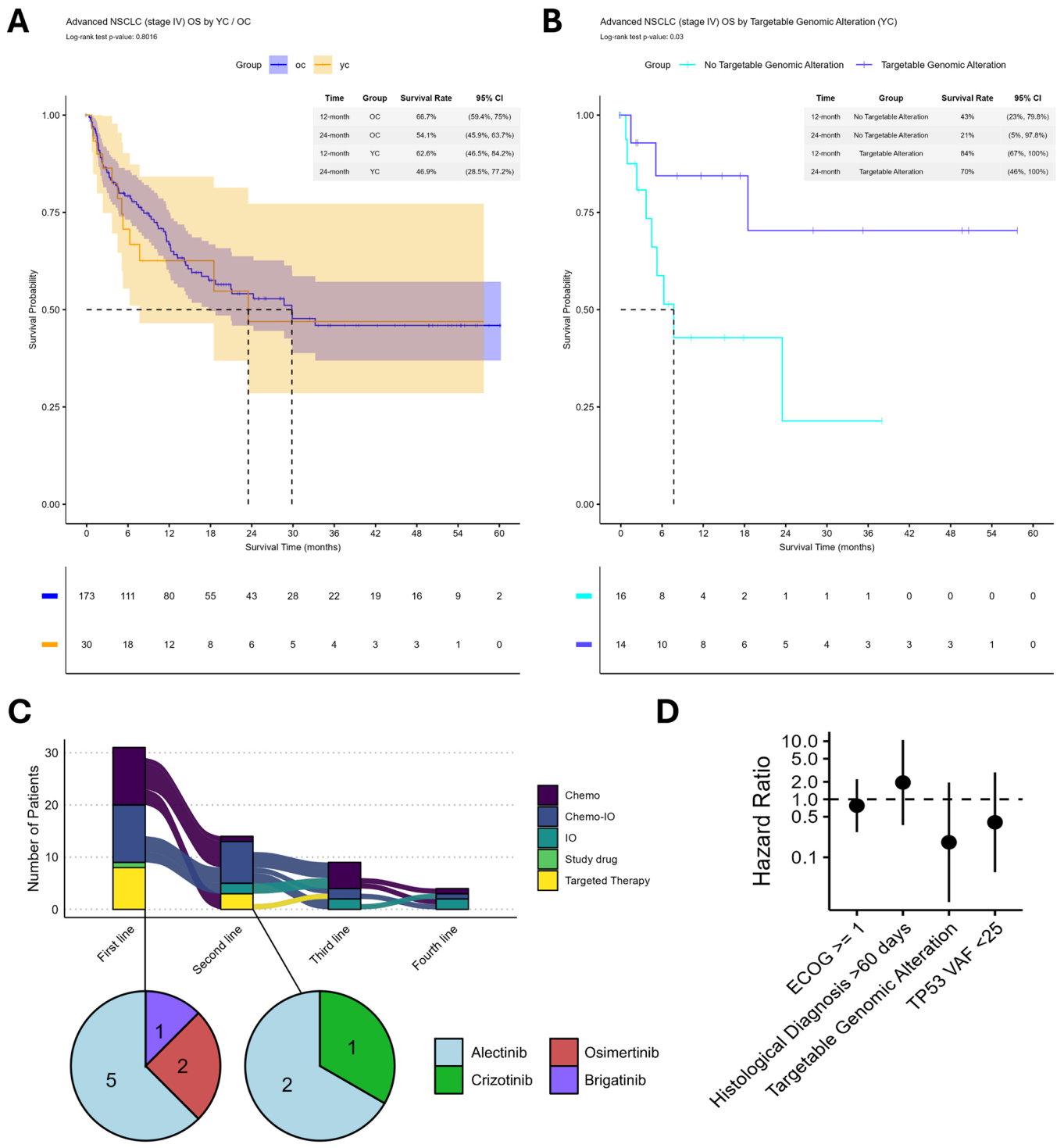

Fig. 4. Systemic therapy and survival outcomes of patients with stage IV NSCLC. OS of patients with advanced NSCLC (stage IVA and IVB) stratified by age at diagnosis (YC / OC) (A). OS of YC patients stratified by targetable genomic alteration (B). Systemic therapy of YC with stage IV NSCLC with targeted therapies in first and second line detailed as pie charts (C). Cox proportional hazard model for OS in YC (D). Dashed line: Median survival (A, B). Statistical test: Log-rank test (A,B). Abbreviations: Chemo: Chemotherapy; Chemo-IO: Chemo and immune checkpoint inhibitor.

Declaration

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CRediT authorship contribution statement

Filiz Oezkan: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Martin Schuler:** Writing – review & editing, Validation, Investigation. **Wilfried E.E. Eberhardt:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Marcel Opitz:** Writing – review & editing, Validation, Investigation. **Halime Kalkavan:** Writing – review & editing, Validation, Investigation. **Christian Taube:** Writing – review & editing, Investigation. **Martin Stuschke:** Writing – review & editing, Investigation. **Fabian Doerr:** Writing – review & editing, Validation, Investigation. **Aleksandra Graw:** Writing – review & editing, Investigation. **Kaid Darwiche:** Writing – review & editing, Investigation. **Servet Bölükbas:** Writing – review & editing, Investigation. **Martin Metzenmacher:** Writing – review & editing, Investigation. **Dirk Theegarten:** Writing – review & editing, Investigation. **Jane Winantea:** Writing – review & editing, Investigation. **Hubertus Hautzel:** Investigation, Writing – review & editing. **Julius Keyl:** Writing – review & editing, Resources, Data curation. **Maximilian Webendörfer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcel Wiesweg:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MWi reports honoraria for an advisory role from Amgen, AstraZeneca (AZ), Bristol-Myers Squibb (BMS), Daiichi Sankyo, GlaxoSmithKline (GSK), Janssen, Novartis, Pfizer, Roche, and Takeda; travel costs from Amgen, Janssen, and Daiichi Sankyo as well as research funding from BMS, and Takeda. JW reports sponsoring for events from Astra Zeneca, Olympus, Erbe Elektromedizin GmbH, and Janssen, financial support for congress attendance from Pierre Fabre and honoraria from Pulmonx, Berlin Chemie, Roche Pharma AG, and Astra Zeneca. MM reports honoraria for consulting from Astra Zeneca, AMGEN, Janssen, MSD, Novartis, Novocure, Pfizer, Roche, and Takeda outside the submitted work. KD reports speaker fees from Astra Zeneca, Böhringer Ingelheim, Boston Scientific, BroncusMedical, Erbe, Olympus, PulmonX, and Storz, consultant activity for bess, Boston Scientific, Böhringer Ingelheim, Broncus Medical, Fujifilm, FreeFlow, Lys Medical, Morair Medtech, Medtronic, Olympus, PulmonX, Siemens, and Storz as well as research grants from Ambu, Broncus, Epigenomics, Gala Therapeutics, Janssen, Novartis, Nuveira, PneumRx, Pulmonx, and Roche. SB reports consultant fees from Becton Dickinson (BD), Livsmed, Lexington Medical, and Karl Storz, speaker fees from AstraZeneca (AZ), Bristol Myers Squibb (BMS), KLS Martin, Roche, and Johnson&Johnson (JJ) and research funding to institution from Janssen, BMS, AZ, Achilles Therapeutics, and BD. MS reports research grants his institution from AZ and honoraria for an advisory role from AZ. MSc reports consultant fees from Amgen, AZ, Blueprint Medicines, BMS, Gilead, GlaxoSmithKline (GSK), Immunocore, JJ, MSD, Novartis, Regeneron, Roche, and Sanofi, honoraria for lectures from Amgen, BMS, GSK, JJ, MSD, and Roche as well as research funding to institution from AZ, BMS, and JJ. WE reports honoraria for advisory board function from AZ, Takeda, Roche, JJ, Pfizer, MSD, BMS, Amgen, Sanofi, Regeneron, Eli Lilly, Boehringer Ingelheim, Pierre Fabre, honoraria for educational lectures from AZ, Takeda, Roche, JJ, Pfizer, MSD, PMS, Amgen, Regeneron, Eli Lilly, Boehringer Ingelheim as well as institutional research grants from AZ. FOE reports honoraria from Genentech Ltd./Roche, Sanofi Aventis, AZ, ERBE Elektromedizin GmbH, and Janssen, research support from Genentech Ltd/Roche, honoraria as a consultant from Genentech Ltd./Roche, and travel support from Genentech Ltd./Roche, AZ, and Janssen. The remaining authors report no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116011.

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