Lung Cancer Resection after Immunochemotherapy Versus Chemotherapy in Oligometastatic Nonsmall Cell Lung Cancer

Stefan Sponholz¹ Agnes Koch¹ Mesut Mese¹ Silvan Becker² Martin Sebastian^{3,4,5} Sebastian Fischer⁶ Stephan Trainer¹ Waldemar Schreiner⁷

¹ Department of Thoracic Surgery, Agaplesion Markus Krankenhaus Frankfurt, Frankfurt, Germany

² Department of Oncology, Agaplesion Markus Krankenhaus Frankfurt, Frankfurt, Germany

³ Department of Medicine II, Hematology/Oncology, University Hospital Frankfurt, Frankfurt, Germany

⁴German Cancer Consortium (DKTK), Partner Site Frankfurt/Mainz and German Cancer Research Center (DKFZ), Heidelberg, Germany

Thorac Cardiovasc Surg 2023;71:656-663.

Address for correspondence Stefan Sponholz, MD, Department of Thoracic Surgery, Agaplesion Markus Krankenhaus, Wilhelm-Epstein-Str. 4, 60431 Frankfurt, Germany (e-mail: Stefan.sponholz@agaplesion.de).

⁶OptiPath, Institution of Pathology, Frankfurt, Germany

- ⁷ Department of Thoracic Surgery, University Hospital Frankfurt, Frankfurt, Germany
- ⁵ Frankfurt Cancer Institute, Goethe University Frankfurt, Frankfurt, Germany

Abstract

Background Neoadjuvant immunochemotherapy is currently being tested in pivotal trials for stage I to III nonsmall cell lung cancer (NSCLC). The impact of immunochemotherapy in patients with oligometastatic disease (OMD) remains undefined. This study aimed to compare the outcomes of radical treatment after the neoadjuvant course of immunochemotherapy versus chemotherapy.

Methods We retrospectively analyzed patients with OMD who were treated with immunochemotherapy or chemotherapy combined with local ablation of metastases and radical primary tumor resection between 2017 and 2021. Group A included eight patients with immunochemotherapy; Group B included seven patients with chemotherapy. Descriptive statistical analysis included the characteristics of the patients, tumors, and outcomes.

Keywords

- nonsmall cell lung cancer
- immunotherapy
- immunochemotherapy
- neoadjuvant therapy
- oligometastatic disease

Results There was no difference in postoperative morbidity rates between the groups (p = 0.626). The 30-day mortality in both groups was 0%. The median overall survival for Group A was not reached, with a median follow-up time of 25 (range: 13–35) months; the median overall survival for Group B was 26 (range: 5–53) months. In Group A, all patients remained alive; in contrast, in Group B, four patients died (p = 0.026). There was no local thoracic recurrence in either group. In Group B, the recurrent disease was identified significantly more often (12.5 vs. 85.75%; p = 0.009). The rates of complete and major pathologic response were 37.5 and 0% in Group A and 42.85 and 14.25% in Group B, respectively.

received December 23, 2022 accepted after revision January 31, 2023 accepted Manuscript online February 6, 2023 article published online March 28, 2023 © 2023. Thieme. All rights reserved. Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany DOI https://doi.org/ 10.1055/a-2028-7955. ISSN 0171-6425. **Conclusion** Despite the small patient number and short-term results, the progression-free and overall survival in patients with OMD after local therapy for metastases and primary tumor resection following a neoadjuvant course of immunochemotherapy might be promising compared with chemotherapy.

Introduction

Currently, immunotherapy (IO) is established for use in the treatment of locally advanced nonsmall cell lung cancer (NSCLC)^{1,2} and is increasingly becoming the focus of attention in the treatment of resectable NSCLC in stages I to III.^{3,4}

Several studies with mostly small patient numbers have shown the feasibility of lung resection after inductive IO with tolerable morbidity rates. In most of these studies, the neoadjuvant course included two cycles of IO and was less frequently performed as immunochemotherapy (IO+ chemotherapy [CTx]).^{5–9} Currently, the results of several prospective randomized trials analyzing the impact of neoadjuvant IO + CTx versus CTx in patients with resectable NSCLC are pending.^{10–12}

However, the impact of neoadjuvant IO + CTx in patients with oligometastatic disease (OMD) remains undefined. This retrospective analysis aimed to compare the perioperative and oncological outcomes after a neoadjuvant course of IO + CTx versus CTx followed by local treatment for primary tumors and metastases in patients with OMD.

Patients and Methods

The Institutional Review Board approved this study, which was conducted according to the revised Declaration of Helsinki and the requirements of good clinical practice.

We retrospectively analyzed our patients treated with IO + CTx and/or CTx followed by curative-intent local treatment of all metastases and radical resection of the primary tumor between January 2017 and September 2021. According to the current definition of OMD, only patients with five or less than five synchronous metastases in a single organ were included.¹³

The standard oncological staging included regular computed tomography of the thorax, magnetic resonance imaging of the brain, and F18-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT). If PET-CT was not performed in a patient, computed tomography of the abdomen and bone scintigraphy were instead performed. Furthermore, all patients received lung and cardiac function tests, including body plethysmography, arterial blood gases, electrocardiography, echocardiography, and ergometry.

All patients were discussed in an interdisciplinary tumor conference with the participation of thoracic surgeons, oncologists, and radiotherapists to define the optimal treatment modality and to review the radiological and clinical tumor response before ablative procedures for the primary tumor and metastasis. All operations had been performed in one center. It was not always the same surgeon, but the surgery was conducted by the same team and under the same standards and conditions.

To compare the neoadjuvant treatments, we defined two groups: Group A included patients treated with IO + CTx and Group B included patients treated with CTx. The patients received two to four cycles of neoadjuvant platin-based CTx with or without additional IO. All patients underwent standard surgical treatment, including anatomic lung resection and systematic lymph node dissection in compartments, 4 to 6 weeks after systemic therapy.

Postoperative morbidity was classified according to minor and major morbidity using the Thoracic Morbidity and Mortality Classification System of Ottawa Hospital.¹⁴ The Charlson Comorbidity Index (CCI) was retrospectively calculated from our hospital records to categorize the preoperative condition of the patients. Because a solid tumor with metastases already accounted for six points in the CCI score, we divided the patients into those with six points on the CCI and those with more than six points.

According to the findings in the pathophysiological analysis, the presence of complete and major pathologic response (MPR) were noted. A complete pathologic response (CPR) was defined as resected tumors without viable cancer cells, and a MPR was defined as \leq 10% viable cancer cells in the tumor specimen.¹⁵

Overall survival was defined as the time from first treatment to the date of death or last follow-up. Recurrence-free survival was defined as the time from the first treatment to the date of first progression or recurrence. Progression and recurrence after complete treatment were diagnosed by histological confirmation or radiological criteria. The follow-up data were retrieved from the clinical data and correspondence with the attending physicians and oncologists. Follow-up was performed by thoracic and abdominal imaging quarterly for the first 2 years and later at longer intervals. Depending on the location of the metastases, additional organ-specific imaging was performed for follow-up.

Descriptive statistical analyses, cross tables and the chisquare test were used to analyze the characteristics of the patients, the tumors, and short-term and long-term outcomes. Values of p less than 0.05 were regarded as significant. All analyses were performed using SPSS 22.0 software (SPSS, Inc., Chicago, IL, United States).

Results

Patient Characteristics

In total, 15 patients fulfilled the study criteria and were included in the study: eight patients in Group A and seven

Table 1 Patients and tumor characteristics

		IOCTx n (%)	CTx n (%)	<i>p</i> -Value
Gender	Female	3 (37)	4 (57)	0.405
	Male	5 (63)	3 (43)	
Age		57 years (range: 51–73)	62 years (range: 44–72)	
ECOG	0	8 (100)	6 (86)	0.467
	1	0 (0)	1(14)	
Charlson Comorbidity Index	6	6 (75)	5 (71)	0.662
	> 6	2 (25)	2 (29)	1
ASA score	2	0 (0)	3 (43)	0.077
	3	8 (100) 4 (57)		
Preoperative FEV1		70% (range:59–79)	73% (range:68–87)	
Former smoking status	Yes	6 (75)	6 (86)	0.554
	No	2 (25)	1 (14)	
Number of metastases	1 >1	6 (75) 2 (25)	4 (57) 3 (43)	0.427
Localization of metastases	Brain	3 (37)	4 (57)	0.555
	Lung	2 (25)	2 (29)	1
	Bone	2 (25)	0 (0)	1
	Extrathoracic lymph node	1 (13)	1 (14)	1
Histology	Adeno	7 (88)	4 (57)	0.351
	Squamous	1 (12)	2 (29)	1
	Other	0 (0)	1 (14)	1
PD-L1 score	0	3 (37)	-	
	1–49	5 (63)	-]
	≥ 50	0 (0)	-	

Abbreviations: CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; IO, immunotherapy; PD-L1, programmed death-ligand 1.

patients in Group B. There were no patients in the study period with OMD and neoadjuvant treatment who could not be operated on. The median patient age of the whole cohort was 58 years (range, 44-73 years), with a median age in Group A of 57 years (range, 51–73 years) and in Group B of 62 years (range, 44-72 years). Sex distribution was not significantly different between the two groups (p = 0.405). Regarding the preoperative constitution of the patients, there was no significant difference in the preoperative CCI (p=0.662), American Society of Anesthesiology score (p=0.077), Eastern Cooperative Oncology Group status (0.467), or former smoking status (0.554). The median preoperative forced expiratory volume in 1 second was 70% (range, 59-79%) in Group A and 73% (range, 68-87%) in Group B (**Table 1**). Besides one patient in Group B, all patients underwent PET-CT before surgery.

Tumor and Treatment Characteristics

The predominant tumor histology in both groups was adenocarcinoma (Group A: 87.5%; Group B: 57.15%). The histology and mutation status of the primary tumor are listed in **-Table 2**. The synchronous metastases in Group A were localized in the brain in three patients, in the bones in two patients, in the lung in two patients, and in an extrathoracic lymph node in one patient. Additionally, in Group B, the most common metastasis localization was the brain in four patients, followed by the lung in two patients and an extrathoracic lymph node in one patient. There was no significant difference in the groups between single metastasis and multiple synchronous metastases (p = 0.427; **-Table 1**). Besides one patient in Group A who declined the third cycle of systemic therapy, all patients in the study had three to four cycles of systemic therapy of the metastases are listed in **-Table 3**.

The resection of the primary tumor was performed in Group A (six lobectomies, one sleeve lobectomy, and one segmentectomy) and in Group B (six lobectomies and one bilobectomy)(**-Table 3**). In both groups, a median of 32 lymph nodes (range, 12–60) was removed per patient and according to the criteria of systematic lymph node dissection.

Short- and Long-Term Outcomes

All patients in Group A had an RO-resection; in Group B, six patients had an RO-resection, and one patient had an R1-

	Histology	ГСГР		Dec 1	DAC		Other	
	HISLOIDGY	EGEK	ALK	KOS-I	KAS	В-КАГ	Other	(TPS)
	•							(
1	Adenocarcinoma	WT	Negative	Negative	Exon-2 G12C Mutation	WT	Negative	1
2	Adenocarcinoma	WT	Negative	Negative	u	WT	u	0
3	Adenocarcinoma	WT	Negative	Negative	WT	WT	PIK3CA/ TP53	5
4	Adenocarcinoma	WT	Negative	Negative	Exon-2 c35.G Mutation	WT	Negative	0
5	Adenocarcinoma	WT	Negative	Negative	u	Negative	u	0
6	Adenocarcinoma	WT	Negative	Negative	WT	u	u	40
7	Adenocarcinoma	WT	Negative	Negative	Exon-2 G12C Mutation	u	Negative	2
8	Squamous cell cancer	u	u	u	u	u	u	10
9	Squamous cell cancer	WT	u	u	u	u	u	-
10	Adenocarcinoma	u	u	u	Exon-2 G12C Mutation	WT	Negative	-
11	Large cell neuroendocrine	WT	Negative	Negative	WT	WT	Negative	-
12	Squamous cell cancer	WT	u	u	u	u	u	-
13	Adenocarcinoma	del15	Negative	Negative	WT	WT	Negative	-
14	Adenocarcinoma	WT	Negative	Negative	u	WT	KEAP1 / TP53	-
15	Adenocarcinoma	WT	Negative	Negative	WT	WT	PIK3CA/ TP53	-

Table 2 Histology and mutation status of the primary tumor

Abbreviations: ALK, anaplastic lymphoma kinase; B-Raf, B-RAF Proto-oncogene; iEGFR, Epidermal Growth Factor Receptor; RAS, Rat Sarcoma Virus; ROS-1, receptor tyrosine kinase-1; TPS, Tumor proportion score; u, unknown; WT, wildtype. Note: White background: Group A; gray background: Group B.

resection of a primary tumor in the left lower lobe associated with tumor invasion of the descending aorta. An adjuvant postoperative radiotherapy with 60 Gy was performed on this patient. Regarding the pathologic response rates, 37.5% of the patients treated with IO + CTx (Group A) had a CPR and none had an MPR; the CPR and MPR rates in Group B were 42.85 and 14.25%, respectively (**-Table 4**).

There was no difference in postoperative morbidity (p = 0.626) or 30-day mortality (0%) between Groups A and B. The postoperative minor and major morbidity rates were 12.5 and 25% in Group A and 28.58 and 0% in Group B, respectively (**-Tables 3** and **4**). The median overall survival for Group A was not reached, but the median follow-up time was 25 months (range, 13–35); in Group B, the median overall survival was 26 months (range, 5–53). All patients in Group A were still alive; in contrast, four patients in Group B died (p = 0.026; **-Table 4**).

Group B patients suffered significantly more often from recurrent disease (p = 0.009). There was no local thoracic recurrence in either group. Only one patient in Group A suffered from a local recurrence of brain metastasis and an additional distant metastasis (12.5%). In Group B, six patients suffered from recurrence (85.75%). In total, four local recurrences at the initial metastatic side and two distant metastases occurred. The median progression-free survival in Group A was not reached, while in Group B, it was 8 months (range, 3–12; **- Table 4**).

Discussion

Currently, there are several studies comparing IO + CTx with CTx as a neoadjuvant therapeutic concept in operable NSCLC

stage IB-IIIA.^{10–12,16} The impact of neoadjuvant IO + CTx and ablation therapy for primary tumors and metastases in patients with OMD is currently undefined. However, the overall survival in these patients after ablative therapies is still heterogeneous,¹⁷ and particularly, synchronous OMD compared with metachronous OMD seems to be a negative prognosticator for survival.¹⁸ Nevertheless, a meta-analysis of patients with synchronous OMD showed improved survival after radical treatment, including local therapy for primary tumors as well as for metastases, compared with patients without additional local therapy.¹⁹ Recently, published retrospective multicenter analyses including surgery have also demonstrated promising survival rates.^{20,21}

The randomized KEYNOTE-407 study comparing placebo plus CTx and pembrolizumab plus CTx in patients with metastatic squamous NSCLC showed a significant improvement in overall survival in the pembrolizumab group, with a median overall and median progression-free survival of 17.1 and 8 months, respectively.²² It remains unclear whether these positive effects are transferable to the OMD setting, but they might be showing the therapeutic impact of IO in the management of metastatic NSCLC.

However, in patients with OMD, synchronous metastases seem to be a negative prognosticator compared with metachronous metastases,¹⁸ but curative-intent treatment, including local ablation of metastases and radical surgery of the primary tumor, improves overall and progression-free survival.^{19,23}

By definition, patients with metastatic tumors already have an elevated CCI and, thus, an increased risk of postoperative morbidity and mortality after NSCLC resection.²⁴

	Age (years)	Localization of the primary cancer	Localization of the metastases	Neoadjuvant therapy (number of cycles)	Type of resection	Morbidity	Progression free survival (months)	Survival (months)
-	53	Right upper lobe	Brain	Cisplatin/Pemetrexed/Pembrolizumab (4)	Lobectomy	I	6	28
5	51	Left upper lobe	Bone	Carboplatin/Pemetrexed/Pembrolizumab (3)	Extrapleural Lobectomy	I	I	25
m	56	Right lower lobe	Brain	Cisplatin/Pemetrexed/Pembrolizumab (4)	Lobectomy	Major	I	25
4	51	Right lower lobe	Bone	Cisplatin/Pemetrexed Pembrolizumab (2)	Sleeve Lobectomy	Minor	I	22
ъ	59	Right upper lobe	ELN	Carboplatin/Pemetrexed/Pembrolizumab (3)	Lobectomy	Minor	I	13
9	71	Left upper lobe	Lung	Cisplatin/Pemetrexed/Pembrolizumab (4)	Segmentectomy	I	I	35
~	58	Left lower lobe	Brain	Cisplatin/Pemetrexed/Pembrolizumab (4)	Lobectomy	I	I	34
∞	73	Right upper lobe	Lung	Carboplatin/Paclitaxel/Pembrolizumab (4)	Lobectomy	I	I	12
6	72	Left lower lobe	Lung	Carboplatin/Paclitaxel (3)	Lobectomy + angioplasty	Minor	12	(a) 29
10	48	Right upper lobe	Brain	Cisplatin/Vinorelbine (3)	Lobectomy	I	10	53 (^a)
=	63	Left upper lobe	ELN	Cisplatin/Etoposid (4)	Lobectomy	Minor	12	12 (^a)
12	66	Right lower lobe	Lung	Cisplatin/Gemcitabine (3)	Bilobectomy	Ι	5	17 (^a)
13	44	Left upper Lobe	Brain	Cisplatin/Pemetrexed (4)	Lobectomy + angioplasty	I	7	26
14	58	Left upper lobe	Brain	Carboplatin/Pemetrexed (4)	Lobectomy	I	3	29
15	62	Right upper lobe	Brain	Cisplatin Vinorelbine (3)	Lobectomy + Chest wall	I	I	5
\bbrev	viations: CR,	complete remission; Cy, cy	/ber knife; ELN, extrathor	acic lymph node; R, resection; Ra, radiation therapy.				

Note: White background: Group A; gray background: Group B. ^aDead.

Lung Cancer Resection after Immunochemotherapy vs. Chemotherapy Sponholz et al. 660

Thoracic and Cardiovascular Surgeon Vol. 71 No. 8/2023 © 2023. Thieme. All rights reserved.

Table 3 Patient and outcome overview

		IOCTx n (%)	CTx n (%)	<i>p</i> -Value
Pathologic	Complete	3 (37)	3 (43)	0.405
response	Major	0 (0)	1 (14)	
	No	5 (63)	3 (43)	
Morbidity	No	5 (63)	5 (71)	0.626
	Minor	2 (25)	2 (29)	
	Major	1 (12)	0 (0)	
30-dmortality	No	8 (100)	7 (100)	1.000
	Yes	0 (0)	0 (0)	
Recurrence	No	7 (88)	1 (14)	0.009
	Yes	1 (12)	6 (86)	
Median progression free survival (months)		NR	8 (3–12)	
Still alive	Yes	8 (100)	3 (43)	0.026
	No	0 (0)	4 (57)	
Median overall survival (months)		NR	26 (5–53)	

 Table 4
 Short- and long-term outcomes

Abbreviation: NR, not reached.

Nevertheless, in our study, even in these patients, no increased morbidity after neoadjuvant IO + CTx compared with neoadjuvant CTx was identified. The recently published morbidity rates after neoadjuvant IO + CTx or IO followed by NSCLC resection were between 39 and 50%.^{7,8} Additionally, the morbidity rate of 37.5% and the mortality rate of 0% of the IO + CTx group in our study are comparable to rates after neoadjuvant IO in other tumor stages or even in patients with advanced-staged NSCLC without neoadjuvant treatment.¹⁶

Additionally, a newly retrospective multicenter analysis including surgery showed a median overall survival of up to 40 months and 5-year survival rates of 36%.^{20,21} In our study, the median overall survival in Group A was not reached, at a median follow-up time of 25 months (range, 13–35 months); in Group B, the median overall survival was 26 months (range, 5–53 months). All patients in Group B had died.

Bott et al described an "increased occurrence of inflammation and/or dense adhesions in either the fissure or surrounding hilar and mediastinal nodal stations" after neoadjuvant IO for locally advanced stages of NSCLC, which potentially led to an increased conversion rate of thoracoscopy to thoracotomy.⁸ These results show that particularly in patients with neoadjuvant therapy, including IO, the intraoperative accessibility of the central anatomical structures, such as veins, arteries, and bronchus, and of lymph nodes is limited by extensive fibrotic changes (-Figs. 1 and 2). Furthermore, inflammation and fibrosis of lymphatic tissues are well known as potential reasons for skipping lymph node metastases. In addition, the frozen section examination by the pathologist might be complicated, and therefore, tumor cells could be overseen. As a consequence, extensive fibrosis potentially leads to tumor understaging. In summary, all of these aspects underline the importance of systematic lymph node dissection in compartments for achieving exact pN staging²⁵ and for reducing the risk of local recurrence. The avoidance of local and distant recurrence is, in our opinion, two cornerstones for good long-term outcomes after radical surgery. The anatomical lung resections in our study were in all patients performed combined with a systematic lymph node dissection, with attention given to an en bloc dissection of the lymph nodes with the surrounding fat tissue. This approach is in our opinion essential to prevent local recurrence and to achieve proper lymph node analysis. On average, 32 lymph nodes were removed per patient in our study. Consequently, during the short-term follow-up, no patient experienced local



Fig. 1 (A) Resected lung hilum showing the bronchus (#) and the vein (+) surrounded by fibrotic and reactive tissue (>) after IO + CTx. (B) Microscopic image of a bronchus (#) and a vessel (+) surrounded by fibrotic and reactive tissue (>) after IO + CTx.



Fig. 2 Microscopic image of a dissected necrotic lymph node with residual lymphoid tissue (#) and fibrotic tissue (>) after IO + CTx.

recurrence. In addition, patients in Group A suffered less often from recurrent metastases (12.5 versus 85.75%; p = 0.009). The most frequent recurrences of the whole study population appeared at the locally treated distant metastases.

According to the literature, a systematic review including 49 studies of patients with OMD treated with locally ablative therapies showed a median progression-free survival of 12 months.¹⁷ These results were recently confirmed by two multicenter studies including patients with synchronous OMD treated with radical surgery with a median progression-free survival of up to 11 months.^{20,21} Bauml et al found a promising progression-free survival of 19.1 months after treatment with pembrolizumab followed by local ablation.²⁶ To date, only one patient in Group A suffered from recurrent disease at a median follow-up time of 25 months.

Regarding the CPR and MPR following IO, our results were comparable to the data reported in the literature. The study of Román et al. showed an MPR rate of 19.5% and a CPR rate of 63.4% after neoadjuvant IO + CTx in patients with stage IIIA NSCLC.⁷ In general, MPR rates of 40.5 to 56.7% and CPR rates of 15 to 33% for neoadjuvant IO in locally advanced NSCLC have been described.¹⁶ Furthermore, a recently published multicenter study including 13 NSCLC patients with OMD identified a CPR rate of 54% after neoadjuvant IO with or without additional CTx.²⁷ One reason for the slightly lower CPR rate of 37.5% in our

patients might be the lower PD-L1 score (**-Table 2**). However, the lack of a 100% remission rate further supports the use of curative-intent resection of the primary tumor and the ablative procedures of metastasis and might lead to a reduced risk of thoracic recurrence.

Conclusion

As a study limitation, the retrospective data analysis of a small patient number should be noted. However, the study demonstrates the feasibility of lung cancer resection after neoadjuvant IO + CTx in patients with synchronous OMD. Although the number of included patients was small, the progression-free survival and overall survival in patients after neoadjuvant IO + CTx might be promising compared with patients after neoadjuvant CTx alone. Regardless of these promising results, further studies with larger case numbers and matched outcomes are required to define the potential superiority of IO + CTx as a neoadjuvant course in patients with synchronous OMD in the future.

Note

The paper has been presented at the 139. Deutscher Chirurgenkongress, Leipzig, 06.04.2022

Conflict of Interest

M.S. receives honoraria AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens and research grants from AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens. All other authors declare no conflict of interest.

References

- 1 Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1positive non-small-cell lung cancer. N Engl J Med 2016;375(19): 1823–1833
- 2 Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 2019;381(21):2020–2031
- ³ Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378(21):1976–1986
- 4 Lee JM, Tsuboi M, Brunelli A. Surgical perspective on neoadjuvant immunotherapy in non-small cell lung cancer. Ann Thorac Surg 2021;114(04):1505–1515
- ⁵ Jia XH, Xu H, Geng LY, et al. Efficacy and safety of neoadjuvant immunotherapy in resectable nonsmall cell lung cancer: a metaanalysis. Lung Cancer 2020;147:143–153
- 6 Huang Z, Wu Z, Qin Y, et al. Perioperative safety and feasibility outcomes of stage IIIA-N2 non-small cell lung cancer following neoadjuvant immunotherapy or neoadjuvant chemotherapy: a retrospective study. Ann Transl Med 2021;9(08):685
- 7 Román AR, Campo-Cañaveral de la Cruz JL, Macía I, et al. Outcomes of surgical resection after neoadjuvant chemoimmunotherapy in locally advanced stage IIIA non-small-cell lung cancer. Eur J Cardiothorac Surg 2021;60(01):81–88
- 8 Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019; 158(01):269–276

- 9 Eichhorn F, Klotz LV, Kriegsmann M, et al. Neoadjuvant antiprogrammed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: First clinical experience. Lung Cancer 2021;153:150–157
- 10 Heymach J, Taube J, Mitsudomi T, et al. P1.18–02 The AEGEAN Phase 3 trial of neoadjuvant/adjuvant durvalumab in patients with resectable stage II/III NSCLC. J Thorac Oncol 2019;14(10): S625–S626
- 11 Tsuboi M, Luft A, Ursol G, et al. 1235TiP perioperative pembrolizumab + platinum-based chemotherapy for resectable locally advanced non-small cell lung cancer: the phase III KEYNOTE-671 study. Annal Oncol 2020;31(04):801–802
- 12 Felip E, Brahmer J, Broderick S, Cai J, Yang R, Forde P. P2.16–03 CheckMate 816: a phase 3 trial of neoadjuvant nivolumab plus ipilimumab or chemotherapy vs chemotherapy in early-stage NSCLC. J Thoracic Oncol 2018;13(10):831–832
- 13 Planchard D, Popat S, Kerr K, et al; ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv192-iv237 Erratum in: Ann Oncol. 2019 May;30(5):863–870. PMID: 30285222
- 14 Seely AJE, Ivanovic J, Threader J, et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg 2010;90(03):936–942
- 15 Hellmann MD, Chaft JE, William WN Jr, et al; University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable nonsmall-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol 2014;15(01): e42–e50
- 16 Cao C, Guo A, Chen C, et al. Systematic review of neoadjuvant immunotherapy for patients with non-small cell lung cancer. Semin Thorac Cardiovasc Surg 2021;33(03):850–857
- 17 Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. Lung Cancer 2013;82(02):197–203
- 18 Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment

of oligometastatic non-small-cell lung cancer. Clin Lung Cancer 2014;15(05):346-355

- 19 Li D, Zhu X, Wang H, Qiu M, Li N. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis. J Thorac Dis 2017;9(02):310–317
- 20 Opitz I, Patella M, Payrard L, et al. Prognostic factors of oligometastatic non-small-cell lung cancer following radical therapy: a multicentre analysis. Eur J Cardiothorac Surg 2020;57(06): 1166–1172
- 21 Spaggiari L, Bertolaccini L, Facciolo F, et al. A risk stratification scheme for synchronous oligometastatic non-small cell lung cancer developed by a multicentre analysis. Lung Cancer 2021; 154:29–35
- 22 Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebocontrolled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. J Thorac Oncol 2020;15(10):1657–1669
- 23 Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multiinstitutional, phase ii, randomized study. J Clin Oncol 2019;37 (18):1558–1565
- 24 Birim O, Maat AP, Kappetein AP, van Meerbeeck JP, Damhuis RA, Bogers AJ. Validation of the Charlson Comorbidity Index in patients with operated primary non-small cell lung cancer. Eur J Cardiothorac Surg 2003;23(01):30–34
- 25 Schirren J, Bergmann T, Beqiri S, Bölükbas S, Fisseler-Eckhoff A, Vogt-Moykopf I. Lymphatic spread in resectable lung cancer: can we trust in a sentinel lymph node? Thorac Cardiovasc Surg 2006; 54(06):373–380 Review
- 26 Bauml JM, Mick R, Ciunci C, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung cancer: a phase 2 trial. JAMA Oncol 2019;5(09):1283–1290
- 27 Boch T, Frost N, Sommer L, et al. Pathologic responses in oligometastatic NSCLC patients treated with neoadjuvant immune checkpoint blockade with and without chemotherapy followed by surgery. Lung Cancer 2022;164:46–51