Diploma Thesis

Prognostic impact of targetable driver alterations in resected early-stage lung cancer

Submitted by

Selma Konjić

Attaining the academic degree

Doktorin der gesamten Heilkunde

(Dr^{in}. med. univ.)

at the

Medical University of Graz

executed at the

University Department of Oncology

under the supervision of

Univ. FÄ Priv.-Doz. Dr.med.univ. Angelika Terbuch

Priv.-Doz.Dr.Dr. Luka Brcic

Graz, 1. Dezember 2025

Affirmation

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

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Graz, 1. Dezember 2025 Selma KONJIC m.p.

Acknowledgement

I would like to begin by expressing my deepest gratitude for the supervision and mentorship of FÄ Priv.-Doz. Dr.med.univ. Angelika Terbuch. I thank her profoundly for the opportunity to work together. It was her continuous guidance, invaluable support and insightful feedback during the whole data collecting and writing process that made this thesis possible.

I would also like to thank my second supervisor Priv.-Doz.Dr.Dr. Luka Brcic for his support, being my first contact and introduction to the fascinating field that is lung cancer.

I am forever thankful to my parents, partner and family for their unconditional love, understanding and constant encouragement during my whole university experience. Attaining this degree is an accomplishment of many great people in my life, not just mine.

Zusammenfassung in Deutsch

Hintergrund: Lungenkrebs ist nach Brustkrebs bei Frauen und Prostatakrebs bei Männern die am zweithäufigsten diagnostizierte Krebsart und die häufigste krebsbedingte Todesursache. Die gezielte Therapie für nicht-kleinzelliges Lungenkarzinom (NSCLC) mit bekannten EGFR Mutationen und ALK-Fusionen hat sich im letzten Jahrzent so entwickelt, dass die Therapie für diese Entitäten nicht mehr auf zytotoxischer Chemotherapie beruht. Außer diesen beiden gut erforschten Mutationen sind andere molekulare Veränderungen, bei denen man eine zielgerichtete Therapie einleiten könnte, derzeit noch irrelevant für die Entscheidungsfindung in adjuvantem Setting beim NSCLC im Frühstadium. Ziel dieser retrospektiven Analyse war es zu untersuchen, ob es einen Unterschied im rezidivfreien Überleben beim NSCLC im Stadium I–III mit medikamentös behandelbaren molekularen Veränderungen im Vergleich zu Subtypen ohne behandelbare molekulare Veränderungen gibt.

Patienten und Methoden: Alle konsekutiven Patient*innen, die zwischen Januar 2015 und Dezember 2020 an drei österreichischen Einrichtungen wegen NSCLC (Stadium I–III) mit behandelbaren Mutationen kurativ operiert wurden, wurden identifiziert und mit Tumoren ohne behandelbare molekulare Veränderungen verglichen. Tumoren mit dem EGFR-mutierten Subtyp wurden aufgrund bereits vorliegender Ergebnisse aus prospektiven Studien ausgeschlossen.

Ergebnisse: 160 Proband*innen hatten Tumoren mit molekularen Veränderungen, 355 Proband*innen dienten als Kontrollgruppe. Bei Patient*innen mit Tumoren mit onkogenen Treibermutationen war die Prävalenz weiblicher Personen ($p < 0,001$) und Nichtrauchern ($p = 0,01$) höher. Die drei häufigsten Veränderungen waren die KRAS G12C-Mutation (n=92), ALK-Fusionen (n=21) und die BRAF V600E-Mutation (n=15). Die geschätzte kumulative Rezidivrate nach 1, 3 und 5 Jahren betrug 16%, 38% und 46% bei Patient*innen ohne molekulare Veränderungen, 16%, 38% und 48% bei Patient*innen mit der KRAS G12C-Mutation und 12%, 33% und 55% bei Patient*innen mit anderen molekularen Veränderungen (P=0,89). Univariable Prädiktoren für ein erhöhtes

Rezidivrisiko waren ein höheres Tumorstadium (P<0,001), Erhalt einer neoadjuvanten Behandlung (P<0,001) und Erhalt einer adjuvanten Behandlung (P=0,03). Der fehlende Zusammenhang zwischen molekularem Veränderungsstatus und Rezidivrisiko blieb auch nach multivariabler Adjustierung für Tumorstadium und perioperative Behandlung bestehen (p=0,82 für KRAS-G12C-Mutation und p=0,43 für jede andere molekulare Veränderung).

Schlussfolgerung: NSCLC-Patient*innen mit resezierten Tumoren, die molekulare Veränderungen aufweisen, haben nach chirurgischer Behandlung und gegebenenfalls Chemotherapie das gleiche Rezidivrisiko wie Patient*innen mit Tumoren ohne molekulare Veränderungen.

Abstract in english

Background: Lung cancer is the second most commonly diagnosed cancer after breast cancer in women and prostate cancer in men, and the most common cause of cancer-related death. Targeted therapy for non-small cell lung cancer (NSCLC) with known EGFR mutations and ALK fusions has evolved over the past decade to the point where treatment for these entities no longer relies on cytotoxic chemotherapy. Besides these two well-studied mutations, other targetable molecular alterations are currently irrelevant for decision-making in the adjuvant setting for early-stage NSCLC. The aim of this retrospective analysis was to investigate whether there is a difference in recurrence-free survival in stage I–III NSCLC with targetable molecular alterations compared to subtypes without targetable molecular alterations.

Patients and Methods: We identified all patients who underwent surgery with curative intent for NSCLC (stage I–III) with targetable mutations between January 2015 and December 2020 at 3 Austrian institutions and compared them to patients with tumors without targetable molecular alterations. The EGFR-mutated subtype tumors were excluded from prospective studies due to previously available results from prospective trials.

Results: 160 subjects had tumors with molecular alterations and 355 subjects served as controls. Among patients with tumors harboring oncogenic driver mutations, the prevalence was higher among females ($p<0.001$) and non-smokers ($p=0.01$). The three most common alterations were the KRAS G12C mutation (n=92), ALK fusions (n=21), and the BRAF V600E mutation (n=15). The estimated cumulative recurrence rates at 1, 3, and 5 years were 16%, 38%, and 46% for patients without molecular alterations, 16%, 38%, and 48% for patients with the KRAS G12C mutation, and 12%, 33%, and 55% for patients with other molecular alterations ($P=0.89$). Univariable predictors of increased recurrence risk included higher tumor stage ($P<0.001$), receipt of neoadjuvant treatment ($P<0.001$), and receipt of adjuvant treatment ($P=0.03$). The lack of association between molecular alteration status and recurrence risk persisted even after multivariable adjustment for tumor stage and perioperative treatment (P=0.82 for KRAS G12C mutation and P=0.43 for any other molecular alteration).

Conclusion: This study has shown that NSCLC patients with resected tumors harboring molecular alterations have the same risk of recurrence when treated surgically and, if appropriate, with chemotherapy as patients with tumors without molecular alterations.

Already released publication

Terbuch A, Konjic S, Schlintl V, Absenger G, Jost PJ, Lindenmann J, Swatek P, John N, John T, Wurm R, Zacharias M, Posch F, Hochmair MJ, Fabikan H, Weinlinger C, Illini O, Horvath L, Gamerith G, Wolf D, Augustin F, Brcic L. Prognostic impact of targetable driver alterations in resected early-stage lung cancer. Transl Lung Cancer Res. 2024 Nov

Abbreviations

ALK	Anaplastic lymphoma kinase
BSC	Best supportive care
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CRT	Chemoradiotherapy
CT	Computed tomography
ctDNA	Circulating tumor DNA
DFS	Disease-free survival
DLCO	Diffusing capacity of the lung for carbon monoxide
EBUS	Endobronchial ultrasound
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EUS	Endoscopic ultrasound
FDG	F-Fluordesoxyglucose
FEV_1	Forced expiratory volume in the first second
KRAS	Kirsten rat sarcoma virus
NSCLC	Non-small cell lung cancer
OS	Overall survival
pCR	Pathological complete response

PD-L1	Programmed death-ligand 1
PET-CT	Positron emission tomography – computed tomography
PFS	Progression free survival
PORT	Post operative radiotherapy
PY	Pack years
RATS	robotic assisted thoracoscopic surgery
RT	Radiotherapy
SBRT	stereotactic body radiotherapy
SCLC	Small-cell lung cancer
TC	Tumor cell
ThRCRI	recalibrated thoracic revised cardiac risk index
TNM	tumor, nodes, metastases
UICC	union internationale contre le cancer
VATS	video assisted thoracoscopic surgery
VO_2max	maximal oxygen consumption

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1 Introduction

1.1 Lung cancer

Lung cancer is an epithelial malignancy originating in the lung, classified in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Approximately 80% of all lung cancers are NSCLC and 15% are SCLC (1). The remaining 5% of reported lung cancer has unclear histology findings. Based on morphology, immunohistochemistry and genetics, non-small cell lung cancers can further be categorized histologically in adenocarcinomas and squamous cell carcinomas (1). Small cell lung cancers fall under the category of neuroendocrine tumors. Because of the high cell division rate, small cell lung cancers grow faster, metastasize earlier and are rarely treated with curative approach, making the prognosis worse. Lung cancers metastasize via the lymphatic system to other lung parts and lymph nodes (mediastinal, scalene and supraclavicular lymph nodes) and via the blood stream to brain, liver, adrenal glands and bones. Adenocarcinomas make up about 62% of diagnosed lung cancers in women, making the ratio for women higher than in men, whose 49% of lung cancers fall under the diagnosis of adenocarcinomas (1).

1.1.1 Epidemiology

Lung cancer is the second most commonly diagnosed cancer (11,7% of total reported cancer cases) with 2,2 million new cancer cases in 2020, right after female breast cancer and prostate cancer in men (2). It is the leading cause of cancer death, accounting for 18,9% of cancer deaths, accounting for 1,8 million cancer deaths in 2020(2). In women, it ranks as the third most common cancer, after breast and colorectal cancer, and as the second most frequent cause for cancer mortality, after breast cancer (2). Incidence and mortality are about 2 times higher in men(2) The median age at diagnosis of lung cancer is 71 years (3). Smoking, being the biggest risk factor for lung cancer, was first established in high income countries, particularly men, which was followed by an unambiguous increase of lung cancer incidence (2). There is a clear dose-response relationship between risk of developing lung cancer and number of cigarettes smoked per day, as well as the age at the start of tobacco use (4). About two-thirds of lung cancer deaths can be attributed to smoking, making tobacco-prevention a large factor in reducing incidence and mortality (2). The prevalence of tobacco use has declined in over 100 countries, especially those with stronger implementation of tobacco policies and regulations, which showcases the importance of such measures (2). Lifetime smokers have a 20-30 times greater risk of developing lung cancer than non-smokers, even passive exposure to tobacco smoke increases the risk by 30-50% (4). Other risk factors include family history of lung cancer and occupational exposure to asbestos, fine dust (e.g. quartz dust), ionizing radiation, some metals (such as arsenic, chrome, nickel, cadmium and uranium), traffic emissions and radon, particularly amongst miners (4). One noticeable interesting high incidence rate is observed in Chinese women, who show low smoking prevalence, which is thought to reflect the influence of air pollution and burning of solid fuels for heating and cooking oil in households in the genesis of lung cancer (4).

1.1.2 Symptoms

Lung cancer is often asymptomatic in the early stage. Symptoms in patients with lung cancer often reflect an already advanced stage (1). They can arise locally from the primary tumor itself, or they can result from distant metastases (1). Typically, the symptomatic patients present with chronic cough, hemoptysis and B-symptoms (unintentional weight loss, night sweats and unexplained fever) (1). Symptoms due to local growth of tumor such as dyspnea, chest pain, dysphagia, hoarseness and superior vena cava congestion can also occur. Bone pain and pathological fractures can result from bone metastases for example, whereas headaches and other neurological symptoms (e.g. dizziness, seizures, neurological deficits) can reflect brain metastases (1). In small cell lung cancer, which will not be further discussed as this work is based on NSCLC patients only, paraneoplastic syndromes are common, because the tumor cells are derived from the neuroendocrine system and thus can produce hormones (1). One special form of locally advanced lung cancer is the Pancoast tumor. This is a peripherally located, fast-proliferating lung cancer in the Lung-apex area, which, due to its fast growth, can penetrate the pleura in this area and infiltrate the stellate ganglion and the brachial plexus, compress the blood vessels to the arm and the superior vena cava and infiltrate the thoracic wall, mostly at the level of the first or second rib, leading to pain. The infiltration of the stellate ganglion leads to Horner syndrome, consisting of ptosis, miosis and enophthalmos, whereas the infiltration of the brachial plexus leads to plexus neuralgia with pain, as well as motoric and/or sensible deficiencies in the arm, such as arm weakness and para- or hypesthesia (1).

1.1.3 Diagnosis

Screening for lung cancer with low dose CT is currently established in many countries and is recommended in current (>30py) or former (<15 years since cessation) smokers aged 55 to 74 based on the results of the National Lung Screening Trial (NLST) and NELSON trial. It has been shown to increase lung cancer diagnosis by factor 2.7 and reduce lung-cancer related mortality by 20% and all-cause mortality by 6,7% (NLST), as well as reduce the fraction of lung cancers diagnosed at stage IV (NELSON) (5). Other screening methods, such as chest X-ray, sputum analysis and biomarkers are not recommended for clinical use (5).

All suspected lung cancers should be pathologically diagnosed before any treatment decision. Pathological diagnosis is recommended to be in line with the 2021 WHO classification for lung tumors (5).

There are different diagnostic tests for diagnosing lung cancer, the most common one being bronchoscopy. Regional lymph nodes are often additionally evaluated by EBUS (endobronchial ultrasound) and/or EUS (endoscopic ultrasound), if N2 or N3 metastases are suspected (5). The samples obtained through lymph node aspirations are often sufficient for molecular analysis with biomarker testing being essential for treatment decision making in stage IB-III patients (5). A CT- or ultrasound-guided biopsy may be indicated for peripheral suspicious pulmonary nodules, which are inaccessible by bronchoscopy. Mediastinal lymph nodes inaccessible to ultrasound can also be reached surgically by mediastinoscopy. (5)

Mandatory imaging techniques to firstly discover the primary tumor and then to further determine the stage of the tumor are chest X-ray, CT-Thorax, PET-CT and MRI brain (5). Conducting all imaging techniques ensures that the size of the tumor is precisely determined, and no metastases are overlooked. Mandatory laboratory examinations include complete blood cell count and chemistry panel including renal function, liver enzymes and LDH (1). Prior to planning the operation, it is mandatory to test the lung function, which determines how much of the lung tissue can be removed during the operation for the lungs to still be able to function sufficiently after a part of it is removed (5).

Biomarkers:

PD-L1 (programmed death-ligand 1) has an important role in planning treatment for lung cancer as well in the neaodjuvant and adjuvant as in the palliative setting. Pathologists should report the total number of PD-L1 positive cells (cells expressing PD-L1), or at least their percentages (5).

Testing for EGFR and ALK is mentioned further in the paper with regards to targeted therapy options that arise from positivity for these oncogenic drivers. The data currently supports only the testing of these markers, but the implementation of broad next-generation sequencing (NGS) routinely in non-squamous NSCLC in stages II-III might be valuable in the future, since the number of mutations with clinical significance for targeted therapy is expected to grow (5).

Circulating tumor DNA (ctDNA) in plasma is a strong postoperative prognostic factor in early stage and locally advanced NSCLC, since ctDNA clearance after curative intent treatment with chemo(immuno)therapy is associated with improved outcome and higher proportion of pathological complete response (pCR), but since the current assays deliver a large percentage of false-negative results, further technological advances are needed before implementing the testing into routine clinical use to (de)escalate treatment (5). Conversely, preoperative ctDNA is a poor prognostic factor (5).

1.1.4 Classification

The current classification is based on the TNM stages according to IASLC (International Association for the Study of Lung Cancer) and UICC (Union for International Cancer Control) Version 9 (6). In case of multiple primary tumors where two or more nodules are found to be separate tumors through histological and molecular examination, a multidisciplinary tumor board is necessary for a final conclusion (5). Following criteria for multiple primaries must be fulfilled: each tumor is malignant, distinct from one another and the possibility of one tumor being a metastasis of the other is excluded. These tumors should then be evaluated and treated accordingly, as each tumor should be given a separate T, N and M category. If both primaries are of the same histological subtype, an NGS analysis is recommended to distinguish between two primaries and one tumor being a metastasis of the other (5).

TNM stages (1):

T (Tumor)	**Tis**	• **carcinoma in situ**
	T1	• **largest diameter <3 cm, surrounded by lung tissue or visceral pleura, main bronchus not involved**
	• **T1a (mi)**	• **minimally invasive adenocarcinoma**
	• **T1a**	• **largest diameter <1cm**
	• **T1b**	• **largest diameter >1 and < 2 cm**
	• **T1c**	• **largest diameter >2 and < 3 cm**
	T2	• **diameter >3 and <5 cm** **or** • **Infiltration of the main bronchus regardless of distance from the carina, but without direct invasion of the carina** • **infiltration of the visceral pleura or** • **tumor-related partial atelectasis or obstructive pneumonia extending into the hilus and involving parts of the lung or the entire lung**
	• **T2a**	• **largest diameter >3 and <4 cm**
	• **T2b**	• **largest diameter >4 and <5 cm**
	T3	• **largest diameter >5 but <7 cm or** • **infiltration of thoracic wall (including parietal pleura and superior sulcus), phrenic nerve, parietal pericardium, or** • **additional tumor nodule in the same lung lobe as the primary tumor**

	T4	• **largest diameter >7cm or with direct infiltration of diaphragm, mediastinum, heart, great vessels (v. cava, aorta, pulmonary artery, pulmonary vein intrapericardially), trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina or** • **additional tumor node in another ipsilateral lung lobe**

N (lymph Node)	**N0**	• **no lymph node metastases**
	N1	• **metastasis in ipsilateral, peribronchial, and/or ipsilateral hilar lymph nodes and/or intrapulmonary lymph nodes or direct invasion of these lymph nodes**
	N2	• **metastasis in ipsilateral mediastinal and / or subcarinal lymph nodes**
	• **N2a**	• **single N2 station involvement**
	• **N2b**	• **multiple N2 station involvement**
	N3	• **metastasis in contralateral mediastinal, contralateral hilar, ipsi or contralateral deep cervical, supraclavicular lymph nodes**

M (Metastasis)	**M0**	• **no distant metastases**
	M1	• **distant metastases**
	• **M1a**	• **separate tumor nodule in a contralateral lung lobe** • **pleura with nodular involvement** • **malignant pleural effusion** • **malignant pericardial effusion**
	• **M1b**	• **isolated distant metastasis in an extrathoracic organ**
	• **M1c**	• **multiple distant metastases (>1) in one or more organs**

Stage	Primary Tumor	Lymph Nodes	Distant Metastases
0	Tis	N0	M0
IA1	T1a(mi) T1a	N0 N0	M0 M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a-c T2a-b T3	N1 N1 N0	M0 M0 M0
IIIA	T1a-c T2a-b T3 T4 T4	N2 N2 N1 N0 N1	M0 M0 M0 M0 M0
IIIB	T1a-c T2a-b T3 T4	N3 N3 N2 N2	M0 M0 M0 M0
IIIC	T3 T4	N3 N3	M0 M0
IVA	each T each T	each N each N	M1a M1b
IVB	each T	each N	M1c

Proposed 9th Ed TNM Categories

Proposed 9th Ed TNM Categories						
T/M	Description	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural / pericardial dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple lesions, 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple lesions, >1 organ system	IVB	IVB	IVB	IVB	IVB

Figure 1: TNM categories according to the 9th Edition of the TNM Classification for lung cancer. (6)

1.1.5 Preoperative evaluation and risk assessment

In future text, only the locoregional, non-metastatic tumors will be addressed, as this is the topic of the current work. In non-metastatic tumors, detailed locoregional staging and cardiopulmonary fitness determine the choice of treatment. Curative intent with surgery and/or radiotherapy leads to acute (following resection) or chronic (gradually, following radiotherapy) loss of pulmonary function, which is why this loss must be estimated before treatment to determine if the patient can undergo this treatment and sustain an acceptable life quality post treatment (5). Pulmonary function can be estimated by forced expiratory volume in the first second (FEV_1) and diffusing capacity of the lung for carbon monoxide (DLCO), further assessment for patients without major comorbidities whose FEV_1 and DLCO values are <80% includes cardiopulmonary exercise testing (CPET) with a maximal oxygen consumption (VO_2max) assessment (5). If the predicted postoperative FEV_1 and DLCO values are ≥60% and no major comorbidities are present in a patient, surgical resection is acceptable and should proceed with no further testing. If FEV_1 and/or DLCO values are <30%, VO_2max testing should be done to estimate postoperative morbidity. Serious postoperative complications can arise if resection is done in patients with a VO_2max <10ml/kg/min, in this case a sublobar resection and non-surgical treatment need to be considered (5). Algorithms for preoperative evaluations of patients are in use. A patient's condition regarding the comorbidities should be optimized before surgery (5). A beneficial effect of lung volume reduction in patients with emphysema, depending on the anatomy of emphysema and location of tumor can potentially be observed. If the tumor is located within the emphysematous tissue, the removal of this tissue might improve the lung mechanics and postoperative pulmonary function tests (7).

For cardiac assessment, there is a recalibrated thoracic revised cardiac risk index (ThRCRI), that takes weighted factors (ischemic heart disease, history of cerebrovascular disease, serum creatinine >2mg/dL and planned pneumonectomy) into account to create class groupings of patients with different levels of risk for lung resection (5).

Assessment of risk regarding radiotherapy is harder to determine than that of a resection, since acute and long-term risks must be considered. Nevertheless, the dose of radiation to the heart must be minimized, considering the known adverse effects of radiotherapy on cardiac function and blood vessels (5).

1.1.6 Treatment

1.1.6.1 Treatment of resectable, early-stage lung cancer

Surgery:

The most important treatment option is surgical removal of the tumor with radical lymph node dissection (5). Complete resection is defined by following criteria: a) all known disease (tumor with the surrounding invaded tissue) must be removed with histologically confirmed negative resection margins and b) mediastinal lymph nodes must be removed with the highest mediastinal node being tumor free and c) absence of extracapsular tumor invasion. If all three criteria are fulfilled, the resection is considered complete and the staging regarding the tumor size and lymph node involvement can be conducted further (5). Except in adenocarcinomas in situ or minimally invasive adenocarcinomas (where even observation alone or wedge-resection might be decided on) and peripheral tumors which are ≤2cm in diameter (stage IA1 and IA2), where sublobar resection (wedge resection or segmentectomy) has been shown to be non-inferior to lobectomy in terms of DFS and OS, thus showing higher locoregional recurrence rate, lobectomy is still the current treatment of choice (5). In case of sublobar resection, intraoperative confirmation of N0 disease is crucial, since N1 finding would result in abandoning the sublobar resection and carrying out a lobectomy instead.

In the newest, 9th TNM Edition (8), there is a new sub-classification of N2 into N2a (single N2 station involvement) and N2b (multiple N2 station involvement), this addition results from the observation that patients with multi-station N2 disease have decreased survival compared to patients with single-station N2 disease (6).

For resectable stage IIIA or selected IIIB disease, neoadjuvant chemoimmunotherapy, followed by resection may be appropriate after consulting with thoracic surgeons in the multidisciplinary team, whereas resection of multistation N2 involvement or bulky N2 disease continues to be evaluated (5,8). However, CheckMate 77T study of perioperative chemoimmunotherapy administration showed patients undergoing successful resection of multiple N2 station involvement having little difference in outcome compared to those with single N2 station disease (9). That shows that even patients with multiple N2 station disease may also profit from pre- or perioperative chemoimmunotherapy, though it is still questionable if these patients benefit more from this approach or if the treatment with concurrent chemoradiotherapy followed by durvalumab as maintenance is more favorable (5). Every case should be individually discussed and decided for in a multidisciplinary team meeting.

Surgical removal of lung cancer is done through either standard thoracotomy or minimally invasive surgery (VATS=video assisted thoracoscopic surgery and RATS=robotic assisted thoracoscopic surgery), whereas minimally invasive surgery results in less postoperative morbidity and mortality, which makes it a preferable and standard approach in patients with stage I-II tumors and considerable in resectable stage III tumors, according to the local expertise (5). Both procedures can result in comparative margin clearance (R0 resection = negative margins) and nodal dissection (5). Advantages of VATS are reduced incisional pain, shorter hospital stay with fewer hospital readmissions and better physical function at 5 weeks (5).

Complete resection with a curative intent should also be strived for in patients with multiple primaries, taking place after discussion in multidisciplinary tumor board. One possibility in this case is a combination of surgical removal and stereotactic ablative radiotherapy (5).

Regarding the lymph nodes management during surgery, following criteria must be fulfilled: a) at least six nodes/stations must be removed, with b) three of them being mediastinal, including the sub-carinal station (preferably all but at least three mediastinal lymph nodes should be removed) and c) the most cranial mediastinal node must be tumor free (5). Mediastinal lymph nodes are removed en bloc with the surrounding fatty tissue. Regarding the intrapulmonary and hilar lymph nodes, the exact number of nodes that should be removed is not specified, since it is thought that these are being resected with the lung specimen. All resected lymph nodes must be examined histologically (5). In stages II and IIIa, systematic lymph node dissection is recommended (with step 1 being the mediastinal lymph node excision with criteria mentioned above and step 2 being hilar- and intrapulmonary node excision in a centrifugal manner), whereas for stage I the overall survival, risk for local recurrence and distant metastases don’t seem to be affected by the method of lymph node management (5). A recent study found significantly better overall survival in patients who underwent systematic nodal dissection compared to patients who underwent merely a selective nodal sampling (10).

Radiotherapy:

In case the risks of surgical tumor removal are too high or not accepted by patients, radiotherapy should be offered. The options here are SBRT (stereotactic body radiotherapy), which is the preferred radiotherapy for localized peripheral stage I lung cancer with curative intent, and hypofractionated high-dose radiotherapy (5). For SBRT, long term control rates of ≥90% and grade 3-5 toxicity in less than 5% of the cases were reported, making it superior to hypofractionated high-dose radiotherapy (5). SBRT has demonstrated favorable outcomes in patients with severe COPD and elderly or frail patients. A prospective STARS study has shown that, in operable stage I NSCLC, VATS lobectomy with mediastinal lymph node dissection has no superiority over SBRT. The 5-year OS and DFS are comparable to those of surgically removed cancers (11). Resection stays an option for operable patients who experienced local recurrence after undergoing SBRT. In lung ART randomized controlled trial, patients with negative resection margins and N2 involvement with extracapsular invasion of the lymph nodes who had undergone post operative radiotherapy (PORT) demonstrated no favorable outcome compared to the patients not receiving PORT (12). Since radiotherapy failed to show a superior DFS and lead to additional side effects, such as pneumonitis and cardiopulmonary toxicity, PORT is not indicated after a complete tumor resection (5). The only favorable outcome of receiving PORT was a decreased incidence of mediastinal relapse (14% vs 28% in the non-receiving arm) (12). PORT may be recommended after R1 resection after a multidisciplinary team evaluation, whereas the order of adjuvant chemotherapy and PORT has to be decided individually.

Systemic therapy:

Systemic therapy can be applied in the neoadjuvant (before surgery), perioperative (before and after surgery) or adjuvant (only postoperative) setting.

Whether a patient may benefit more from a neoadjuvant or perioperative therapy or initial surgery followed by adjuvant therapy, should be decided on an individual case basis in a a multidisciplinary team meeting based on many factors, such as tumor stage, resectability, biomarkers, comorbidities, performance status (ECOG or Karnofsky Index) and patients's preference (5).

Neoadjuvant therapy (for EGFR- and ALK wild type cancers):
Adding immunotherapy to chemotherapy in the neoadjuvant and perioperative setting has led to adopting a new standard in treating patients with resectable stage II-III lung cancer.
Checkmate 816 study with nivolumab added to platinum-based chemotherapy for three cycles versus chemotherapy alone in the neoadjuvant setting showed increased pCR (24% vs. 2,2%) and improved event-free survival in resectable stage IB-IIIA NSCLC (13). Furthermore, the incidence of adverse effects was not greater than that with chemotherapy alone. Significant improvement of 5-year OS (65,4% vs. 55,0%) and especially in patients with pCR (95,3% OS rate) has also been proven (13). Whereas Checkmate 816 study evaluated nivolumab only in the neoadjuvant setting, another study, Checkmate 77T evaluated nivolumab in both neoadjuvant and adjuvant setting (9). In the checkmate 77T study, patients with resectable stage II to IIIB NSCLC received either 4 cycles of neoadjuvant chemotherapy plus nivolumab or neoadjuvant chemotherapy plus placebo, followed by surgery and adjuvant nivolumab or placebo every four weeks for a year. It has shown a significant improvement in EFS and pCR (25,3% for nivolumab vs. 4,7% for placebo/chemotherapy only) (9).
Keynote 671 study showed that neoadjuvant pembrolizumab in combination with cisplatin-based chemotherapy followed by surgery and then adjuvant pembrolizumab administration led to significant benefit in EFS, 3-year OS (71% vs. 64%) and pCR (18,1% vs. 4%) in patients with stage resectable stage II-IIIB NSCLC when compared to placebo instead of pembrolizumab in both neoadjuvant and adjuvant settings (14). Incidence of grade ≥3 treatment-related adverse effects was 44,9% for pembrolizumab vs. 37,3% for placebo.
AEGEAN study evaluated the administration of 4 cycles of platinum-based chemotherapy plus durvalumab or placebo neoadjuvantly before surgery, followed by adjuvant administration of durvalumab or placebo every four weeks for 12 cycles in patients with II to IIIB stage NSCLC (15). EFS and pCR (17,2% vs. 4,3%) showed

significant improvement compared to neoadjuvant chemotherapy alone. Adverse effects were comparable for durvalumab (42,4%) and placebo (43,2%).
More studies are required to evaluate which patient groups need only neoadjuvant chemoimmunotherapy vs. continued immunotherapy after surgery. Patients who do not achieve pCR or have persistent ctDNA in plasma have shown poor EFS and OS in studies.

Adjuvant chemotherapy:
Effects of adjuvant chemotherapy in patients with resected stage IA NSCLC were shown to be deleterious (16), however, it's relevance in cases of stage I NSCLC with high risk features, such as visceral pleural or lymphovascular invasion or high grade histology is unknown .
For patients with stages II and III (N1 and N2 status), adjuvant chemotherapy has been found to be beneficial. It has resulted in an overall survival (OS) improvement of 4-5% at 5 years, demonstrated in the LACE meta-analysis (17). The results are based on 5 of the largest trials of cisplatin-based chemotherapy, administering three to four cycles of cisplatin with the dose being at least 300mg/m^2, in combination with vinorelbine, gemcitabine or docetaxel in squamous NSCLC and pemetrexed in non-squamous NSCLC. Adding bevacizumab to the combination hasn't shown favorable effects (18). There is not enough data on carboplatin in the adjuvant setting, it may be recommended for patients with renal, neurological or other contraindications for cisplatin (5). Although the combination of cisplatin with vinorelbine is studied the most, other agents have at least equivalent therapeutic benefit. What has shown to be essential was the proper post-operative recovery and the absence of major comorbidities (19). A recent analysis of the National Cancer Database has shown that patients who are treated even after a longer post-operative recovery period of the usual 6 weeks, mostly shown in the studies before, also have a similar outcome (19). The value of systemic therapy in stage I is less clear, it's administering in Stage IA even resulting in a worse outcome (17)and leading to a small overall benefit in stage IB, limited to tumors with a size of >4cm. Therefore, in resected stage IB disease with tumors >4cm in diameter, systemic chemotherapy in an adjuvant setting can be considered.

Unlike the adjuvant chemotherapy, neoadjuvant chemotherapy hasn't been evaluated as much. Through administering neoadjuvant chemotherapy, size-reduction and down-staging might be achieved, which could result in a more limited resection (19).

Adjuvant immunotherapy:

There are still ongoing trials using anti PD-1 and anti PD-L1 checkpoint inhibitors in stage I-III (neo)adjuvant setting. One phase III study has shown significant improvement of DFS and a tendency toward improving of OS in patients with stage IB to IIIA NSCLC and PD-L1 TC ≥1% after administering atezolizumab for one year after four cycles of cisplatin-based chemotherapy in comparison to best supportive care after chemotherapy, showing superior benefit for PD-L1 TC≥50% (20).

In the same stages (IB to IIIA), administering pembrolizumab for one year after complete resection, significantly improved DFS in comparison to placebo after resection. Adjuvant chemotherapy was to be considered for stage IB and strongly recommended for stages II to IIIA. The results were regardless of PD-L1 expression (21).

No significant DFS improvement has been shown in a study with durvalumab compared to placebo in stages IB to IIIA after resection, regardless of PD-L1 expression (22).

Adjuvant targeted therapy:

Based on the phase III ADAURA trial, osimertinib, a targeted agent, is recommended as adjuvant therapy for 3 years for patients with EGFR Mutations (exon 19 deletion or exon 21 L858R mutations) after a complete resection in stages IB-IIIA (23). The ADAURA trial has demonstrated a prolonged disease-free survival (DFS)(23) and a significant overalls survival (OS) (24) when compared to placebo. On the other hand, another study has shown that in these patients, a targeted therapy with gefitinib does not prolong DFS or overall survival (OS) compared to the combination therapy consisting of cisplatin and vinorelbine, it merely appeared to prevent early relapse, since the Kaplan-Meier curves crossed around 4 years after surgery, showing no statistical significance (25). However, it might be of use for patients ineligible for combination chemotherapy, since it has shown comparable DFS and OS.

Similarly to Osimertinib for EGFR mutated NSCLC, adjuvant alectinib for 2 years provides improved DFS to patients with NSCLC stage IB to IIIA and ALK fusion, when compared to the administration of four cycles of platinum-based adjuvant chemotherapy (26).
It is unclear whether the patients with other mutations, for which effective treatments are available in the metastatic setting, should receive targeted adjuvant therapy after surgery. Targeted therapies still have an undefined role in the early-stage setting.

ALK fusion and EGFR Mutations (exon 19 deletion or exon 21 L858R variants) exclude the administration of (neo)adjuvant immunotherapy, since they are less responsive to ICIs (while being responsive to targeted agents mentioned above), which is again showcasing the importance of testing for these oncogenic drivers (5). Adjuvant cisplatin- (or carboplatin, if needed) based chemotherapy is recommended in patients with EGFR mutated disease in stages II-III before targeted therapy. In patients with ALK fusion, adjuvant chemotherapy might be considered before administering alectinib (5)

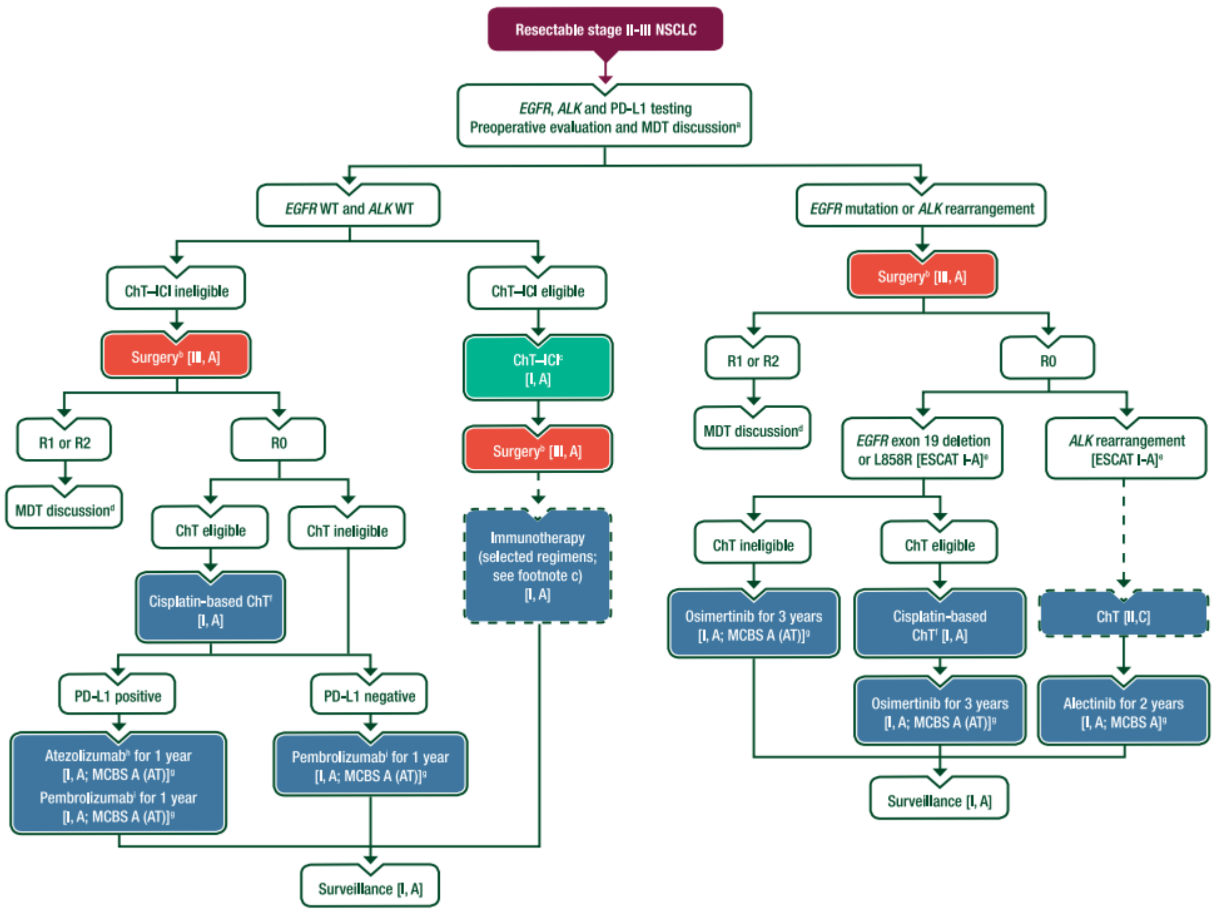

Figure 2: Management of resectable stage II-III NSCLC. Source: (5)

1.1.6.2 Treatment of unresectable stage III lung cancer

In a case that a surgery is not expected to deliver complete resection with negative margins (R0) even after neoadjuvant therapy, a tumor will be deemed unresectable after a discussion in a multidisciplinary team including an expert in thoracic surgery (19). Treatment of choice then becomes a cisplatin-based chemoradiotherapy (19).

In a meta-analysis comparing concomitant versus sequential chemoradiotherapy in locally advanced NSCLC, a consensus has been reached in favor of concurrent/concomitant chemoradiotherapy, since it has been proven to lead to higher 5-year survival rates, probably due to a better locoregional control, a higher rate of reversible esophagitis being the cost of it (27) If concurrent CRT is impossible for any reason, for example in elderly patients with poor fitness or patients with clinically relevant comorbidities, then sequential chemotherapy followed by definitive radiotherapy should be favored (19). The radiotherapy should be delivered with a total dose of 60-66 Gy over a period not longer than 7 weeks, delivering 2 Gy per fraction in 30-33 daily fractions (19). Based on one meta-analysis, higher doses per fraction of 2,6-3 Gy should be given only in case of a sequential CRT or RT alone for stage III NSCLC, thus accelerating the radiotherapy treatment and shortening the overall treatment time, because an absolute benefit of 2,5% in 5-year OS has been proven to exist in this case (28).

The concomitant cisplatin-based chemotherapy should be given in 3 to 4 cycles perioperatively, the cumulative dosis of cisplatin should be at least 300mg/m^2 (19).

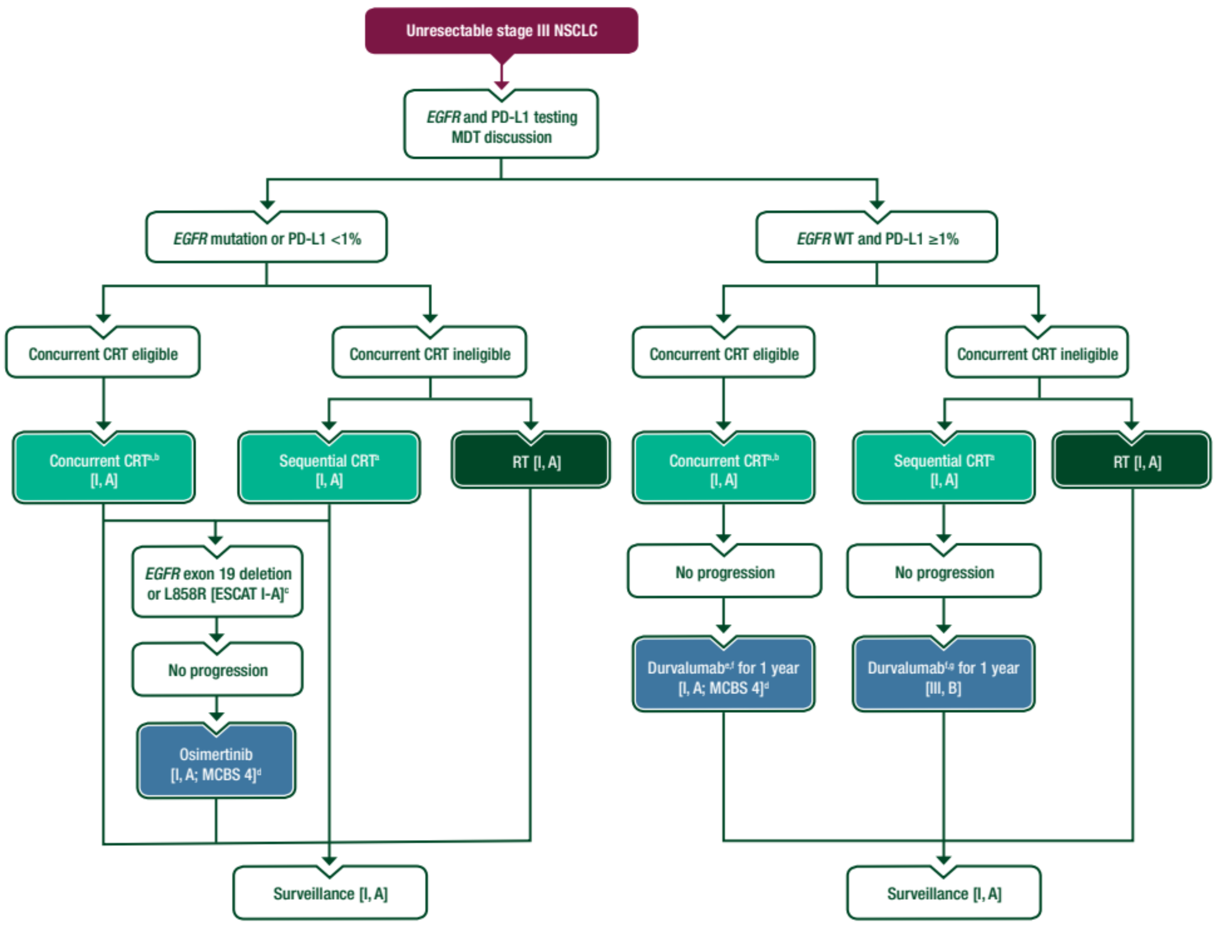

Figure 3: Management of unresectable stage III NSCLC. Source: (5)

2 Patients and methods

2.1. Study cohort

Patients with early-stage NSCLC have been analyzed for driver mutations and programmed cell death ligand 1 (PD-L1) expression at our institutions since 2015.

In this study, we retrospectively identified all consecutive patients who underwent surgery with curative intent for NSCLC (stage I–III) with targetable mutations between January 2015 and December 2020 at the Medical University of Graz, the Medical University of Innsbruck, and the Klinik Floridsdorf. We excluded all patients with EGFR-mutated subtype NSCLC, since results from earlier prospective trials are already available. However, patients with ALK-translocated NSCLC were included, because at the time of study initiation, there were no established results from prospective trials. The same methods and testing platforms were used at the Medical University of Graz and the Medical University of Vienna. In all non-squamous NSCLC, reflex testing was performed using separate DNA and RNA-based analyses. DNA-based analysis was performed using the Ion Ampliseq Colon and Lung Cancer Research Panel panel covering hotspot mutations in 22 genes (KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1 and FGFR2). For the RNA-based analysis, from 2015–2019, the Ion Torrent Ampliseq Lung Fusion Panel was used. It included over 70 ALK, RET, ROS1, and NTRK1 transcripts. Its improved version, Archer FusionPlex Panel (Integrated DNA Technologies, USA), was introduced in 2020. It analyses 17 genes (ALK, BRAF, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, KRAS, MET, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PIK3CA, RET and ROS1) using open-ended targeted amplification enabling detection of both novel and known fusions. Sequencing was performed on an Ion Torrent sequencer (Thermo Fisher Scientific, Waltham, MA, USA).

Cases from Innsbruck (13% of patients with molecular alterations) were tested with RT-PCR for EGFR mutations from 2015 to 2016 and Sanger Sequencing and PyroSequencing for EGFR, KRAS and TP53 mutations from 2016 to 2018. Innsbruck, FISH was used until 2020 to test for ALK, ROS, MET and from 2018 also RET fusion, then Archer FusionPlex Panel was introduced. Since March 2020, detection of variants on DNA-level was primarily performed using the AmpliSeq for Illumina Cancer Hotspot Panel v2 or AmpliSeq for Illumina Focus Panel. Both panels target hotspot regions of 50 genes including KRAS, EGFR, BRAF, PIK3CA, ERBB2, PTEN, NRAS, STK11, ALK, CTNNB1, MET, TP53, SMAD4, NOTCH1, ERBB4, FGFR1, FGFR2 and FGFR3. As control cohort, three hundred and fifty-five patients with resected NSCLC without targetable molecular alterations treated at the Medical University of Graz were used. Notably, only patients with KRAS G12C mutation were excluded from the control cohort, other KRAS mutations were allowed. Five hundred and twenty-nine patients were identified (all Caucasians) overall, of which 160 subjects had tumors with molecular alterations. Due to nine unclear follow-up stata and five perioperative deaths, 14 patients had to be excluded from further analysis overall. The surveillance of patients for recurrence was conducted with continuous CT scans, in compliance with the international guidelines.

2.2 Statistical analysis

Statistical analyses were all performed with Stata 18.0 (Stata Corp., Houston, TX, USA). Medians (25th–75th percentile) were used to summarize continuous variables, and absolute frequencies for count data (column %). Rank-sum-tests, $\chi 2$-tests, and Fisher's exact tests were used for comparison of variable distributions among patients with and without molecular alterations. Cumulative incidence of recurrence and death from other or unknown causes, as the competing event of interest, served as the primary endpoint of the time-to-event analysis. For overall survival, an exploratory analysis was also conducted. Date of cancer diagnosis and, for 2 patients with missing date of diagnosis, the date of surgery were used as a baseline date for the recurrence endpoint. The date of recurrence was used as a baseline date for the analysis of overall survival. The follow-up period was limited to 5 years from baseline. Reverse Kaplan-Meier estimator was used to estimate the median follow-up period (29). The cumulative incidence of recurrence was computed with a competing risk cumulative incidence estimator (30), compared between two or more groups with Gray's tests(31), and modeled with uni- and multivariable Fine & Gray competing risk regression models (32), respectively. Kaplan-Meier estimators and log-rank tests were used to analyze overall survival. Table

1 reports for missing date and a multiple imputation with a chained equations algorithm and 10 imputation datasets was used to account for missing baseline data in time-to-event models (33).

3 Results

3.1 Cohort description

Molecular alterations were found in 160 patients (31%). The three most common alterations were the Kirsten rat sarcoma proto-oncogen (KRAS) G12C mutation (n=92), ALK fusions (n=21), and the BRAF V600E mutation (n=15) (Figure 4). The baseline characteristics are shown in Table 1. There was a significant difference between the cohort with mutations and the control cohort regarding sex distribution. 56% of patients with molecular alterations were female compared to the 37% female patients in the control cohort. Statistical significance was also observed for smoking behaviour, with more non-smokers (never-smokers and ex-smokers, defined as someone who has smoked more than 100 cigarettes in life-time but has not smoked in the last 28 days) among patients with molecular alterations compared to controls (21% vs. 7%, respectively). Histology showed that adenocarcinoma was the histology in 98% of tumors with molecular alterations compared to 56% of controls. There was no significant difference between the two groups regarding the patients' age (Table 1).
The median follow-up time was 3.1 years after cancer diagnosis with 75% and 25% of the cohort being followed for at least 1.8 and 4.4 years, respectively. Over the course of this follow-up period, a total of 179 recurrences (35%) and 149 deaths (29%) were recorded. Deaths were due to tumor progression (n=81), treatment (n=12), other causes (n=23), and unknown causes (n=33). The corresponding 6-month, 1-year, 3-year, and 5-year competing risk cumulative incidence estimates of recurrence were 8% [95% confidence interval (CI): 6–10%], 16% (95% CI: 13–19%), 37% (95% CI: 33–42%), and 46% (95% CI: 40–52%), respectively (Supplementary figure 1).

Table 1: Baseline characteristics of the study population—distribution overall and by molecular alteration status (n=515)

Variable	N (%miss.)	Overall (n=515)	No molecular alteration (n=355)	Molecular alteration (n=160)	P*
Age at diagnosis (years)	513 (<1%)	66 [59–73]	65 [59–73]	66 [59–73]	0.58
Female sex	515 (0%)	220 (43%)	130 (37%)	90 (56%)	<0.001
ECOG ≥1 point	222 (57%)	104 (47%)	54 (54%)	50 (41%)	0.053
Smoking status	235 (54%)	–	–	–	0.01
Never smoker	–	36 (15%)	6 (7%)	30 (21%)	–
Former smoker	–	111 (47%)	43 (48%)	68 (47%)	–
Current smoker	–	88 (37%)	40 (45%)	48 (33%)	–
Adenocarcinoma	515 (0%)	354 (69%)	198 (56%)	156 (98%)	<0.001
Type of primary treatment	515 (0%)	–	–	–	<0.001
Lobectomy	–	413 (84%)	305 (86%)	126 (79%)	–
Pneumonectomy	–	36 (7%)	33 (9%)	3 (2%)	–
Atypical resection	–	16 (3%)	12 (3%)	4 (3%)	–
SBRT	–	8 (2%)	2 (1%)	6 (4%)	–
Definitive CRT	–	6 (1%)	3 (1%)	3 (2%)	–
Surgery NOS	–	18 (4%)	0 (0%)	18 (11%)	–
Postoperative stage**	513 (<1%)	–	–	–	0.09
I	–	227 (44%)	146 (41%)	81 (51%)	–
II	–	136 (27%)	103 (29%)	33 (21%)	–
III	–	147 (29%)	103 (29%)	44 (28%)	–
IV	–	3 (1%)	3 (1%)	0 (0%)	–
Neoadjuvant treatment	515 (0%)	58 (11%)	39 (11%)	19 (12%)	0.77
Adjuvant treatment	513 (<1%)	123 (24%)	88 (25%)	35 (22%)	0.45

n (%miss.) reports the number of patients with observed variable (% missing). Reported data are medians [25^{th}–75^{th} percentile] for continuous data and absolute frequencies (column %) for count data. *, P values are from ranksum-tests, χ^2-tests, and Fisher's exact tests, as appropriate. **, in 7 patients with missing postoperative stage we imputed the missingness with the preoperative stage. ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiotherapy; CRT, chemoradiation; NOS, not otherwise specified.

3.1.1 Molecular alterations and recurrence risk

A highly similar recurrence risk was observed in patients with and without molecular alterations. The 1-, 3-, and 5-year cumulative incidence of recurrence estimates were 16% (95% CI: 13–21%), 38% (95% CI: 32–43%), and 46% (95% CI: 39–52%) in patients without molecular alterations (n=355); 16% (95% CI: 9–25%), 38% (95% CI: 26–49%), and 48% (95% CI: 30–64%) in patients with the KRAS G12C mutation (n=92); and 12% (95% CI: 5–22%), 33% (95% CI: 20–47%), and 55% (95% CI: 21–79%) in patients with other molecular alterations (n=68), respectively (Gray's test P=0.89, Figure 5). The hypothesis-generating sub-analysis of recurrence risk according to the most common other molecular alterations including the BRAF V600E mutation, ALK fusions, MET exon 14 skipping, and EGFR exon 20 insertions (Gray's test P=0.47, Supplementary figure 2) also demonstrated no correlation between molecular alteration status and recurrence risk. Recurrences were not recorded in patients with ALK-fusions who received adjuvant treatment [adjuvant chemotherapy 2, adjuvant tyrosine kinase inhibitor (TKI) 3], but statistical testing was not performed, because of a small total number of these patients (n=5).

Recurrence risk was comparable in patients with and without molecular alterations in univariable competing risk regression (Table 2). Factors associated with an increased risk of recurrence in univariable analysis included extensive local treatment (pneumonectomy and definitive chemoradiation), stage III disease, receipt of neoadjuvant treatment, and receipt of adjuvant treatment. Molecular alteration status wasn't found to be associated with recurrence risk neither after adjusting for tumor stage (Figure 6), nor after full multivariable adjustment for all other variables under study (Table 2). Furthermore, all other univariable predictors of an adverse recurrence risk experience except adjuvant therapy prevailed upon multivariable adjustment (Table 2). The used perioperative treatment regimens are listed in supplementary table 1. The chemotherapy regimen most commonly administered in patients without molecular alterations was platinum-vinorelbine (used for 60% of treated patients), while in patients with molecular alterations platinum-pemetrexed (used for 40% of treated patients) was the most frequent regimen.

It is reasonable to suggest that patients with stage III disease are in a more advanced disease, which is why we also performed a subanalysis restricted to patients with stage I and II disease. Recurrence risk was shown to be similar in patients with and without druggable molecular alterations in this case also (Supplementary figure 3). We conducted a subanalysis restricted to patients with adenocarcinomas, because molecular alterations were mainly found in this histological subtype (98%). There was a highly comparable recurrence risk in patients with and without molecular alterations. The 1-, 3-, and 5-year cumulative incidence of recurrence estimates were 16% (95% CI: 11–21%), 38% (95% CI: 31–45%), and 44% (95% CI: 36–52%) in patients without molecular alterations (n=198); 16% (95% CI: 9–25%), 39% (95% CI: 27–50%), and 49%

(95% CI: 31–65%) in patients with the KRAS G12C mutation (n=90); and 11% (95% CI: 4–21%), 32% (95% CI: 19–47%), and 55% (95% CI: 21–79%) in patients with other molecular alterations (n=66), respectively (Gray's test P=0.85, Supplementary figure 4).

3.1.2 Molecular alterations and OS after recurrence (n=179)

Among the 179 patients who experienced recurrence, 46 (26%) had druggable molecular alterations while 133 (74%) had no druggable molecular alterations. Relapse was observed in 28 (30%) of the 92 overall patients with a KRAS G12C mutation. Chemoimmunotherapy was received as palliative first-line treatment in a majority of patients (n=11). Targeted therapy with a KRAS inhibitor was administered to 2 patients in the first-line setting and 2 patients in the second-line setting. Nine patients were treated locally (stereotactic beam radiotherapy or surgery) for oligo-progressive disease and four patients did not receive any palliative tumor-specific treatment at all. Among patients harboring ALK fusions (n=21), 5 (24%) patients relapsed of whom 4 received a TKI as first-line treatment and one patient underwent no palliative treatment aside from BSC. Regarding the 15 patients with a BRAF V600E mutation, recurrence was observed in 7 (47%) of them, three patients received targeted therapy as first-line treatment and one patient as second-line treatment. Stereotactic body radiotherapy for oligo-progressive disease was administered to 2 patients and 1 patient underwent no palliative treatment at all. There were 5 patients with RET fusion, of whom 1 (20%) relapsed and received targeted therapy in the first-line setting. Out of 11 patients with a MET exon 14 skipping mutation, 2 (18%) relapsed and received a targeted therapy in as a first-line treatment. Relapse was also observed in 2 (50%) out of 4 patients with a HER2 mutation and one of them received targeted therapy with an antibody drug-conjugate as first-line treatment in the palliative setting. Relapse was recorded in 1 patient with an exon 20 insertion, who did not undergo any treatment aside from BSC. The 1-, 3-, and 5-year overall survival estimates were 44% (95% CI: 35–53%), 17% (95% CI: 10–27%), and 6% (95% CI: 1–19%) in patients without druggable molecular alterations (n=133); 73% (95% CI: 46–88%), 20% (95% CI: 1–55%), and not defined in patients with the KRAS G12C mutation (n=28); and 74% (95% CI: 43–89%), 55% (95%

CI: 25–77%), and not defined in patients with other druggable molecular alterations (n=18), respectively (log-rank P=0.002, Figure 7).

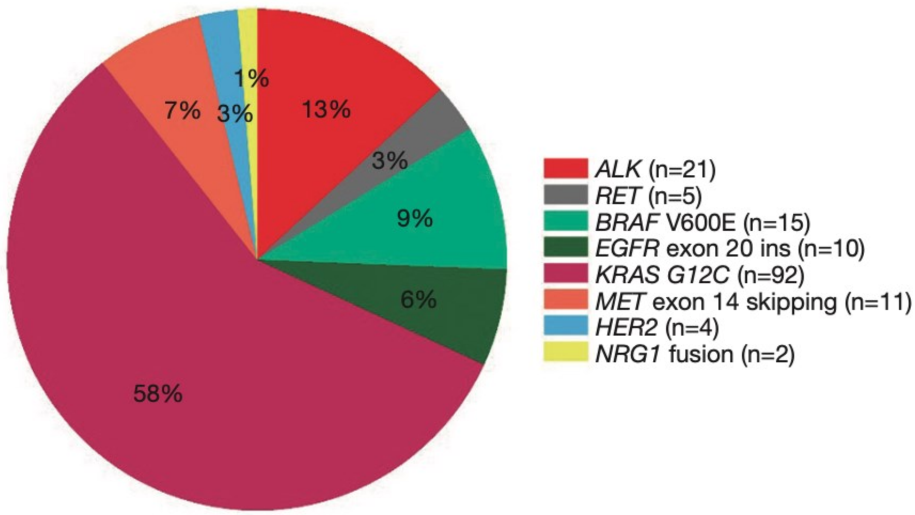

Figure 4: Pie chart of molecular alterations (n=160). ALK, anaplastic lymphoma kinase fusions; RET, rearranged during transfection; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus; MET, hepatocyte growth factor receptor gene; HER2, human epidermal growth factor receptor 2; NRG1, neuregulin 1.

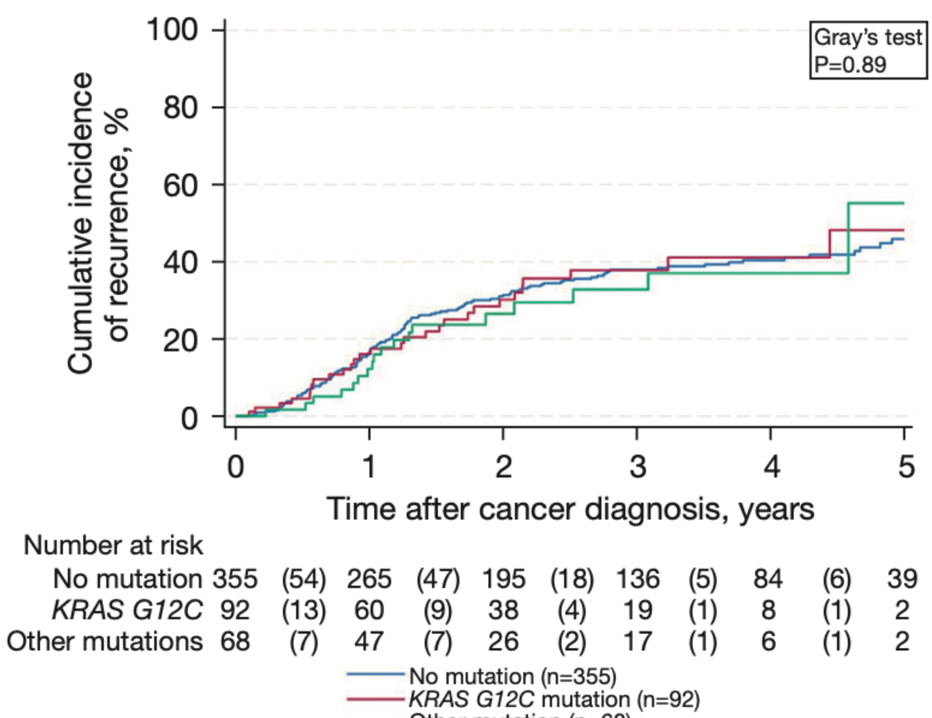

Figure 5: Cumulative incidence of recurrence according to molecular alteration status (n=515). Curves were obtained with competing risk cumulative incidence estimators treating death- from-other-or-unknown-causes as the competing event of interest. Numbers in brackets represent the number of events within the corresponding year.

Table 2: Predictors of recurrence: uni- and multivariable competing risk regression

Variable	Univariable analysis			Multivariable analysis		
	SHR	95% CI	P	SHR	95% CI	P
Presence of any molecular alteration	0.96	0.68–1.33	0.79	N/A	N/A	N/A
No molecular alteration	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
KRAS G12C mutation	1.00	0.67–1.51	0.99	0.95	0.59–1.51	0.82
Any other molecular alteration	0.89	0.55–1.44	0.63	0.80	0.45–1.40	0.43
Age at diagnosis (per 5 years increase)	0.97	0.89–1.04	0.39	1.02	0.93–1.12	0.61
Female sex	0.98	0.73–1.32	0.91	1.07	0.78–1.48	0.67
ECOG ≥1 point	1.05	0.73–1.51	0.80	1.20	0.79–1.83	0.38
Former or current smoker	1.02	0.62–1.69	0.94	1.06	0.55–2.05	0.86
Adenocarcinoma	0.93	0.68–1.27	0.64	1.19	0.82–1.73	0.36
Pneumonectomy + definitive CRT	2.74	1.78–4.23	<0.001	1.90	1.13–3.19	0.02
Postoperative stage III–IV	2.79	2.06–3.77	<0.001	2.26	1.50–3.39	<0.001
Neoadjuvant treatment	2.32	1.59–3.37	<0.001	1.78	1.13–2.82	0.01
Adjuvant treatment	1.45	1.04–2.01	0.03	1.05	0.69–1.60	0.81

Data are from uni- and multivariable Fine & Gray regression models. SHR, subdistribution hazard ratio; CI, confidence interval; P, Wald test P value; N/A, not applicable (we chose the three-level mutation status variable below for multivariable analysis); Ref., reference category; ECOG, Eastern Cooperative Oncology Group; CRT, chemoradiation therapy.

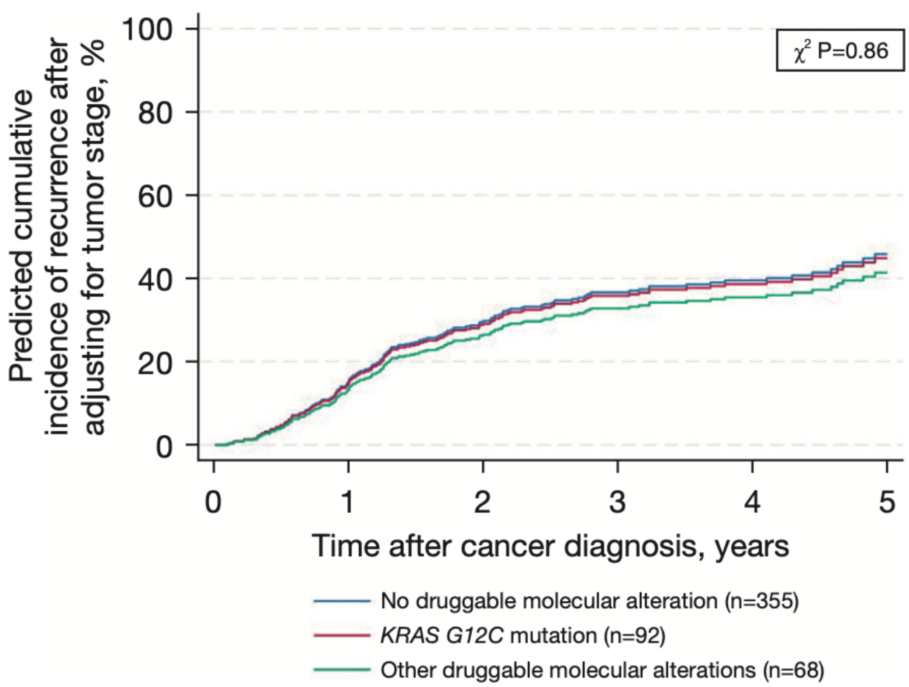

Figure 6: Tumor-stage-adjusted cumulative incidence of recurrence according to molecular alteration status (n=513). Curves are predicted cumulative incidences that were obtained from a multivariable Fine & Gray model with two variables (molecular alteration status, tumor stage I/II vs. III/IV). A complete-case-analysis was performed (n=2 missing). The P value is from a post-estimation χ2-test jointly testing the molecular alteration status variable.

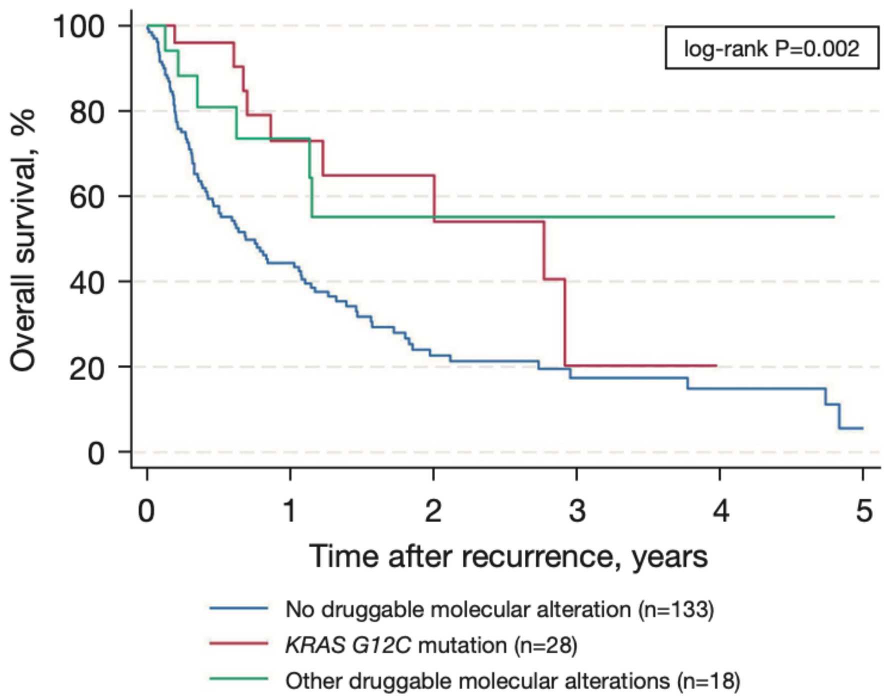

Figure 7: Overall survival after recurrence according to molecular alteration status (n=179). Curves were obtained with Kaplan-Meier estimators.

4 Discussion

This study has shown that the recurrence risk is the same in NSCLC patients with resected tumors with molecular alterations and patients with tumors without molecular alterations, if treated with surgery and adjuvant chemotherapy.

The characteristics of NSCLC patients with oncogenic driver mutations from our early-stage cohort are similar to what we already know from existing data from the advanced stage (34–37). In patients with oncogenic-driven tumors, we observed a higher prevalence of female sex and never-smokers. The KRAS G12C Mutation, being the most common type of mutation in patients with metastatic NSCLC (38–40), also made up the largest group in our study cohort. This mutation has been associated with female sex as well, but is generally observed in smokers with NSCLC (41–43). Sotorasib became the first approved drug for advanced KRAS G12C-mutated NSCLC after at least one line of therapy following many years of attempts to target this mutation (40). There is limited and conflicting evidence regarding the prognosis of the KRAS G12C mutated NSCLC in the early stage setting. It was reported by Nadal et al. that these tumors were associated with poor outcome compared to KRAS wildtype tumors. Nevertheless, the study comprised 85 resected lung cancer patients with KRAS mutations with only 35 patients carrying the KRAS G12C mutation (42). Jones et al. studied a cohort of 95 patients with a somatic KRAS G12C mutation and concluded that KRAS G12C mutations were associated with worse disease free survival when compared to other KRAS mutant tumors, but not when compared to the KRAS wildtype group (43). We could not find a difference for the recurrence-risk between patients with KRAS G12C mutations and our control cohort in our study. However, other KRAS mutations than the specific KRAS G12C mutation were allowed in the control cohort. Considering the limited size of the subgroups, we did not identify any additional driver alteration linked to a better or worse recurrence-free survival in comparison to the control cohort.

Encouragingly, the opposite was shown in the overall survival analysis for our study cohort. Significantly better overall survival was observed in patients with molecular alterations. This has also been proven in the subset of patients with KRAS G12C mutations. A recent study in Denmark, which included 328 KRAS G12C mutated advanced NSCLC patients, reported a similar survival in KRAS G12C mutated patients when compared to any other KRAS mutation or to wildtype patients with the implementation of checkpoint inhibitors (44). Our cohort's KRAS G12C mutated subgroup having a better overall survival might be attributed to the fact that 32% had oligo-progressive disease and received local treatment at the metastatic site.

Regarding ALK fusions, we came to the same conclusion as a retrospective analysis by Schmid et al., that the recurrence risk in patients with stage I–III ALK-rearranged NSCLC is identical to patients without molecular alterations (45). Tumors with certain molecular alterations are sensitive to cytotoxic chemotherapy, especially to platinum-pemetrexed combinations. In a retrospective analysis, a significant difference in PFS has been found by Shaw et al. for patients with ALK positive tumors compared to the wild type group when treated with a platinum-pemetrexed combination as front-line treatment (median PFS of 8.5 vs. 5.4 months, respectively, P<0.001) (46). In the retrospective RET-MAP trial, for patients with tumors carrying a RET fusion platinum-pemetrexed demonstrated a better performance over single agent chemotherapy or immune-checkpoint blockade (47), while tumors with ROS1 fusions profit as well from single agent pemetrexed as from platinum-pemetrexed combinations in comparison with wild type tumors. Although ALINA trial brought advantageous results, using alectinib as adjuvant treatment for tumors with ALK fusions does not address the potential additional benefit of adding chemotherapy to alectinib (26). The aim of adjuvant treatment is to eradicate minimal residual disease, but a major concern of targeted therapy is, that it only suppresses rather than eliminates cancer cells and so functions as tumor-static but not tumor-toxic treatment. Despite the significant DFS and OS benefit for adjuvant osimertinib in EGFR-mutated tumors, the DFS curves begin to converge at the end of adjuvant TKI-treatment (23).

There are several ongoing trials investigating neoadjuvant and adjuvant therapy with TKIs for patients with genetic alterations besides common EGFR mutations. The largest ongoing trial is the NAUTIKA1 study (NCT04302025) which includes patients with ALK, ROS1, NTRK, RET or BRAF V600E mutation. In this single-arm trial, 8 weeks of neoadjuvant targeted therapy is administered, followed by resection, adjuvant chemotherapy and cohort-specific target treatment. First results in the ALK positive cohort were reassuring. Out of 8 resected patients, 3 pathologic complete responses and 3 major pathologic responses were achieved. The Alchemist trial (NCT02194738), a phase III randomized, double-blind placebo-controlled trial, has patients receiving adjuvant crizotinib vs. placebo for 24 months, while the Libretto-432 trial investigates the RET inhibitor selpercatinib vs. placebo as adjuvant treatment for RET positive resected stage IB to IIIA NSCLC patients. A key challenge of these trials is the slow recruitment, attributable to the low prevalence of driver mutations.

This study has several limitations, the first one being its retrospective nature and second its molecular testing. The panels of molecular testing have changed as described above as the time passed and we might have missed some patients with targetable genetic changes (especially in Innsbruck before March 2020, when DNA-based testing was relatively limited). Nevertheless, even considering this limiting factor, we are providing real-world results from a country with an advanced testing approach in early-stage carcinomas, since molecular testing in all centers was performed based on international recommendations at every stage. Additionally, the approval of immune checkpoint inhibitors in the neoadjuvant and adjuvant setting is now the new standard in resectable early-stage lung cancer in contrast to our historic study population. A notable improvement of event-free survival for adjuvant, neoadjuvant or perioperative treatment strategies combining chemotherapy and checkpoint inhibition has been shown by a number of trials. However, not in all of these early-stage trials molecular testing was mandatory and mostly, only patients with known EGFR mutations or ALK translocations were excluded. Accordingly, the advantage of immunotherapy for patients with oncogene-driven NSCLC in the early-stage setting is still uncertain (13,15,20,21). Perioperative prospective randomized clinical trials are including targeted therapies nowadays, but due to the recruitment being slow for druggable alterations with low prevalence, retrospective studies like this one provide important information for clinical decision-making. Moreover, our study results suggest that combining chemotherapy with targeted therapies in the adjuvant setting should be explored in future clinical trials.

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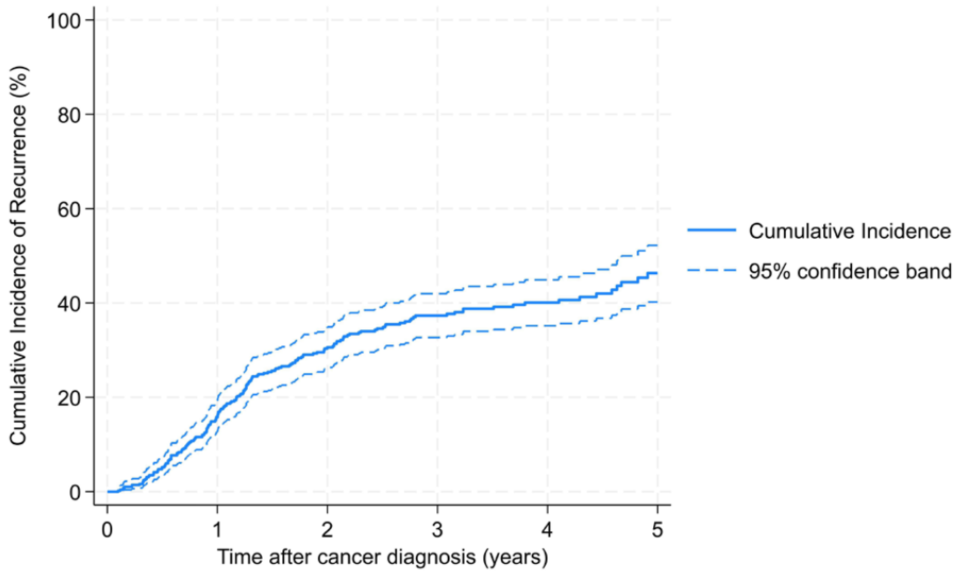
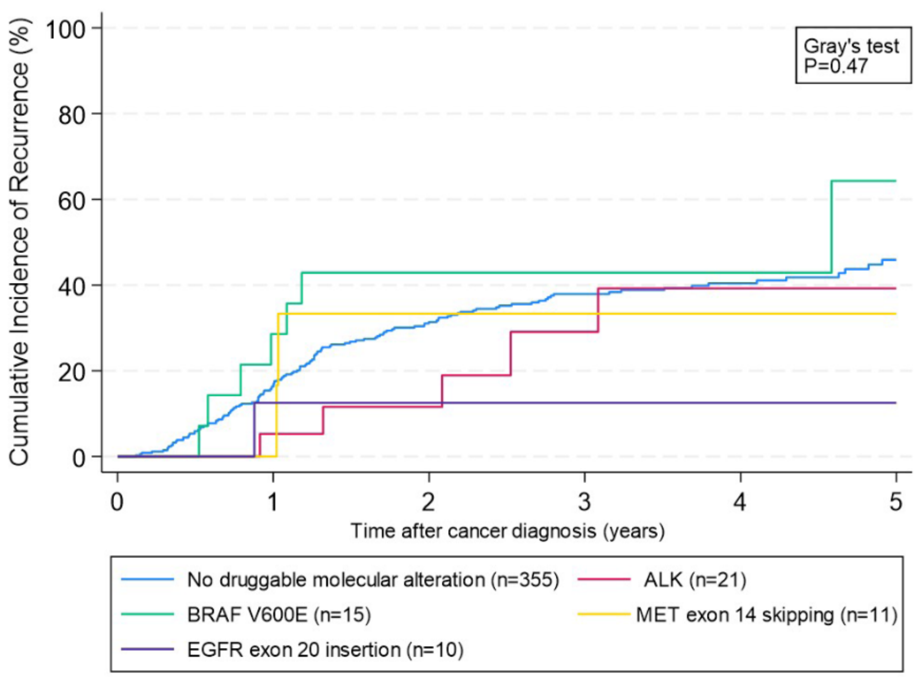
Supplementary:



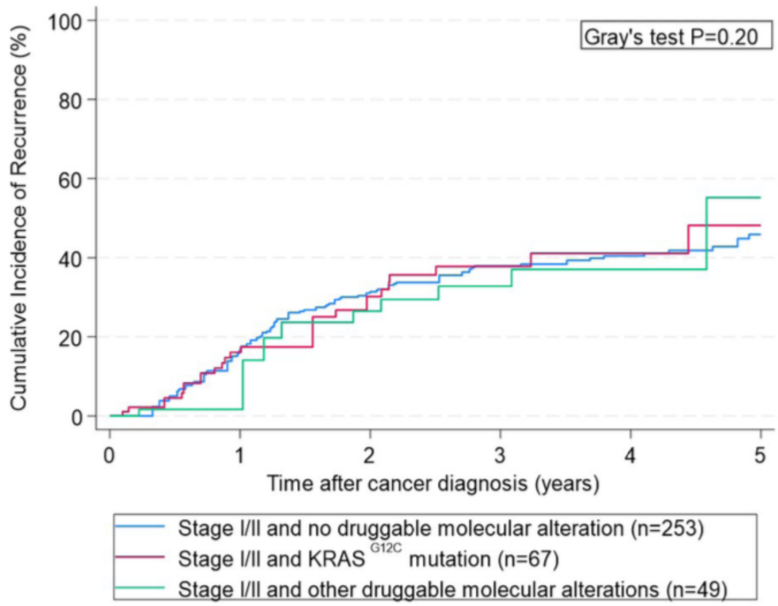
Supplementary figure 1: Cumulative incidence of recurrence in the overall study population (n=515). Curves represent the cumulative incidence (solid line) and 95% confidence bands (dashed lines) of recurrence obtained with competing risk cumulative incidence estimators treating death-from-other-or-unknown-causes as the competing event of interest.



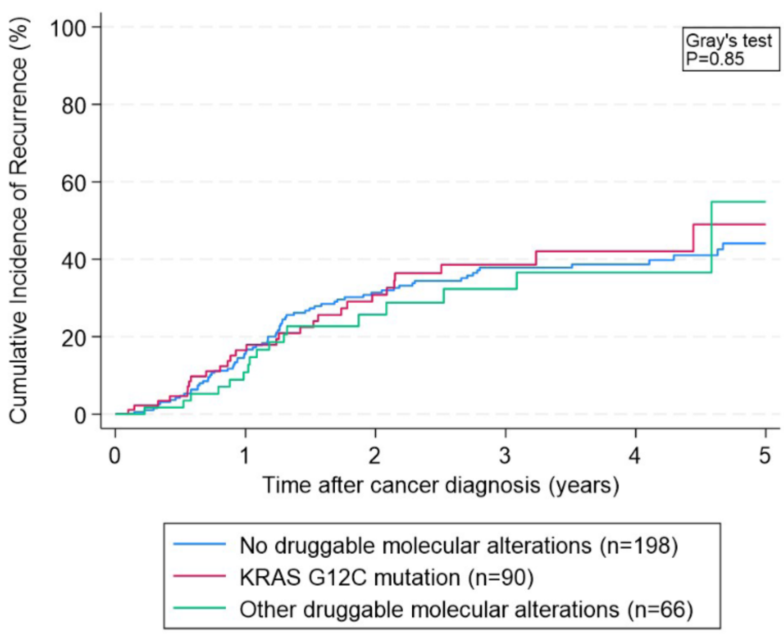
Supplementary figure 2: Cumulative incidence of recurrence according to the four most common molecular alterations compared to patients with no molecular alterations (n=412). Curves were obtained with competing risk cumulative incidence estimators treating death-from-other-or-unknown-causes as the competing event of interest. ALK, anaplastic lymphoma kinase fusions; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; MET, hepatocyte growth factor receptor gene.

Supplementary table 1: Type of treatment regimens used in the perioperative setting

Type of treatment regimens	No mutation (n=355)	ALK (n=21)	RET (n=5)	$BRAF^{V600E}$ (n=15)	EGFR Ex20ins (n=10)	$KRAS^{G12C}$ (n=92)	METex14skipping (n=11)	HER2 (n=4)	NRG1 fusion (n=2)
Neoadjuvant treatment									
No neoadjuvant therapy	317 (89%)	17 (81%)	5 (100%)	11 (73%)	10 (100%)	83 (90%)	9 (82%)	2 (50%)	2 (100%)
Platinum/vinorelbine	12 (3%)	1 (5%)	0	0	0	0	0	0	0
Platinum/pemetrexed	5 (1%)	1 (5%)	0	1 (7%)	0	4 (4%)	1 (9%)	2 (50%)	0
Platinum/docetaxel	11 (3%)	0	0	1 (7%)	0	1 (1%)	0	0	0
Platinum/paclitaxel	0	0	0	1 (7%)	0	0	0	0	0
Platinum/etoposide	5 (1%)	0	0	0	0	0	0	0	0
Platinum/gemcitabine/durvalumab	1 (0.3%)	0	0	0	0	1 (1%)	0	0	0
Platinum/gemcitabine	4 (1%)	0	0	0	0	0	0	0	0
Alectinib	0	2 (10%)	0	0	0	0	0	0	0
Afatinib	0	0	0	0	0	0	1 (9%)	0	0
Platinum/pemetrexed/pembrolizumab	0	0	0	1 (7%)	0	2 (2%)	0	0	0
Platinum/pemetrexed/atezolizumab	0	0	0	0	0	1 (1%)	0	0	0
Adjuvant treatment									
No adjuvant therapy	286 (81%)	16 (76%)	4 (80%)	12 (80%)	7 (70%)	74 (80%)	9 (82%)	4 (100%)	2 (100%)
Platinum/vinorelbine	52 (15%)	0	0	1 (7%)	2 (20%)	11 (12%)	0	0	0
Platinum/pemetrexed	7 (2%)	2 (10%)	1 (20%)	2 (13%)	1 (10%)	5 (5%)	1 (9%)	0	0
Platinum/docetaxel	1 (0.3%)	0	0	0	0	0	0	0	0
Platinum/paclitaxel	0	0	0	0	0	1 (1%)	0	0	0
Platinum/etoposide	2 (0.6%)	0	0	0	0	0	0	0	0
Platinum/gemcitabine/durvalumab	0	0	0	0	0	0	0	0	0
Platinum/gemcitabine	6 (2%)	0	0	0	0	0	0	0	0
Alectinib	0	3 (14%)	0	0	0	0	0	0	0
Afatinib	0	0	0	0	0	0	1 (9%)	0	0
Platinum/pemetrexed/pembrolizumab	0	0	0	0	0	0	0	0	0
Platinum/pemetrexed/atezolizumab	0	0	0	0	0	0	0	0	0
Durvalumab	1 (0.3%)	0	0	0	0	0	0	0	0
Pembrolizumab	0	0	0	0	0	1 (1%)	0	0	0



Supplementary figure 3: Cumulative incidence of recurrence according to molecular alteration status in the subgroup of patients with postoperative stage I/II disease (n=369). Curves were obtained with competing risk cumulative incidence estimators treating death-from-other-or-unknown-causes as the competing event of interest.



Supplementary figure 4: Cumulative incidence of recurrence according to molecular alteration status in the subgroup of patients with adenocarcinomas (n=354). Curves were obtained with competing risk cumulative incidence estimators treating death-from-other-or-unknown-causes as the competing event of interest.