Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-258-z Pembrolizumab

Stand: November 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab **[zur adjuvanten Behandlung des NSCLC nach Resektion]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Post-operative (adjuvante) Strahlentherapie (Stadium III)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** Osimertinib: Beschluss vom 16.12.2021 Atezolizumab: Beschluss vom 05.01.2023
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01XC18 Keytruda	Anwendungsgebiet laut Zulassung vom 12.Oktober 2023: KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum based chemotherapy (for selection criteria, see section 5.1). KEYTRUDA ist als Monotherapie zur adjuvanten Behandlung des nicht-kleinzelligen Lungenkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion und Platin-basierter Chemotherapie bei Erwachsenen angezeigt.
Monoklonale Antikörper	
Atezolizumab L01FF05 Tecentriq	<u>Nicht-kleinzelliges Lungenkarzinom (non-small cell lung cancer, NSCLC) im Frühstadium</u> Tecentriq als Monotherapie wird angewendet zur adjuvanten Behandlung des NSCLC nach vollständiger Resektion und platinbasierter Chemotherapie bei erwachsen Patienten mit hohem Risiko für ein Rezidiv und deren Tumoren eine PD-L1-Expression auf ≥ 50 % der Tumorzellen (tumour cells, TC) aufweisen und kein EGFR(epidermal growth factor receptor, epidermaler Wachstumsfaktorrezeptor)-mutiertes oder ALK(anaplastische-Lymphomkinase)-positives NSCLC haben.
Osimertinib L01EB04 Tagrisso	TAGRISSO ist als Monotherapie angezeigt zur adjuvanten Behandlung nach vollständiger Tumorresektion bei erwachsenen Patienten mit nicht-kleinzelligem Lungenkarzinom (NSCLC) im Stadium IB-IIIA, deren Tumoren Mutationen des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR) als Deletion im Exon 19 oder Substitutionsmutation im Exon 21 (L858R) aufweisen.
Zytostatika	
Cisplatin L01XA01 PlatiCept	Lungenkarzinom (kleinzellig und nicht kleinzellig): Im Rahmen von etablierten Kombinationstherapien mit anderen Chemotherapeutika oder zusätzlich zu einem entsprechenden chirurgischen Eingriff und/oder einer Radiotherapie. Cisplatin mit Paclitaxel ist eine etablierte Kombinationschemotherapie zur Behandlung des fortgeschrittenen nicht kleinzelligen Lungenkarzinoms.
Vinorelbin	Vinorelbin ist bei erwachsenen Patienten angezeigt zur Behandlung von:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01CA04 Navelbine	- als adjuvante Behandlung von nicht-kleinzelligem Bronchialkarzinom in Kombination mit einer platinbasierten Chemotherapie

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-052 (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	31. März 2023

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Abkürzungsverzeichnis

ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CI/KI	Konfidenzintervall
CRS	neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy
CrI	Kredibilitätsintervall
CSC	neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy
DFS	Disease-free survival
EBMC	Evidence Based Medicine Committee
EGFR	Epidermal Growth Factor Receptor
G-BA	Gemeinsamer Bundesausschuss
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LA	Locally advanced
LRFS	Local-regional recurrence survival
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
NSCLC	Non-small cell lung cancer
OR	Odds Ratio
OS	Overall Survival
PD-L1	Programmed cell death ligand-1
PFS	Progression Free Survival
PORT	Postoperative radiation therapy
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
TNM	Tumor, Nodes, Metastases
WHO	World Health Organization

1 Indikation

Monotherapie bei Erwachsenen zur adjuvanten Behandlung des nicht-kleinzelligen Lungenkarzinoms (NSCLC) in den Tumorstadien IB (T2 ≥ 4cm), II oder IIIA nach vollständiger Resektion

Hinweise zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt. Informationen hinsichtlich Erwachsenen im Anwendungsgebiet, die eine Mutation (bspw. EGFR) aufweisen, sind ebenfalls über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *nicht-kleinzelliges Lungenkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 03.06.2021 durchgeführt, die folgenden am 13.06.2022 und 17.11.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 3548 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 8 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Lei, T. et al., 2021 [11].

Postoperative radiotherapy for patients with resectable stage III-N2 non-small cell lung cancer: a systematic review and meta-analysis.

Fragestellung

Meta-analysis to reassess the data of PORT in stage III-N2 NSCLC patients, to figure out whether these patients can benefit from PORT.

Methodik

Population:

- completely resected III-N2 NSCLC patients

Intervention/Komparator

- postoperative radiotherapy ((neo-) adjuvant chemotherapy was allowed)

Endpunkte:

- overall survival (OS) or disease-free survival (DFS) or local-regional recurrence survival (LRFS)

Recherche/Suchzeitraum:

- EMBASE, PubMed, and the Cochrane Library published studies before November 6, 2020

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- seven randomized controlled trials (1,318 participants)

TABLE 1 | Details and results of certain included studies.

Author	Recruitment	Phase of trials	Median age	N	RT technique	Chemotherapy Regimen	Primary end-point	DFS	OS	LRFS
				Patients				HR	HR	HR
Debevec et al. (13)	1988 to 1992	NA	59 (35–80)	35	Linac	without chemotherapy	NA	NA	0.91 (0.44–1.87), NA	NA
				39	–			–	–	–
Stephens et al. (14)	July 1986 to October 1993	NA	62	52	megavoltage x-ray /Cobalt	without chemotherapy	NA	NA	0.74 (0.48–1.15), P = 0.18	0.55 (0.29–1.05), P = 0.07
				54	–			–	–	–
Perry et al. (15)	May 1998 to June 2000	Phase III	NA	19	NA	sequential chemoradiotherapy	NA	NA	0.95 (0.40–2.28), P = 0.91	NA
				18	–			–	–	–
Shen et al. (16)	April 2004 to March 2009	Phase III	NA	66	3DCRT with linac	concurrent chemoradiotherapy	OS and DFS	0.67 (0.45–0.98), P = 0.041	0.69 (0.457–1.044), P = 0.073	HR = 0.48(0.28–0.83), P = 0.009
				69	–			–	–	–
Sun et al. (17)	June 2009 to September 2014	Phase II	60 (38–78)	51	3DCRT with linac	concurrent chemoradiotherapy	DFS	0.94 (0.58–1.52), P = 0.400	1.33 (0.71–2.49), P = 0.38	0.75 (0.36–1.58), NA
				50	–			–	–	–
Hui et al. (18)	January 2009 to December 2017	Phase III	NA	184	3D-CRT/sIMRT	sequential chemoradiotherapy	DFS	0.85 (0.65–1.10), 1-sided P = 0.10	1.01 (0.68–1.51), P = 0.94	0.71 (0.51–0.97), P = 0.03
				180	–			–	–	–
Le Pechoux et al. (19)	August 2007 to July 2018	phase III	61 (36–85)	252	3D-CRT	prior (neo)-adjuvant CT	DFS	0.85 (0.67–1.07), P = 0.16	NA	NA
				249	–			–	–	–

NA, not available.

TABLE 2 | The detail of radiotherapy and chemotherapy of included studies.

Trial	Radiotherapy dose				Prescription Technique	Clinical target volume	Chemotherapy
	Total dose (Gy)	Fractions	Durations (weeks)	Gy/day			
Debevec et al. (13)	30	10 or 12	2	2.5 or 3.0	Linac	isolateral hilum and mediastinum	No chemotherapy
Stephens et al. (14)	40	15	3	2.7	megavoltage X-ray and Cobalt	NA	No chemotherapy
Perry et al. (15)	50	25	5	2.0	NA	the mediastinum, supraclavicular fossae, and ipsilateral hilum	Paclitaxel and carboplatin
Shen et al. (16)	50.4	28	6	1.8	3DCRT with linac	ipsilateral mediastinum, hilum and subcarinal lymph node area	paclitaxel and cisplatin
JongMu Sun et al. (17)	50	25	5	2.0	3DCRT with linac	mediastinal lymphatic stations and the immediately adjacent lymph node stations	Adjuvant paclitaxel and carboplatin
Hui et al. (18)	50	25	6	2.0	3D-CRT/sIMRT	Ipsilateral hilum, subcarinal region and ipsilateral mediastinum	platinum based chemotherapy
Le Pechoux et al. (19)	54	27–30	6	1.8–2.0	3D-CRT	NA	prior (neo)-adjuvant CT was allowed

NA, not available.

Qualität der Studien:

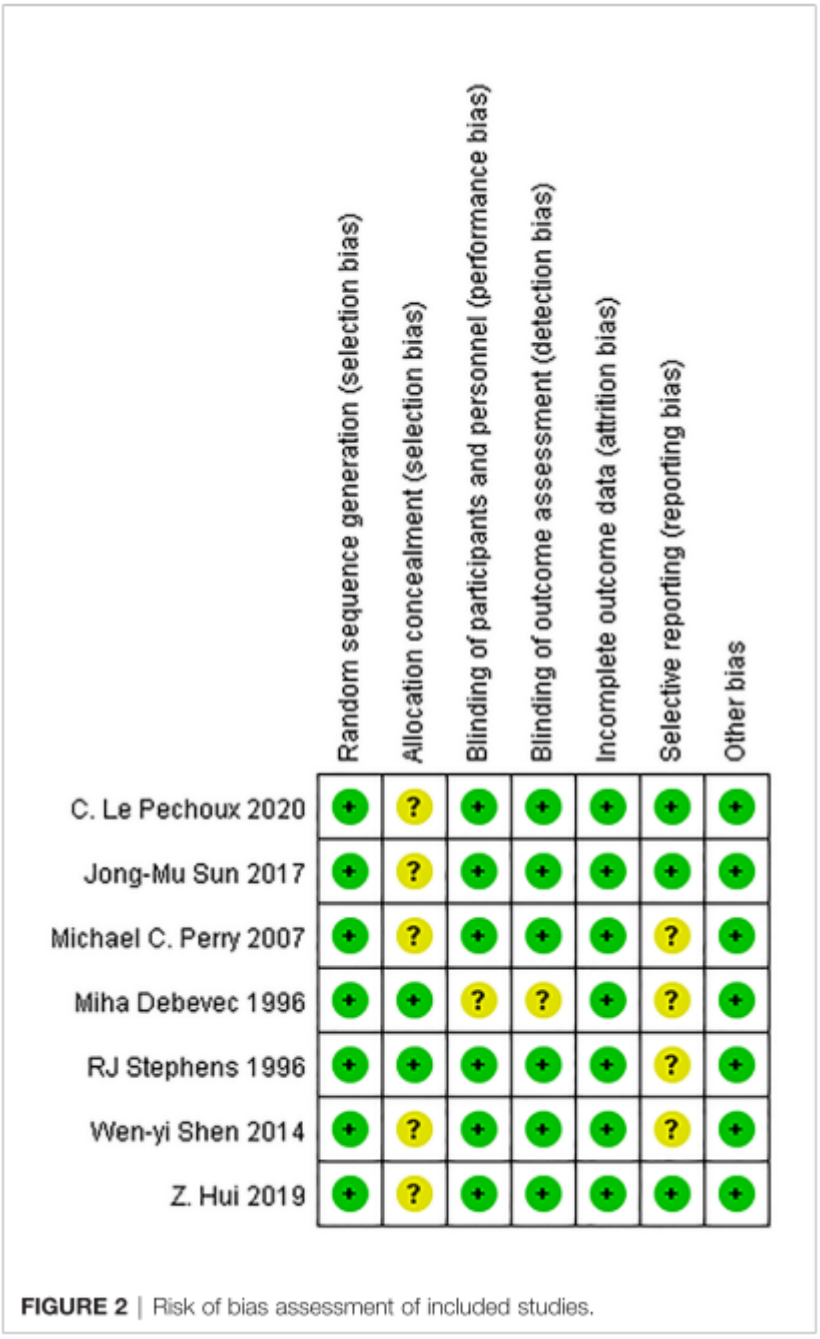

FIGURE 2 | Risk of bias assessment of included studies.

Studienergebnisse:

- Analyses show no benefit of PORT on OS (HR, 0.87; 95% CI, 0.71 to 1.07; p = 0.18)
- Significantly different effect of PORT on DFS (HR, 0.83; 95% CI, 0.71 to 0.97; p = 0.02) and LRFS (HR, 0.64; 95% CI, 0.50 to 0.81; p = 0.0003).
- There is not enough evidence of a difference in the effect on survival by the utility of chemotherapy along with PORT though subgroup analysis of no chemotherapy group, concurrent chemoradiotherapy and sequential chemoradiotherapy group.

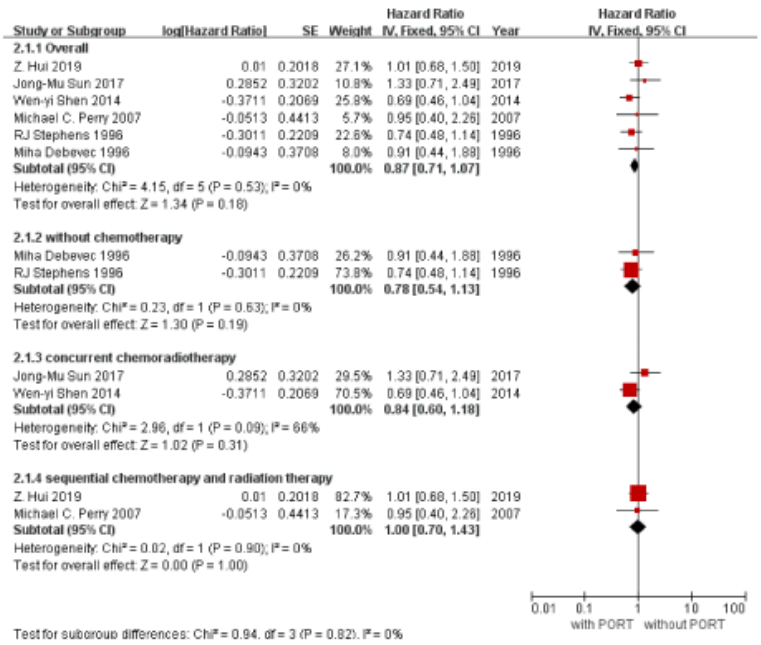

FIGURE 3 | Overall survival. PORT, post-operative radiotherapy; HR, Hazard Ratio.

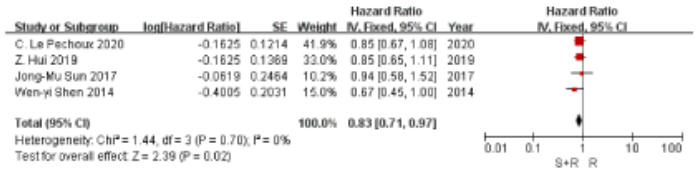

FIGURE 4 | Disease Free Survival. PORT, post-operative radiotherapy; HR, Hazard Ratio.

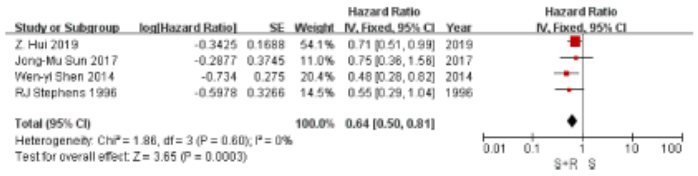

FIGURE 5 | Local-regional recurrence-free survival. PORT, post-operative radiotherapy; HR, Hazard Ratio.

Fazit der Autoren

Our findings illustrate that in the postoperative treatment for patients with stage III-N2 NSCLC, PORT contributes to a significantly increased DFS and LR and may not associate with an improved OS, indicating a cautious selection.

Cheng H et al., 2019 [1].

A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer.

Fragestellung

to compare adjuvant EGFR-TKIs with a placebo or adjuvant chemotherapy among patients with resected non-small cell lung cancer (NSCLC).

Methodik

Population:

- patients with resected NSCLC

Intervention:

- Adjuvant EGFR-TKIs

Komparator:

- chemotherapy or a placebo

Endpunkte:

- DFS, OS, adverse events

Recherche/Suchzeitraum:

- PubMed, Scopus, EMBASE; between January 1, 2010 and June 30, 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Five RCTs / RCTs including three RCTs that compared adjuvant EGFR-TKIs with a placebo, and two RCTs that compared adjuvant EGFR-TKIs with chemotherapy

Charakteristika der Population:

Table 1
Baseline characteristics of included studies. *NA, not assessable.

Trials	Intervention	No.	AgeMedian	Stage (No.)	Adjuvant chemotherapy		Primary endpoint	EGFR mutation positive patients	Median follow up(year)	Median TKI treatment duration (month)
					Yes	No				
RADIANT [10]	erlotinib	N = 623	62	IB to IIIA	315(50.6%)	308(49.4%)	DFS	N = 102	3.9	11.9
	Placebo	N = 350	62	IB to IIIA	200(57.1%)	150(42.9%)	DFS	N = 59		
Br.19 [11]	gefitinib	N = 251	66	IB to IIIA	43(17%)	208(83%)	OS and DFS	N = 7	4.7 (range, 0.1–6.3)	4.8
	placebo	N = 252	67	IB to IIIA	44(17%)	208(83%)	OS and DFS	N = 8		
Li [9]	chemotherapy-gefitinib	N = 30	59.5	IIIA N2	30	0	DFS	N = 30	2.5 (range, 0.3–4.39)	6
	chemotherapy	N = 30	54.6	IIIA N2	30	0	DFS	N = 30		
Feng [8]	Chemotherapy-Icotinib	N = 21	57	IB to IIIA	21	0	DFS	21	2	NA*(Range, 4–8)
	chemotherapy	N = 20	55	IB to IIIA	18	2	DFS	20		
CTONG1104 [12]	gefitinib	N = 111	58	II–IIIA (N1–N2)	0	0	DFS	N = 111	3.04(IQR 1.98–3.73)	21.9
	Vinorelbine plus cisplatin	N = 111	60	II–IIIA (N1–N2)	111	0	DFS	N = 111		
EVAN [13]	erlotinib	N = 51	59	IIIA	0	0	2 year DFS	N = 51	2.75(IQR1.48-3.59)	23.9(IQR20.7–24
	Vinorelbine plus cisplatin	N = 51	57	IIIA	51	0	2 year DFS	N = 51		

Qualität der Studien:

- The study by Li et al. was not a double-blinded trial and had a moderate risk of bias (performance bias and detective bias). The other four included trials were well designed and were at a low risk of bias.

Studienergebnisse:

- For unselected intent-to treat patients who received adjuvant EGFR-TKIs versus a placebo, the hazard ratio (HR) of disease-free survival (DFS) was 0.88 (n.s.).

- For patients with an EGFR mutation, the DFS after adjuvant EGFR-TKIs was superior to that after a placebo, with a HR of 0.59 (95% CI: 0.40–0.88; P=0.009).
- For patients with an EGFR mutation, the DFS after EGFR-TKIs was greater than that after chemotherapy, with a HR of 0.42 (95% CI: 0.19–0.93; P=0.03).
- For patients with wild-type EGFR, the DFS of adjuvant EGFR-TKIs was similar to the placebo, with a RR of 1.00 (n.s.).
- Treatment with EGFR-TKIs resulted in more adverse events compared with the placebo, with a risk ratio (RR) of 2.72, (95% CI: 2.23–3.33; P < 0.00001), but fewer adverse events compared with chemotherapy, with an RR of 0.26 (95% CI: 0.18–0.38; P < 0.00001).

Anmerkung/Fazit der Autoren

In conclusion, patients with resected EGFR-mutant NSCLC treated with adjuvant EGFR-TKIs had an improved DFS compared with placebo or adjuvant chemotherapy. Adjuvant EGFR-TKIs were not effective among patients with wild type EGFR NSCLC. Treatment with adjuvant EGFR-TKIs resulted in more adverse events than the placebo but fewer adverse events compared with adjuvant chemotherapy. Ongoing studies are therefore needed to further confirm the possible benefits of adjuvant EGFR-TKI therapy in patients with NSCLC.

Kommentare zum Review

- Inhomogeneous study design including patients with wild type EGFR, different stage, different treatment regimen and duration -> Die untersuchte Gesamtpopulation ist nicht auf Patientinnen und Patienten mit EGFR-Mutation beschränkt.
- Still many questions that need to be answered regarding treatment with EGFR-TKIs. For patients with EGFR mutations, which stage of lung cancer benefits most from adjuvant EGFR-TKIs after radical resection?

Li R et al., 2019 [6].

Comparing the benefits of postoperative adjuvant chemotherapy vs. observation for stage IB non-small cell lung cancer: a meta-analysis.

Fragestellung

to compare the benefits of postoperative adjuvant chemotherapy vs. observation for stage IB non-small cell lung cancer (NSCLC).

Methodik

Population:

- resected NSCLC patients; p-stage IB (T2N0M0) NSCLC

Intervention:

- adjuvant chemotherapy

Komparator:

- observation

Endpunkte:

- OS, DFS, local recurrence, distant metastasis

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library databases from the earliest publications to June 2018

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- nine RCTs
- 1,645 patients who were assigned to the adjuvant chemotherapy (n=820) and observation (n=825) groups

Charakteristika der Population:

Table 1 Characteristics of the included studies for the meta-analysis

The study of stage IB	Year	Accrual year	Country	Study design	Postoperative adjuvant chemotherapy	Size	Outcome	Journal
Butts *et al.* (9)	2010	1994–2001	Canada	RCT	Cisplatin (50 mg/m^2) d1, d8, 4 weeks; vinorelbine (25 mg/m^2), weekly 16 weeks	219	5-year OS	*Journal of Clinical Oncology*
Strauss *et al.* (10)	2008	1996–2003	USA	RCT	Paclitaxel (200 mg/m^2), carboplatin (AUC =6); every 3 weeks	344	5-year OS; 5-year DFS	*Journal of Clinical Oncology*
Douillard *et al.* (11)	2006	1994–2000	France	RCT	Vinorelbine (30 mg/m^2), cisplatin (100 mg/m^2); every 4 weeks	301	5-year OS	*Lancet Oncology*
Roselli *et al.* (12)	2006	1988–1994	Italy	RCT	Cisplatin (100 mg/m^2) d1, etoposide (120 mg/m^2) d1, 2, 3; every 4 weeks	140	5-year OS; 5-year DFS; local recurrence; distant metastasis	*International Journal of Cancer*
Park *et al.* (13)	2005	1989–1998	Korea	RCT	Mitomycin C (10 mg/m^2) d1, vinblastine (6 mg/m^2) d1, cisplatin (100 mg/m^2) d1–d5; every 3 weeks	97	5-year OS; 5-year DFS	*European Journal of Cardio-thoracic Surgery*
Nakagawa *et al.* (14)	2005	1992–1994	Japan	RCT	Uracil and tegafur 400 mg/d	111	5-year OS	*Annals of Oncology*
Kato *et al.* (15)	2004	1994–1997	Japan	RCT	Uracil and tegafur 250 mg twice a day	263	5-year OS; 5-year DFS	*The New England journal of Medline*
Waller *et al.* (16)	2004	1995–2001	UK	RCT	Cisplatin (50 mg/m^2), mitomycin (6 mg/m^2), ifosfamide (3 g/m^2); vinblastine (6 mg/m^2); cisplatin (50 mg/m^2), vindesine (3 mg/m^2), vinorelbine (30 mg/m^2); 3 weeks	103	5-year OS	*European Journal of Cardio-thoracic Surgery*
Mineo *et al.* (17)	2001	1988–1994	Italy	RCT	Cisplatin (CDDP) (100 mg/m^2) given on day 1 and etoposide (VP16) (120 mg/m^2) administered on days 1–3; every 4 weeks	66	5-year OS; 5-year DFS; local recurrence; distant metastasis	*European Journal of Cardio-thoracic Surgery*

RCT, randomized controlled trial.

Qualität der Studien:

Table 2 The risk of bias analysis of the included RCTs

Study	A	B	C	D	E	F	G	Grade
Butts *et al.* (9)	+	+	+	?	+	+	?	B
Strauss *et al.* (10)	+	+	+	?	+	+	–	B
Douillard *et al.* (11)	+	+	+	+	+	+	+	A
Roselli *et al.* (12)	+	+	+	+	+	+	?	A
Park *et al.* (13)	+	+	+	+	–	+	?	B
Nakagawa *et al.* (14)	+	+	+	?	+	+	?	B
Kato *et al.* (15)	+	+	+	+	–	+	?	B
Waller *et al.* (16)	+	+	+	+	+	?	?	B
Mineo *et al.* (17)	+	+	+	+	?	?	?	B

A, random sequence generation; B, allocation concealment; C, blinding of participants and personnel; D, blinding of outcome assessment; E, incomplete outcome data; F, selective reporting; G, other bias; +, low risk of bias; –, high risk of bias; ?, uncertain risk of bias. RCT, randomized controlled trial.

Studienergebnisse:

- No significance in the 5-year OS and 5-year DFS between the postoperative adjuvant chemotherapy and observation groups.
- However, there was a significant difference in local recurrence (RR =0.43; 95% CI: 0.23–0.80; P=0.007) and distant metastasis (RR =0.68; 95% CI: 0.48–0.97; P=0.03) between the two groups.

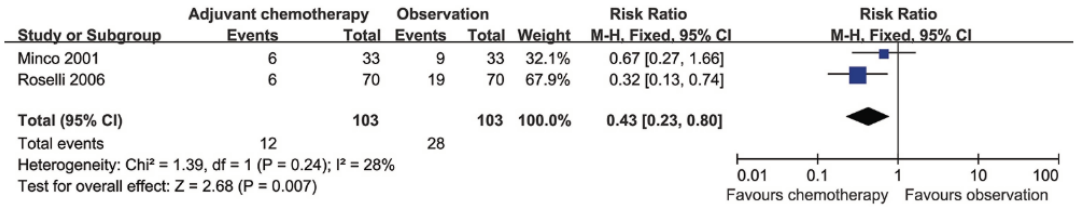

Figure 4 Forest plot of local recurrence associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. NSCLC, non-small cell lung cancer.

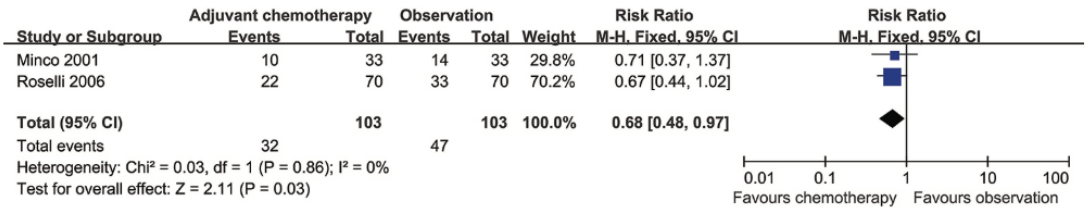

Figure 5 Forest plot of distant metastasis associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. NSCLC, non-small cell lung cancer.

Fazit der Autoren

The 5-year OS and 5-year DFS of stage IB NSCLC patients were not improved by adjuvant chemotherapy. In addition, there was not enough evidence to show that adjuvant chemotherapy reduced the risks of local recurrence and distant metastasis after surgery, because these results might be influenced by sample size in the meta-analysis. In conclusion, adjuvant chemotherapy might not be recommended for stage IB NSCLC patients.

Lu D et al., 2019 [7].

Differential effects of adjuvant EGFR tyrosine kinase inhibitors in patients with different stages of non-small-cell lung cancer after radical resection: an updated meta-analysis.

Fragestellung

to compare the beneficial effects of adjuvant tyrosine kinase inhibitor (TKI) therapy with those of traditional therapy on NSCLC patients, specifically on EGFR-mutant and stage II–IIIA patients, who might benefit most from such treatment.

Methodik

Population:

- patients diagnosed with pathological stage I–IIIA NSCLC suitable for adjuvant chemotherapy or chemoradiotherapy

Intervention/Komparator:

- adjuvant EGFR-TKIs vs chemotherapy or placebo, or adjuvant combination of TKIs and chemotherapy vs chemotherapy alone

Endpunkte:

- DFS, OS

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and the Cochrane Library without any restrictions on publication status/date

Qualitätsbewertung der Studien:

- Newcastle–Ottawa scale / Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Six randomized control trials and three retrospective cohort studies of 2,467 patients

Charakteristika der Population:

Table 1 Main characteristics of all the studies included in the meta-analysis

Study	EGFR mutation (%)	Usage of drug	Median treatment duration	Size	Design	Women (%)	Stage			Control arm	TKI arm number	Control arm number
							I	II	III			
Yue et al (2018) (EVAN)[17]	100	E	12 m	102	RCT	NA	0	0	102	C	51	51
Wu et al (2017) (ADJUVANT)*	100	G	18 m	222	RCT	58.5	0	74	143	C	111	111
Kelly et al (2015) (RADIANT)[13]	16.5	E	11.9 m	973	RCT	65.1	499	320	153	P	623	350
Feng et al (2015)*	100	I	8 m	39	RCT	30.7	17	10	12	C	21	18
Lv et al (2015)[9]*	100	G/E/I	18 m	138	RCS	41.6	69	21	48	C	31	107
Li et al (2014)[7]	100	G	6 m	60	RCT	40.9	0	0	60	C	30	30
Goss et al (2013) (BR19)[14]	4	G	48 m	503	RCT	46.1	260	175	67	P	251	252
D'Angelo et al (2012)*	100	G/E	18.6 m	286	RCS	73.4	213	32	42	P	84	202
Janjigian et al (2011)*	100	G/E	20 m	167	RCS	68.1	117	25	25	P	56	111

Abbreviations: C, chemotherapy; E, erlotinib; G, gefitinib; I, icotinib; P, placebo; RCS, retrospective comparative study; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor.

- The overall EGFR mutation rate was 48.62%

Qualität der Studien:

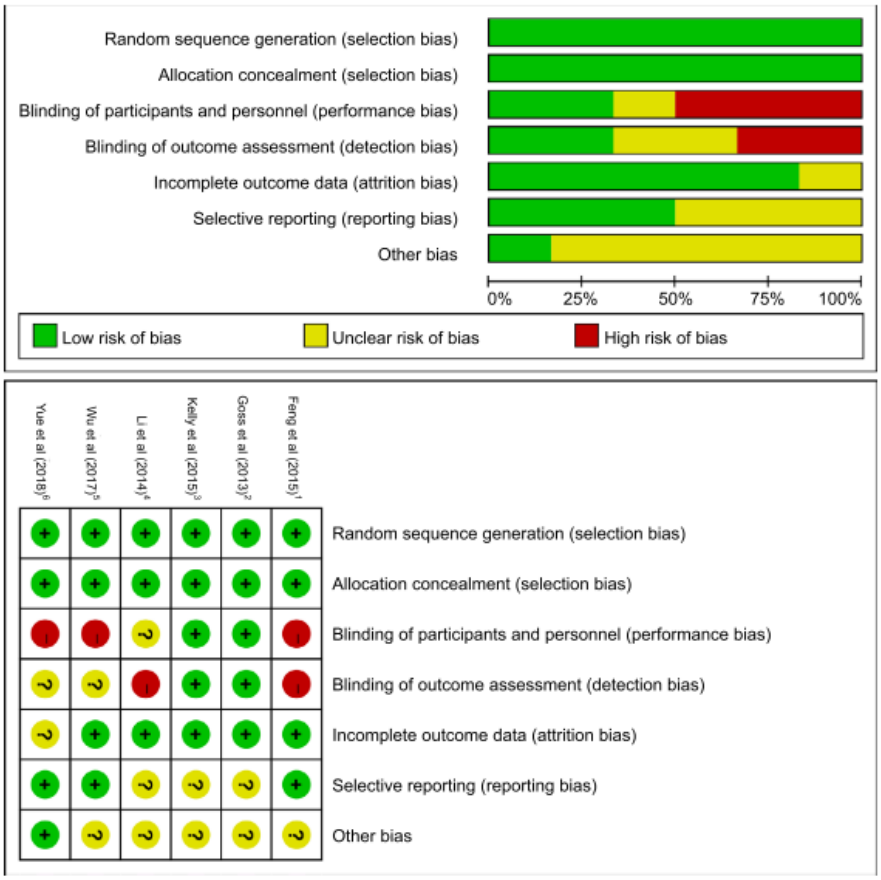

Figure S1 Risk-of-bias graph and summary for the included randomized control trials.

Table S1 Newcastle–Ottawa scale for quality assessment of non-randomized cohort studies

Study	Selection				Comparability	Exposure			Total score
	1	2	3	4	1	1	2	3	
D'Angelo et al (2012)[7]	b	a	a	b	ab	a	a	A	8
Janjigian et al (2011)[8]	b	a	a	a	ab	a	a	B	9
Lv et al (2015)[9]	b	a	a	b	a	a	a	A	7

Studienergebnisse:

- DFS was significantly improved in all the patients (HR, 0.77; 95% CI, 0.68–0.88) and in the subgroup of EGFR-mutant patients (HR, 0.49; 95% CI, 0.40–0.61).
- The difference of 5-year OS in the subgroup of EGFR-mutant patients (HR, 0.48; 95% CI, 0.31–0.72) was statistically significant, while in all the patients (HR, 1.01; 95% CI, 0.85–1.19), the difference was not significant.

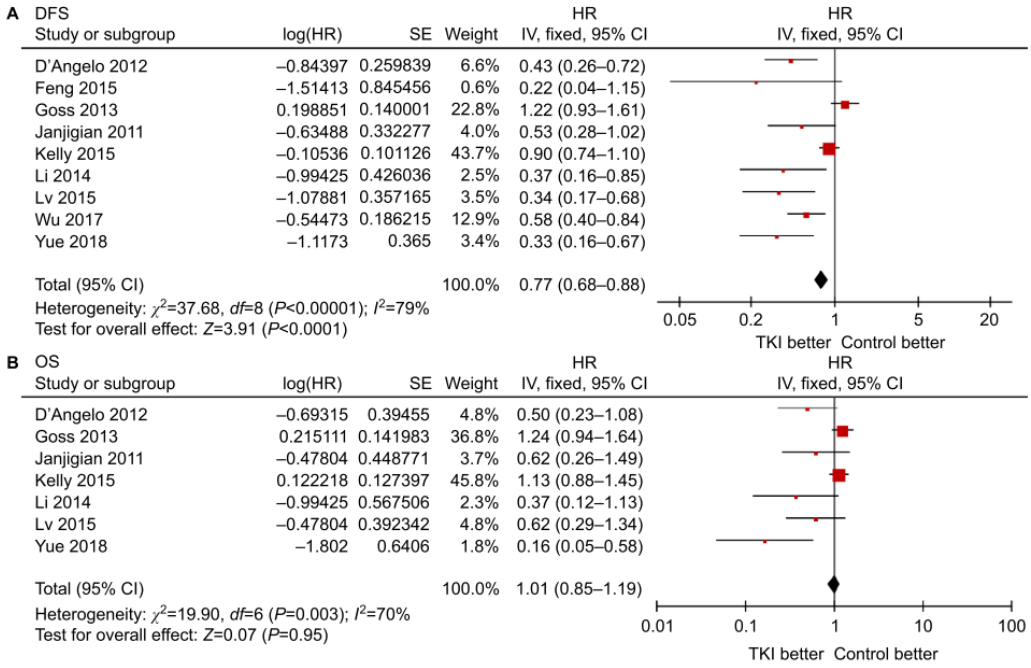

Figure 2 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in patients with NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

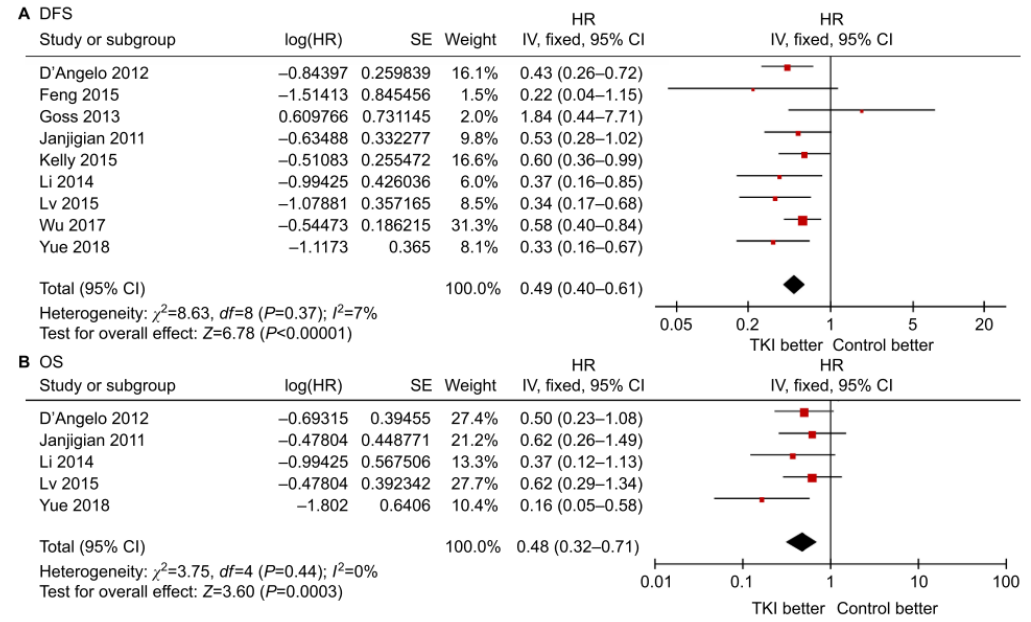

Figure 3 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in patients with EGFR-mutant NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

- In the subgroups of studies in which <50% of patients were in stage I (HR, 0.46; 95% CI, 0.35–0.60) and >30% of patients were in stage IIIA (HR, 0.46; 95% CI, 0.35–0.60), DFS was significantly improved, while in the subgroups of studies in which <30% of patients were in stage IIIA (HR, 0.90; 95% CI, 0.77–1.04) and >50% of patients were in stage I (HR, 0.90; 95% CI, 0.77–1.04), DFS was not significantly improved.

Table 2 Effects of adjuvant TKIs on DFS in relation to proportions of stage I and III NSCLC

Category		Studies divided into subgroups	HR [95% CI]
Stage I	>30	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19]	0.85 [0.74–0.99]
	≤30	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	>40	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19]	0.85 [0.74–0.99]
	≤40	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	>50	D'Angelo et al (2012)[28], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15]	0.90 [0.77–1.04]
	≤50	Wu et al (2017) (ADJUVANT)[16], Feng et al (2015)[18], Li et al (2014)[27], Lv et al (2015)[19], Yue et al (2018) (EVAN)[17]	0.46 [0.35–0.60]
Stage III	>30	Feng et al (2015)[18], Li et al (2014)[27], Lv et al (2015)[19], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.47 [0.36–0.60]
	≤30	D'Angelo et al (2012)[28], Goss et al (2013) (BR19)[14], Janjigian et al (2011)[29], Kelly et al (2015) (RADIANT)[15]	0.92 [0.79–1.07]
	>40	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	≤40	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19], Janjigian et al (2011)[29]	0.85 [0.74–0.99]
	>50	Li et al (2014)[27], Wu et al (2017) (ADJUVANT)[16], Yue et al (2018) (EVAN)[17]	0.49 [0.36–0.67]
	≤50	D'Angelo et al (2012)[28], Feng et al (2015)[18], Goss et al (2013) (BR19)[14], Kelly et al (2015) (RADIANT)[15], Lv et al (2015)[19], Janjigian et al (2011)[29]	0.85 [0.74–0.99]

Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; TKIs, tyrosine kinase inhibitors.

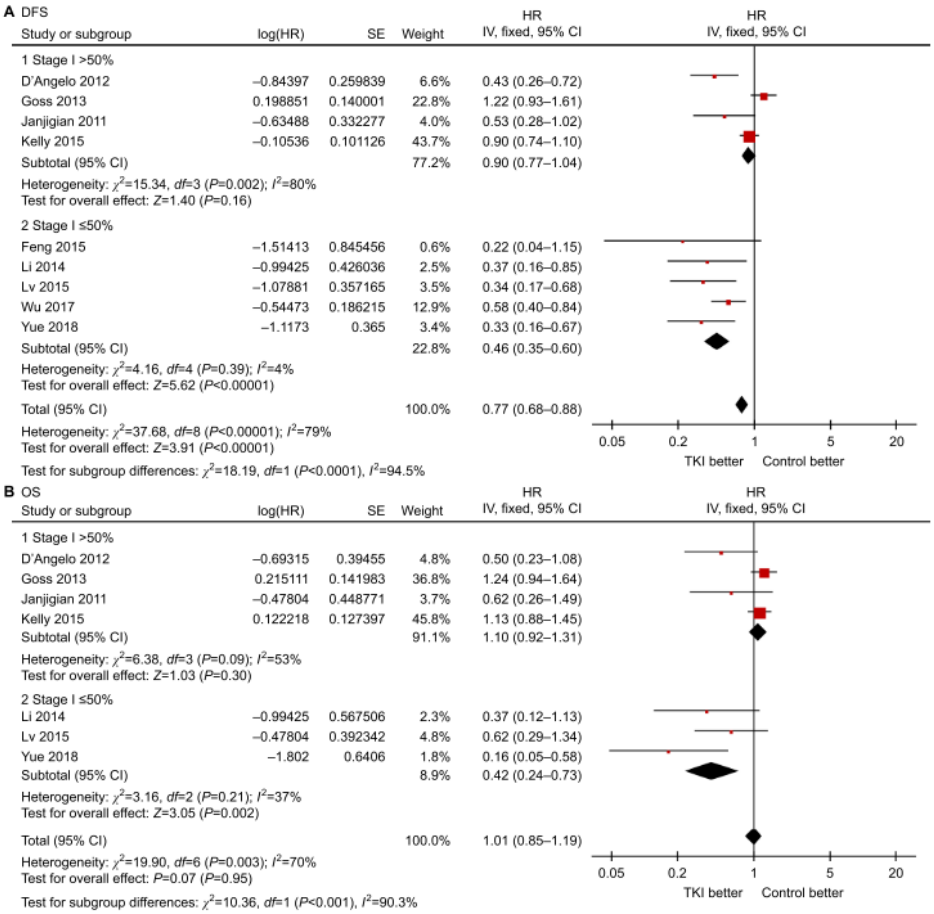

Figure 4 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in subgroups in which >50% and <50% of patients were diagnosed with stage I NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

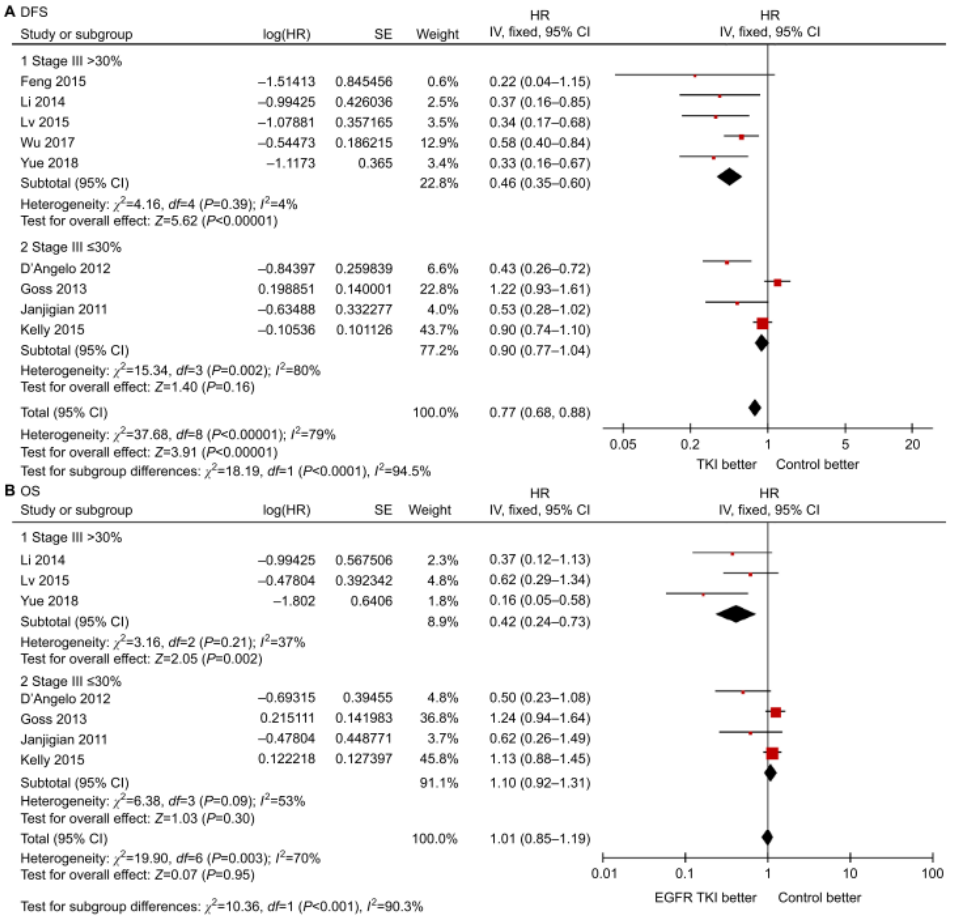

Figure 5 Forest plots of the HR of DFS (**A**) and OS (**B**) of adjuvant EGFR-TKI therapy vs control in subgroups in which >30% and <30% of patients were diagnosed with stage III NSCLC after radical resection.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

Anmerkung/Fazit der Autoren

This meta-analysis indicated that postoperative adjuvant EGFR-TKI treatment may provide significant benefits in terms of DFS and OS in patients with EGFR-mutated NSCLC, especially those with regional lymph node metastasis (N1 and N2), but may not be beneficial in patients with stage I NSCLC.

Kommentare zum Review

- Die untersuchte Gesamtpopulation ist nicht auf Patientinnen und Patienten mit EGFR-Mutation beschränkt. Siehe „Charakteristika der Population“.
- Etwa 24% der untersuchten Population entstammen retrospektiven Kohortenstudien, die mit einem erhöhten Verzerrungspotential ggü. RCTs einhergehen.

3.3 Leitlinien

Daly ME et al., 2022 [2].

American Society of Clinical Oncology (ASCO)

Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline.

Zielsetzung/Fragestellung

To provide evidence-based recommen dations to practicing clinicians on management of patients with stage III non–small-cell lung cancer (NSCLC).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium und Patientenvertretung dargelegt;
- Interessenkonflikte und Angaben zur Finazierung dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz zutreffend;
- Formale Konsensusprozesse dargelegt; externes Begutachtungsverfahren: "[…] reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC)";
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität: laufende Aktualisierung geplant, Änderungseinträge und Gültigkeitsdauer jedoch unklar: "ASCO's formal updating process select existing guidelines are developed as living guidelines. The living guideline model requires constant updating of the literature and ongoing expert review and approval to provide current, user-friendly, high-quality, and evidence-based recommendations"

Recherche/Suchzeitraum:

- PubMed (January 1990-August 2021) and Cochrane Library (January 2010-August 2021) of SRs and phase II and III randomized clinical trials (RCTs)

LoE/GoR:

- The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Recommendations

Surgery

- Recommendation 2.1. For patients with stage IIIA (N2) NSCLC, induction therapy followed by surgery (with or without adjuvant therapy) may be offered if all of the following conditions are met: (1) A complete resection (R0) of the primary tumor and involved lymph nodes is deemed possible; (2) N3 lymph nodes are deemed to be not involved by multidisciplinary consensus; (3) Perioperative (90-day) mortality is expected to be low (≤ 5%) (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak)
- Recommendation 2.2. For selected patients with T4N0 disease (by size or extension), surgical resection may be offered if medically and surgically feasible following multidisciplinary review (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: weak).

Adjuvant therapy.

- Recommendation 4.1. Patients with resected stage III NSCLC who did not receive neoadjuvant systemic therapy should be offered adjuvant platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).
- Recommendation 4.2. Patients with resected stage III NSCLC with EGFR exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).
- Recommendation 4.3. For patients with completely resected NSCLC with mediastinal N2 involvement without extracapsular extension who have received neoadjuvant or adjuvant platinum-based chemotherapy, postoperative radiation therapy should not be routinely offered (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak).

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Leitlinienprogramm Onkologie Leitlinie, 2022 [4,5].

Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, Arbeitsgemeischaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms.

Zielsetzung/Fragestellung

- Unterstützung von Ärzten, betroffenen Patienten und Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom bei medizinischen Entscheidungendurch evidenzbasierte und formal konsentierte Empfehlungen
- Schaffung einer Grundlage für inhaltlich gezielte ärztliche Aus-, Fort- und Weiterbildungsmaßnahmen
- flächendeckende Umsetzung einer multidisziplinären, qualitätsgesichertenund sektorübergreifenden Versorgung des Lungenkarzinoms
- Optimierung der Diagnosekette und der stadiengerechten Therapie sowohlbei der Ersterkrankung als auch beim Rezidiv bzw. bei einer Metastasierung

Durch die Umsetzung dieser Ziele soll mittel- und langfristig die Mortalität der Patienten mit Lungenkarzinomen gesenkt und die Lebensqualität erhöht werden

Methodik

Grundlage der Leitlinie

Update - Aktualisierung der S3-Leitlinie Lungenkarzinom 2019-2022

- Repräsentatives Gremium zutreffend;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Jährliche Überprüfung der Aktualität. Gültig bis max. 2027 bzw. bis zur nächsten Aktualisierung

Recherche/Suchzeitraum:

- von Juni 2016 (Ende Suchzeitraum der Vorgängerversion der Leitlinie) bis Dezember 2021

LoE

- entsprechend der Vorgaben des Oxford Centre for Evidence-Based Medicine

GoR

- Hinsichtlich der Stärke der aktualisierten Empfehlung (gekennzeichnet mit „2022“) werden in der Leitlinie drei Empfehlungsgrade unterschieden (A/B/0), die sich auch in der Formulierung der Empfehlungen widerspiegeln. Für die Empfehlungen, die nicht im Rahmen der Aktualsierung bearbeitet wurden (gekennzeichnet mit „2010“ gelten weiterhin die Empfehlungsgraduierung der Version aus 2010. Diese sieht vier Empfehlungsgrade (A/B/C/D) vor

Tabelle 7: Schema der Empfehlungsgraduierung für Empfehlungen 2018 und 2022

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
C	Empfehlung offen	kann

Tabelle 8: Konsensusstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Empfehlungen

8 Therapie des nicht-kleinzelligen Lungenkarzinoms

8.3 Stadium I/II

8.3.2 Therapie bei funktionell operablen Patienten

(Methodikeranmerkung: Empfehlungen, die sich allein auf die Resektion beziehen, werden vorliegend nicht dargestellt und könnnen der LL entnommen werden)

8.21	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad B	Nach R1-Resektion sollten im Thorax-Onkologischen Tumorboard die weiteren Therapiemöglichkeiten (z.B. Nachresektion oder Strahlentherapie) besprochen werden.	
Level of Evidence 3b	[624]	
	Starker Konsens	

8.3.4 Postoperative Systemtherapie

8.24	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Nach R0-Resektion und systematischer Lymphknotendissektion soll Patienten im Stadium II in gutem Allgemeinzustand (ECOG 0/1) eine adjuvante Chemotherapie angeboten werden.	
Level of Evidence **1a**	[653], [654], [655], [656], [657]	
	Starker Konsens	

8.25	Evidenzbasierte Empfehlung	geprüft 2022
Empfehlungsgrad **B**	Die adjuvante Chemotherapie sollte nach Abschluss der Wundheilung innerhalb von 60 Tagen nach der Resektion beginnen.	
Level of Evidence	[658], [659], [660]	
	Starker Konsens	

8.26	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	In der adjuvanten Chemotherapie soll bei Patienten in gutem Allgemeinzustand (ECOG 0/1) die Gabe einer cisplatinhaltigen Kombination über 4 Zyklen erfolgen.	
Level of Evidence **1a**	[654], [655], [661], [656]	
	Starker Konsens	

8.27	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad 0	Patienten im Stadium II und einer aktivierenden EGFR Mutation (nur Exon 19 Deletion, Exon 21 L858R) kann nach kompletter Resektion und adjuvanter Chemotherapie eine adjuvante Therapie mit Osimertinib über 3 Jahre angeboten werden.	
Level of Evidence 1b	[662]	
	Konsens	

8.28	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad B	Patienten im Stadium II mit einer PD-L1 Expression ≥ 50 % (ohne EGFR oder ALK Alteration) sollte, nach R0-Resektion und durchgeführter adjuvanter Chemotherapie, eine adjuvante Therapie mit Atezolizumab über 1 Jahr angeboten werden.	
Level of Evidence 1	[663]	
	Starker Konsens	

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8.3.5 Postoperative Radiotherapie

8.29	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Im Stadium I, II soll nach R0-Resektion eine adjuvante Strahlentherapie nicht angeboten werden.	
Level of Evidence **1a**	[670], [680], [681], [682], [683], [684], [685], [686]	
	Starker Konsens	

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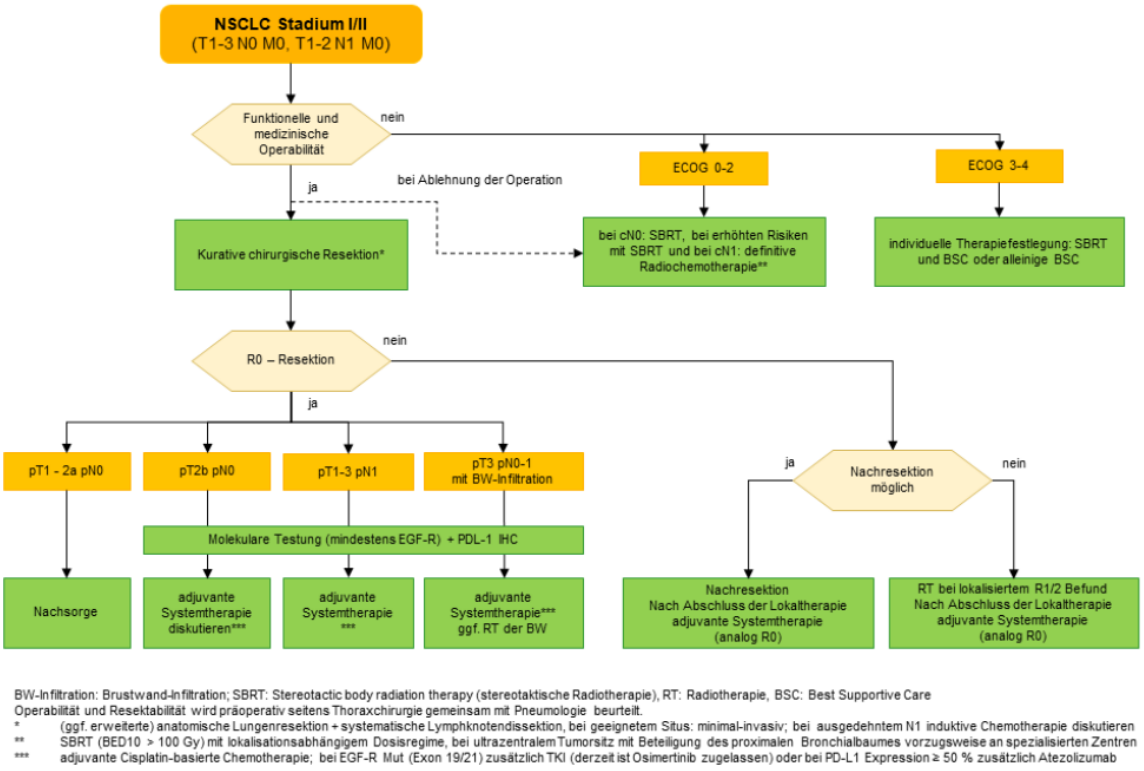

BW-Infiltration: Brustwand-Infiltration; SBRT: Stereotactic body radiation therapy (stereotaktische Radiotherapie), RT: Radiotherapie, BSC: Best Supportive Care
Operabilität und Resektabilität wird präoperativ seitens Thoraxchirurgie gemeinsam mit Pneumologie beurteilt.
* (ggf. erweiterte) anatomische Lungenresektion + systematische Lymphknotendissektion, bei geeignetem Situs: minimal-invasiv; bei ausgedehntem N1 induktive Chemotherapie diskutieren
** SBRT (BED10 > 100 Gy) mit lokalisationsabhängigem Dosisregime, bei ultrazentralem Tumorsitz mit Beteiligung des proximalen Bronchialbaumes vorzugsweise an spezialisierten Zentren
*** adjuvante Cisplatin-basierte Chemotherapie; bei EGF-R Mut (Exon 19/21) zusätzlich TKI (derzeit ist Osimertinib zugelassen) oder bei PD-L1 Expression ≥ 50 % zusätzlich Atezolizumab

Abbildung: „8. 36 Algorithmus Stauium I/II“

8.4 Pancoast-Tumor

(Methodikeranmerkung: Das Kapitel 8.4 kann der LL entnommen werden.)

8.5 Stadium III (T1-3N2 / T1-3N3 / T4N0-3)

8.5.2 Inzidentelles Stadium IIIA(N2) beim NSCLC – Stadium IIIA1 und IIIA2 nach Robinson-Einteilung – Multimodale Therapiekonzepte

8.42	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Im Stadium III mit inzidentellem N2-Status (IIIA1 bzw. IIIA2) soll nach kompletter Resektion (R0) und systematischer Lymphknotendissektion, bei fehlender Kontraindikation, eine adjuvante Kombinationschemotherapie erfolgen. Die Chemotherapie soll nach Abschluss der Wundheilung innerhalb von 60 Tagen nach Resektion erfolgen.	
Level of Evidence **1a**	[654], [697], [766], [767], [768], [769], [770], [679], [771], [667], [670], [671], [660], [772]	
	Starker Konsens	

8.43	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Die Chemotherapie soll bei fehlender Kontraindikation als eine cisplatinhaltige Kombination über 4 Zyklen erfolgen. Nur bei Kontraindikation gegen Cisplatin soll der Einsatz von Carboplatin erwogen werden.	
Level of Evidence **1b**	[770], [693], [776], [777], [778], [779], [780], [781], [782], [783], [784], [785], [786], [787], [769], [788], [789], [667], [670], [671], [660], [678], [790], [756], [791], [772]	
	Starker Konsens	

8.44	Konsensbasierte Empfehlung	modifiziert 2022
EK	Bei Patienten mit klinisch relevanter Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen sollte die Durchführung einer adjuvanten Kombinationschemotherapie individuell geprüft und in einem interdisziplinär ausgerichteten Team mit entsprechender Erfahrung erfolgen.	
	Starker Konsens	

8.45	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **0**	Patienten im Stadium Stadium IIIA1 und IIIA2 und einer aktivierenden EGFR Mutation (nur Exon 19 Deletion, Exon 21 L858R) kann nach kompletter Resektion und adjuvanter Chemotherapie eine adjuvante Therapie mit Osimertinib über 3 Jahre angeboten werden.	
Level of Evidence **1b**	[662]	
	Starker Konsens	

8.46	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **B**	Patienten im Stadium IIIA mit einer PD-L1 Expression ≥ 50 % (ohne EGFR oder ALK Alteration) sollte, nach R0-Resektion und durchgeführter adjuvanter Chemotherapie, eine adjuvante Therapie mit Atezolizumab über 1 Jahr angeboten werden.	
Level of Evidence **1**	[663]	
	Starker Konsens	

8.47	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **A**	Für Patienten mit inkompletter Resektion soll primär die Möglichkeit einer Nachresektion geprüft werden. Sofern keine R0-Resektion sinnvoll zu erzielen ist, soll innerhalb eines multimodalen Gesamtkonzeptes nach Indikationsstellung im Thorax-Onkologischen Tumorboard eine postoperative Strahlentherapie angeboten werden.	
Level of Evidence **2**	[609], [809], [810], [811], [812], [813], [814], [815], [816], [817], [693], [352], [615], [683], [795], [818]	
	Starker Konsens	

8.48	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **B**	Für Patienten mit R0 Resektion und mediastinalem Lymphknotenbefall im Stadium IIIA1 bzw. IIIA2 sollte zusätzlich zur adjuvanten Chemotherapie die Indikation zur postoperativen Mediastinalbestrahlung individuell geprüft aber nicht routinemäßig gestellt werden.	
Level of Evidence **1a**	[820], [821], [822], [823], [824], [825], [826]	
	Starker Konsens	

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8.5.3 Stadium IIIA3 nach Robinson-Einteilung beim NSCLC – Multimodale Therapiekonzepte

8.49	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Patienten im Stadium IIIA3 und technischer und funktioneller Operabilität sollen multimodal behandelt werden. Derzeitige multimodale Optionen sind die definitive Radiochemotherapie +/- Durvalumab und die Operation nach neoadjuvanter Therapie.	
Level of Evidence **1a**	[829], [815], [792], [781], [768], [830], [831], [832], [833], [834], [835], [836], [837], [838], [839], [840], [841], [842], [358], [685], [843], [756], [818], [844], [845], [846], [847], [848]	
	Konsens	

8.50	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **B**	Wird im Rahmen einer Induktion eine Phase alleiniger Chemotherapie eingesetzt, sollte präferentiell eine Kombination aus Cisplatin und einem Taxan eingesetzt werden.	
Level of Evidence **1b**	[850], [851], [852], [781], [792], [693], [853]	
	Konsens	

8.51	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **B**	Bei alleiniger Induktionschemotherapie sollte nach Operation und R0-Resektion im Stadium IIIA3 eine Evaluation im Thorax-Onkologischen Tumorboard und bei erhöhtem lokoregionärem Rezidivrisiko eine mediastinale Radiotherapie erfolgen. Die Dosis sollte 50-54 Gy in 5-6 Wochen betragen.	
Level of Evidence **2b**	[855], [810], [792], [698], [856], [857], [858], [859], [860], [821], [861], [862], [863], [864], [865], [866], [824]	
	Starker Konsens	

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8.5.4 Stadium IIIA beim NSCLC ohne N2 (T4N0 und T4N1) – Multimodale Therapiekonzepte

8.52	Konsensbasiertes Statement	modifiziert 2022
EK	In den Subgruppen T4N0 und T4N1 (jeweils Stadium IIIA) ist nach interdisziplinärer Evaluation im Thorax-Onkologischen Tumorboard die primäre Operation bzw. die Integration der Operation in das Gesamtbehandlungskonzept bei technischer und funktioneller Operabilität möglich. Dies sollte gegen die Vorteile eines neoadjuvanten Vorgehens (siehe Empfehlungen 8.48 und 8.49) abgewogen werden.	
	Starker Konsens	

8.53	Konsensbasierte Empfehlung	neu 2022
EK	Bei primär eingeschmolzenen Tumoren sollten Risiken einer (Radio)chemotherapie gegenüber denen einer primären Operation abgewogen werden.	
	Starker Konsens	

8.5.5 Stadium IIIA4 nach Robinson-Einteilung und IIIB beim NSCLC – Multimodale Therapiekonzepte inklusive Operation

8.54	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **0**	Für selektierte Patienten im Stadium IIIA4 / IIIB kann nach interdisziplinärer Evaluation im Thorax-Onkologischen Tumorboard ein multimodaler Behandlungsansatz unter Integration der Operation erfolgen, sofern eine R0 Resektion sehr wahrscheinlich ist.	
Level of Evidence **1b**	[842], [693], [810], [792], [780], [884], [885], [886], [887], [888], [889], [715], [880], [879], [839], [843], [756], [689]	
	Starker Konsens	

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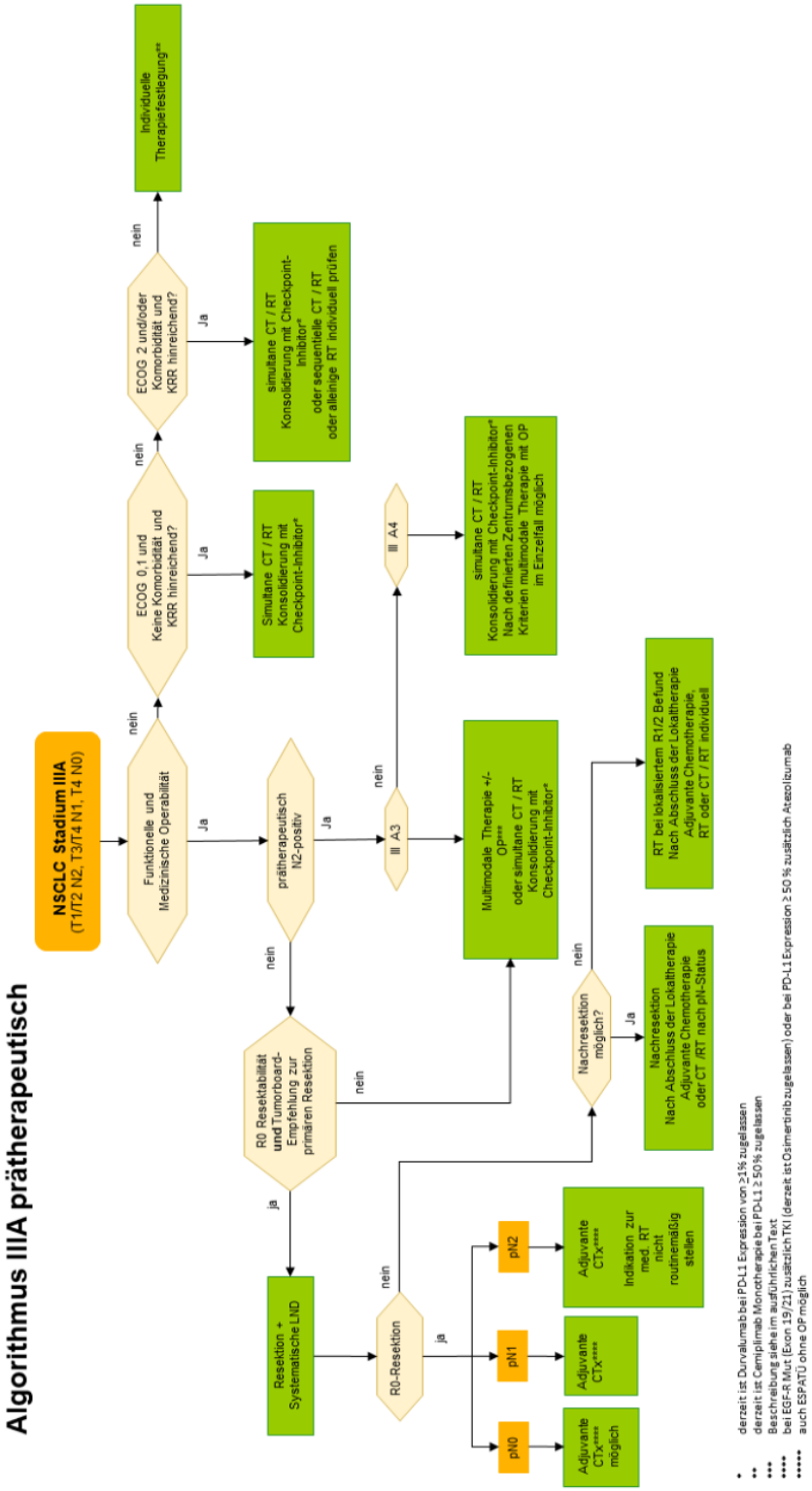

Abbildung: 8.5.7 Algorithmen Stadium IIIA

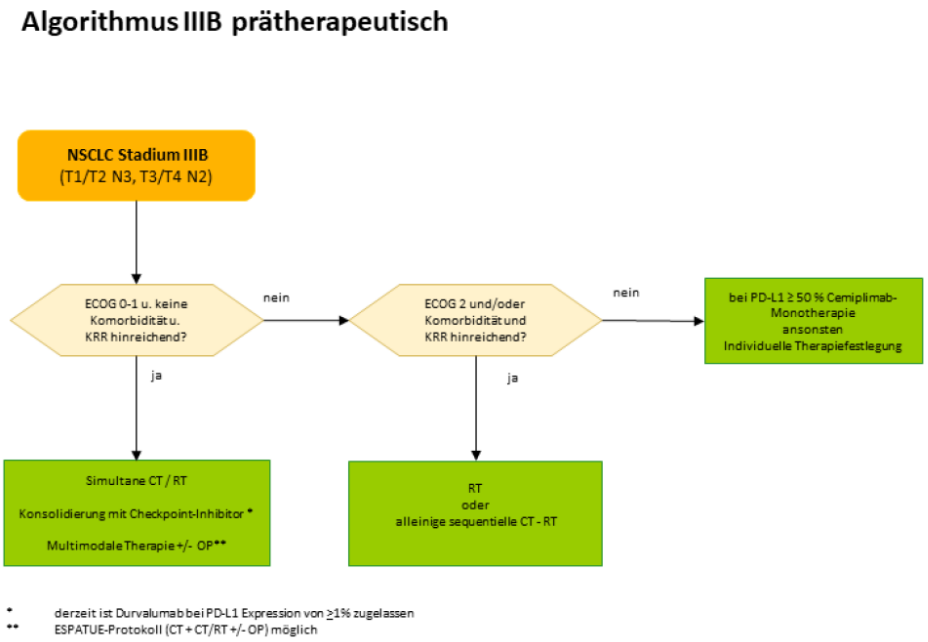

Abbildung: 8.5.7 Algorithmen Stadium IIIB

National Institute for Health and Care Excellence (NICE), 2019 [8].

Lung cancer: diagnosis and management

Leitlinienorganisation/Fragestellung

This guideline covers diagnosing and managing non-small-cell and small-cell lung cancer. It aims to improve outcomes for patients by ensuring that the most effective tests and treatments are used, and that people have access to suitable palliative care and follow-up.

Methodik

Grundlage der Leitlinie

- Update (This guideline replaces CG121, and is the basis of QS17); Last updated: 14 March 2023
- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- The sources for the 2019 and 2022 versions are the same:
  - Cochrane Database of Systematic Reviews – CDSR
  - Cochrane Central Register of Controlled Trials – CENTRAL
  - Database of Abstracts of Reviews of Effects – DARE

  - Health Technology Assessment Database – HTA
  - EMBASE (Ovid)
  - MEDLINE (Ovid)
  - MEDLINE In-Process (Ovid)
- The searches were conducted between October 2017 and April 2018 for 9 review questions (RQ).
- Searches were re-run in May 2018

LoE/ GoR

- RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I too
- Systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups (High, Moderate, Low)
- A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses

Sonstige methodische Hinweise (Updates)

- March 2023: We added the NICE technology appraisal guidance on mobocertinib to the systemic anti-cancer therapy treatment pathways for advanced non-small-cell lung cancer.
- September 2022: We added the NICE technology appraisal guidance on tepotinib to the systemic anti-cancer therapy treatment pathways for advanced non-small-cell lung cancer.
- August 2022: We have changed how the information on systemic anti-cancer therapy for advanced non-small-cell lung cancer is presented.
- In March 2019: We reviewed the evidence and made new recommendations on mediastinal lymph node assessment, brain imaging, prophylactic cranial irradiation, radical radiotherapy and operable stage IIIA disease. These recommendations are marked [2019].

Updates-Kennzeichnung:

These recommendations are marked [2005, amended 2019] or [2011, amended 2019].

Recommendations marked [2005] or [2011] last had an evidence review in 2005 or 2011. In some cases, minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

Empfehlungen

1.7 Combination treatment for non-small-cell lung cancer

- 1.7.2 Ensure that all people for whom multimodality treatment is potentially suitable (surgery, radiotherapy and chemotherapy in any combination) are assessed by a thoracic oncologist and by a thoracic surgeon. [2011]
- 1.7.3 Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC. [2011]
- 1.7.4 Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter. [2011]

- 1.7.5 Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. [2011]
- 1.7.6 For people with stage I–II NSCLC that are suitable for surgery, do not offer neo-adjuvant treatment outside a clinical trial. [2011, amended 2019]
- 1.7.7 Ensure eligible people have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy. [2011]
- 1.7.8 Treat Pancoast tumours in the same way as other types of NSCLC. Offer multimodality therapy according to resectability, stage of the tumour and performance status of the person. [2011]
- 1.7.9 For people with operable stage IIIA–N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery. [2019]
- 1.7.10 Discuss the benefits and risks with the person before starting chemoradiotherapy with surgery, including that:
  - chemoradiotherapy with surgery improves progression-free survival
  - chemoradiotherapy with surgery may improve overall survival. [2019]
- 1.7.11 For people with stage IIIA–N2 NSCLC who are having chemoradiotherapy and surgery, ensure that their surgery is scheduled for 3 to 5 weeks after the chemoradiotherapy. [2019]
- 1.7.12 Multidisciplinary teams that provide chemoradiotherapy with surgery should have expertise in the combined therapy and in all of the individual components. [2019]
- 1.7.13 Centres performing lung resections for lung cancer should validate their data for the Royal College of Physicians Lung Cancer Clinical Outcomes publication and the National Lung Cancer Audit. [2019]

Passiglia F et al., 2020 [9].

Italian Association of Medical Oncologyg (AIOM)

Diagnosis and treatment of early and locally advanced non-small-cell lung cancer: The 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines.

Leitlinienorganisation/Fragestellung

Evidence-based guideline for the management of lung tumors.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium, Patientenvertretung nicht angegeben;
- Interessenkonflikte dargelegt, finanzielle Unabhängigkeit nicht erwähnt;
- Systematische Suche, Auswahl und Bewertung der Evidenz zutreffend;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht erwähnt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über die Hintergrundinformationen dargestellt;
- Regelmäßige Überprüfung der Aktualität: keine Angabe zu Gültigkeit bzw. Aktualisierung

Recherche/Suchzeitraum:

- Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019.

LoE/GoR

- GRADE
- The global quality of evidence was defined as follow:
  - High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
  - Moderate (moderate grade of confidence in the study results): moderate probability that the estimated effect is similar to the true effect, but limited possibility that it is substantially different.
  - Low (low grade of confidence in the study results): limited probability that the estimated effect is similar to the true effect, with high possibility that it is substantially different
  - Very low (very low grade of confidence in the study results): very limited probability that the estimated effect is similar to the true effect, with very high possibility that it is substantially different.

- The strength of clinical recommendations is graduated on four levels according to their clinical relevance, considering the benefit/risk outcomes ratio, the quality of evidence and other additional variables (equity, acceptability, feasibility, and patients' preference):
  - Strong for: The intervention should be considered as the treatment of choice (benefits are higher than risks)
  - Conditional for: The intervention may be considered as treatment of choice (not sure that benefits are higher than risks)
  - Conditional against: The intervention should not be considered as treatment of choice, except for selected cases after discussion with the patient (not sure that benefits are higher than risks)

Recommendations

Clinical Recommendations for the Diagnosis and Treatment of Early and Locally Advanced NSCLC.

Global quality of evidence GRADE	Clinical recommendation	Strenght of recommendation
Moderate	For patients with resectable NSCLC and abnormal mediastinal lymph-nodes at CT/PET scan, invasive sampling by endosonography should be considered as treatment of choice (compared to mediastinoscopy).	Conditional for
Moderate	For patients with stage I NSCLC, video-assisted thoracoscopic surgery (VATS) should be considered as treatment of choice	Conditional for
High	For patients with surgically resected, stage I-IIIA NSCLC, cisplatin-doublets adjuvant chemotherapy should be considered as a treatment of choice	Strong for
High	For patients with surgically resected, stage I-II NSCLC, post-operative radiotherapy must not be considered as a treatment option	Strong against
High	For patients with unresectable stage III NSCLC and ECOG-PS 0–1, definitive concurrent chemoradiation should be considered as treatment of choice	Strong for
High	For patients with unresectable stage III NSCLC, a cisplatin-based combination regimen should be considered as treatment of choice in association to definitive radiotherapy	Strong for
Low	For patients with unresectable stage III NSCLC, with partial response or stable disease (RECIST v1.1) after definitive chemoradiation, and tumor PD-L1 $\geq$ 1 %, consolidation treatment with durvalumab for 12 months should be considered as treatment of choice	Strong for

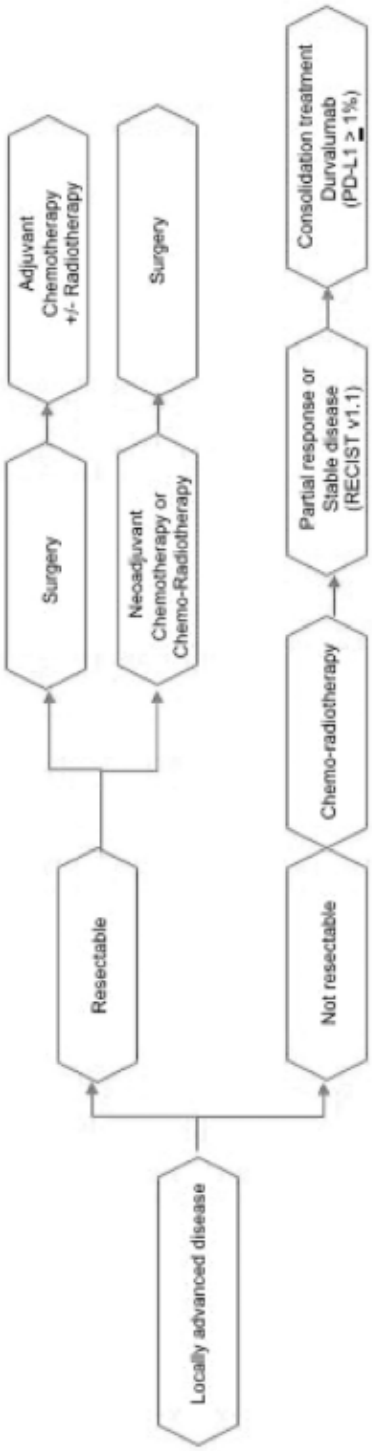

Fig. 3. Treatment of Locally Advanced NSCLC.

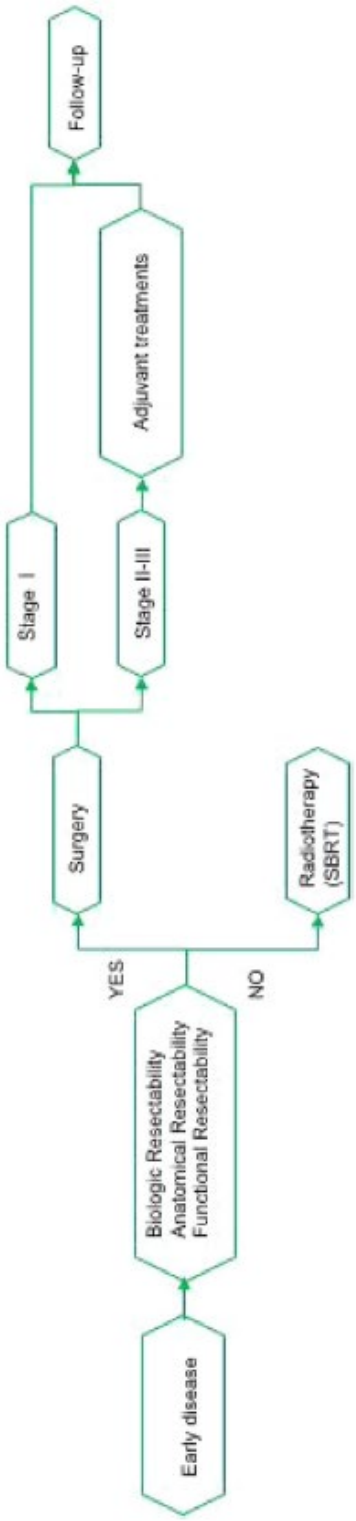

Fig. 2. Treatment of Early Stage NSCLC.

Hintergrund

5. Treatment of early disease

5.3. Adjuvant treatments

Post-operative platinum-based chemotherapy is recommended for all patients with stage II and III surgically resected disease, with performance status (ECOG PS) of 0–1 and without significant comorbidities (Table 1). Two meta-analysis demonstrated that post-operative platinum-based chemotherapy led to more than 10 % reduction in the risk of death, resulting in about 5 % absolute 5-years OS and diseasefree survival (DFS) improvement. Incidence of severe toxicities was about 65 %, with grade 3–4 neutropenia reported in 37 % of cases (Pignon et al., 2008; Burdett et al., 2015). Although the optimal interval between surgery and adjuvant treatment, emerging from randomized studies, is actually considered 6–8 weeks, a recent analysis of the National Cancer Database showed a comparable outcome in patients treated after a longer interval (Salazar et al., 2017). Data coming from the LACE meta-analysis suggested that adjuvant chemotherapy efficacy and tolerability are the same in the small subgroup of>70 years old patients, while prospective data on patients> 75 years old are lacking (Pignon et al., 2008). The majority of studies investigating carboplatin-based adjuvant regimens failed to show any survival benefit (Strauss et al., 2008; Ou et al., 2010; Felip et al., 2010), while direct comparison with cisplatin-doublets are currently lacking. Based on the results of the JBR.10 and ANITA trials (Douillard et al., 2006; Butts et al., 2010), cisplatin-vinorelbine is currently considered as the best regimen for adjuvant setting. Third generation agents, with at least comparable efficacy, such as gemcitabine, may be considered as an alternative valid option. Even if platinum-pemetrexed showed equal efficacy and better tolerability profile in phase II-III studies (Kreuter et al., 2016; Kenmotsu et al., 2019), it is not currently reimbursed and recommended as adjuvant therapy in Italy. In the decision process for adjuvant chemotherapy, several factors, including, age, pre- and post-operative morbidities, should be considered and discussed within a multidisciplinary team (Fig. 2). Several studies investigated the role of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in the adjuvant setting showing conflicting results, with a potential benefit likely limited to EGFR-mutated NSCLC (Kelly et al., 2015; Goss et al., 2013; Yue et al., 2018; Zhong et al., 2018; Li et al., 2014). The high heterogeneity of included populations, comparator arms, and treatment regimens, among these studies, along with the absence of OS data, do not allow to draw any definitive conclusion about the efficacy of these agents. Waiting for the ongoing prospective randomized trials investigating the efficacy of third-generation TKIs in biomarker-selected NSCLC patients, the use of EGFR-TKIs is not currently recommended in the adjuvant setting. Several studies and meta-analyses clearly demonstrated that postoperative radiotherapy (PORT) in patients with stage I-II NSCLC, is associated with higher risk of death [HR 1.18 (95 % CI 1.07–1.31)], disease recurrence [HR 1.10 (IC 95 % 0.99–1.21)], and local recurrence [HR 1.12 (IC 95 % 1.01–1.24), with absolute 5 % decrease in survival rate at 2 years (PORT Meta-analysis Trialists Group, 1998; Burdett et al., 2016). Therefore, it cannot be recommended as part of adjuvant strategies (Table 1).

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6. Treatment of locally advanced disease

6.1.3. Adjuvant treatments

Several studies included in the LACE meta-analysis (Pignon et al.,2008) demonstrated a 4.2 % absolute 5 years survival rate improvement for the subgroup of patients with stage IIIA-IIIB (N1 or single station N2) NSCLC who received adjuvant chemotherapy after surgical resection, suggesting cisplatin-doublets as the best regimen.

Although the results of the PORT meta-analysis (PORT Meta-analysis Trialists Group, 2000) showed a not clear survival benefit in patients with stage III, N2 pathological disease undergoing radiotherapy after radical surgery, more recent meta-analyses demonstrated that PORT is associated to a reduction in risk of loco-regional and systemic recurrences

(Billiet et al., 2014; Li et al., 2016; Liu et al., 2019), with a significant increase in OS in the subgroup of patients with extensive pN2 involvement (HR = 0.85; 95 % CI: 0.79-0.92) (Liu et al., 2019). Waiting for the final results of the prospective LungArt trial, PORT may be considered as an effective treatment for surgically resected patients with extensive N2 pathological involvement or R1 disease, and should be evaluated in the context of an experienced multidisciplinary team.

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Pisters, K. et al., 2022 [3,10].

American Society of Clinical Oncology (ASCO)

Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small-cell lung cancer: ASCO Guideline Rapid Recommendation Update.

Zielsetzung/Fragestellung

What is the role of adjuvant systemic therapy and adjuvant radiation therapy in patients with completely resected stage I to IIIA non–small-cell lung cancers (NSCLCs)?

In 2017, ASCO with Ontario Health—Cancer Care Ontario published a guideline on adjuvant therapy in resected stage I-III NSCLCs. Two RCTs were published in 2020 and 2021 and prompted this amendment to the 2017 guideline.

Methodik

<u>Grundlage der Leitlinie</u>

Update: Amendment to the 2017 guideline

- Repräsentatives Gremium, keine Patientenvertretung angegeben;
- Interessenkonflikte dargelegt, Angaben zur Finazierung fehlen;
- Systematische Suche, Auswahl und Bewertung der Evidenz zutreffend;
- Formale Konsensusprozesse dargelegt; externes Begutachtungsverfahren: "[…] independently reviewed and approved by the EBMC";
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität: laufende Aktualisierung geplant, Änderungseinträge und Gültigkeit jedoch unklar: "ASCO's formal updating process select existing guidelines are developed as living guidelines. The living guideline model

requires constant updating of the literature and ongoing expert review and approval to provide current, user-friendly, high-quality, and evidence-based recommendations"

Recherche/Suchzeitraum:

- Update-Recherche: targeted electronic literature search to identify RCTs of osimertinib and atezolizumab in this patient population was conducted, keine Angabe bzgl. Suchzeitraum

LoE/GoR

- GRADE

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.
- Certainty of evidence: The quality of evidence used to inform a given recommendation is assessed to evaluate its validity, reliability, and consistency. The quality of evidence is rated for each outcome across studies. Factors assessed when rating the quality of evidence include study design, consistency of results, directness of evidence, precision, publication bias, magnitude of effect, confounding, and dose-response gradient. This assessment considers the individual study quality ratings, the overall risk of bias, and the overall validity and reliability of the total body of evidence. The summary rating is an indication of the Expert Panel's confidence that an estimate of the effect is adequate to support a particular recommendation. The certainty of the evidence is defined as one of four grades: high, moderate, low, or very low. Definitions are available in Table 1.

Recommendations

2021 UPDATED RECOMMENDATION

- Recommendation 1.2.1
  - Adjuvant cisplatin-based chemotherapy and/or atezolizumab are not recommended for routine use in this patient group. A postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks of adjuvant therapies for each patient. Factors to consider other than tumor stage when making a recommendation for adjuvant therapy are outlined after the adjuvant systemic therapy section of the 2017 guideline (Type: evidence based and panel consensus, benefits outweigh harms, especially in patients with larger tumors; Evidence quality: intermediate; Strength of recommendation: moderate).

- Recommendation 1.3
  - Stages IIA, IIB, and IIIA: Adjuvant cisplatin-based chemotherapy is recommended for all patients. […] Adjuvant atezolizumab is recommended for all patients with PD-L1 ≥ 1% after cisplatin-based chemotherapy except for patients with sensitizing EGFR mutations (Type: evidence based and panel consensus; Evidence quality: high; Strength of recommendation: strong).

    Note: the guideline recommendations are based on the 7th edition staging system used in the studies as opposed to the current 8th edition staging system for lung cancer.[5]

Referenzen zu den Empfehlungen
2. Wu YL, Tsuboi M, He J, et al: Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 383:1711-1723, 2020
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randomised, multicentre, open-label, phase 3 trial. Lancet 398:1344-1357, 2021
5.AJCC 8th Edition for Lung cancer. AJCC Cancer Staging Manual (ed 8) New York, NY: Springer, 2017

2016 RECOMMENDATION (*Guideline 2017-unverändert*)

- Recommendation 2.1. Stages IA/B and IIA/B: Adjuvant radiation therapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Intermediate; Strength of recommendation: Strong[2]).
- Recommendation 2.2. Stage IIIA (N2): Adjuvant radiation therapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiotherapy for each patient with N2 disease (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: Intermediate[4]; Strength of recommendation: Moderate).

Referenzen zu den Empfehlungen
2. Pisters KM, Evans WK, Azzoli CG, et al: Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline. J Clin Oncol 25:5506-5518, 2007
3. Bradbury P, Sivajohanathan D, Chan A, et al: Postoperative adjuvant systemic therapy in completely resected non–small-cell lung cancer. Clin Lung Cancer [epub ahead of print on July 12, 2016]
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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2022) am 17.11.2022

#	Suchfrage
1	[mh “Carcinoma, Non-Small-Cell Lung”]
2	[mh ^"Lung Neoplasms"]
3	{OR #1-#2}
4	((((non NEXT small) OR nonsmall) NEXT cell NEXT lung) OR pulmon*):ti,ab,kw
5	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
6	#4 AND #5
7	nsclc*:ti,ab,kw
8	{OR #3, #6-#7}
9	#8 with Cochrane Library publication date from Nov 2017 to present

Systematic Reviews in PubMed am 17.11.2022

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[majr]
2	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw]

#	Suchfrage
	OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	((#5) AND ("2017/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 17.11.2022

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Carcinoma, Non-Small-Cell Lung"[mh]
2	Lung Neoplasms/therapy/drug therapy
3	Medical Oncology/methods/standards
4	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
5	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
6	lung[ti] AND #5
7	(#4 AND #5) OR #6
8	#1 OR #2 OR #3 OR #7

#	Suchfrage
9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
10	(((#9) AND ("2017/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.11.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- *Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)*
- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Cheng H, Li XJ, Wang XJ, Chen ZW, Wang RQ, Zhong HC, et al.** A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer. Lung Cancer 2019;137:7-13.

2. **Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al.** Management of stage III non-small-cell lung cancer: ASCO guideline. J Clin Oncol 2022;40(12):1356-1384.

3. **Kris MG, Gaspar LE, Chaft JE, Kennedy EB, Azzoli CG, Ellis PM, et al.** Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario clinical practice guideline update. J Clin Oncol 2017;35(25):2960-2974.

4. **Leitlinienprogramm Onkologie, (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).** Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Leitlinienreport 2.0 [online]. AWMF-Registernummer 020-007OL. Berlin (GER): Leitlinienprogramm Onkologie; 2022. [Zugriff: 18.11.2022]. URL: https://register.awmf.org/assets/guidelines/020-007OLm_S3_Praevention-Diagnostik-Therapie-Nachsorge-Lungenkarzinom_2022-11.pdf.

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6. **Li R, Yang G, Tian Y, Tian D.** Comparing the benefits of postoperative adjuvant chemotherapy vs. observation for stage IB non-small cell lung cancer: a meta-analysis. J Thorac Dis 2019;11(7):3047-3054.

7. **Lu D, Wang Z, Liu X, Feng S, Dong X, Shi X, et al.** Differential effects of adjuvant EGFR tyrosine kinase inhibitors in patients with different stages of non-small-cell lung cancer after radical resection: an updated meta-analysis. Cancer Manag Res 2019;11:2677-2690.

8. **National Institute for Health Care and Excellence (NICE).** Lung cancer: diagnosis and management [online]. 14.03.2023. London (GBR): NICE; 2019. [Zugriff: 14.03.2023]. (NICE guideline; Band 122). URL: https://www.nice.org.uk/guidance/ng122/resources/lung-cancer-diagnosis-and-management-pdf-66141655525573.

9. **Passiglia F, Bertolaccini L, Del Re M, Facchinetti F, Ferrara R, Franchina T, et al.** Diagnosis and treatment of early and locally advanced non-small-cell lung cancer: the 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines. Crit Rev Oncol Hematol 2020;148:102862.

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11. **Qian X, Guo X, Li T, Hu W, Zhang L, Wu C, et al.** Efficacy of immune checkpoint inhibitors in EGFR-mutant NSCLC patients with EGFR-TKI resistance: a systematic review and meta-analysis. Front Pharmacol 2022;13:926890.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-052

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) Bundesärztekammer, Dezernat 1 – Ärztliche Versorgung und Arzneimittel, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	17.04.2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
ist als Monotherapie zur adjuvanten Behandlung des nicht-kleinzelligen Lungenkarzinoms in den Tumorstadien IB (T2 ≥ 4cm), II oder IIIA nach vollständiger Resektion bei Erwachsenen angezeigt
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Eine adjuvante Monotherapie nach vollständiger Resektion ist als Anschlusstherapie nach adjuvanter, platinbasierter Chemotherapie zugelassen. Nach Ausschluss therapierbarer Treibermutationen (EGFR, ALK) ist seit Kurzem als Behandlungsstandard bei Patientinnen und Patienten mit Expression von PD-L1 auf > 50 % Tumorzellen eine Monotherapie mit dem Immuncheckpoint-Inhibitor (ICI) Atezolizumab über den Zeitraum von einem Jahr in Abständen von 21 Tagen etabliert. Dies gilt insbesondere für Patientinnen und Patienten im Stadium II. Im sehr heterogenen Stadium IIIA ist neben diesem Konzept je nach Subgruppe und individuellen Risikofaktoren alternativ ein multimodales Konzept unter Einschluss einer neoadjuvanten Chemotherapie nach Diskussion im Tumorboard zu erwägen. Für das Stadium IB nach aktuell gültiger TNM-Klassifikation (8. Version, IB = T2a, 3–4 cm) besteht keine Zulassung für die Immuntherapie. Kontraindikationen gegen die Immuntherapie sind in jedem Fall zu beachten.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Die Wirksamkeit der adjuvanten Anschlusstherapie mit ICI nach Resektion und adjuvanter Chemotherapie wurde im Vergleich zu Placebo in der Studie IMpower010 untersucht (1). Ein positiver Effekt von Atezolizumab auf das krankheitsfreie Überleben (DFS, *disease free survival*) wurde bei PD-L1-Expression > 1 % auf Tumorzellen nach median 32 Monaten gezeigt, dieser Effekt war in der Subgruppe mit PD-L1-Expression > 50 % am deutlichsten (Hazard Ratio [HR] 0,43; 95 % Konfidenzintervall [CI] 0,62–0,88). Eine signifikante Verbesserung des Gesamtüberlebens (OS) wurde inzwischen in der Subgruppe der Patientinnen und Patienten mit PD-L1-Expression > 50 % im Immuntherapie-Arm als Abstract publiziert mit einer HR von 0,45; 95 % CI 0,24–0,78 (2). Auf dieser Basis erfolgte die Zulassung von Atezolizumab bei Patientinnen und Patienten mit hoher PD-L1-Expression. Studien mit anderen ICI kamen hinsichtlich der Bedeutung der PD-L1-Expression in Interimsanalysen zu abweichenden Resultaten (3). In der nationalen Leitlinie wird gemäß Zulassung die adjuvante Therapie mit Atezolizumab in der angegebenen Indikation in den Stadien II und IIIA bei Patientinnen und Patienten mit PD-L1-Expression > 50 % auf Tumorzellen empfohlen (4). Als alternative Therapieoption sollte insbesondere im Stadium IIIA eine neoadjuvante Systemtherapie diskutiert werden. Für die Wahl des neoadjuvanten Ansatzes können die folgenden Faktoren sprechen: erhöhtes Risiko einer unvollständigen Resektion ohne systemische Vorbehandlung, Komorbiditäten sowie die in den meisten Studien höhere Compliance und Abschlussrate der Systemtherapie im Vergleich zur adjuvanten Therapie. Eine Phase-III-Studie zur Einbeziehung von ICI in die neoadjuvante Therapie des resektablen NSCLC vs. adjuvanter Chemotherapie wurde 2022 publiziert (5). Insgesamt sind als Kriterien zur Durchführung der adjuvanten Anschlusstherapie mit ICI derzeit also folgende Punkte zu nennen: 1. Nachweis einer hohen Expression von PD-L1 auf Tumorzellen (Voraussetzung gemäß Zulassung). 2. Einschätzung des individuellen Risikos für schwere UAW der Immuntherapie. 3. Abwägung der Vor- und Nachteile einer neoadjuvanten vs. adjuvanten Therapie insbesondere im Stadium IIIA.

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4. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms: https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/ (letzter Zugriff: 17. April 2023). AWMF-Register-Nummer: 020/007OL, Langversion 2.1, Dezember 2022.
5. Forde PM, Spicer J, Lu S et al.: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022; 386: 1973-1985.

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-052

Verfasser	
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP) Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (AIO) Pneumologisch-Onkologische Arbeitsgemeinschaft der DKG (POA)	
Datum der Erstellung	10. Mai 2023

Indikation
ist als Monotherapie zur adjuvanten Behandlung des nicht-kleinzelligen Lungenkarzinoms in den Tumorstadien IB (T2 ≥ 4cm), II oder IIIA nach vollständiger Resektion bei Erwachsenen angezeigt
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Zusammenfassung

Adjuvante systemische Therapie führt bei Patientinnen und Patienten (Pat.) mit nicht-kleinzelligem Lungenkarzinom (NSCLC) in den Stadien IB (T2 ≥4cm, TNM 7) – IIIA zur Senkung der Rezidivrate und kann zur Verlängerung der Gesamtüberlebenszeit führen. Die Indikation richtet sich nach dem Stadium und biologischen Faktoren. Standard sind:

- Adjuvante, Cisplatin-basierte Chemotherapie
- sequenziell bei PD-L1-Expression ≥50% und Ausschluss einer *EGFR*- oder *ALK*-Alteration: adjuvante, Cisplatin-basierte Chemotherapie, gefolgt von Atezolizumab über 1 Jahr
- sequenziell bei *EGFR* Mutation *del19* oder *L858R*: adjuvante, Cisplatin-basierte Chemotherapie, gefolgt von Osimertinib über 3 Jahre

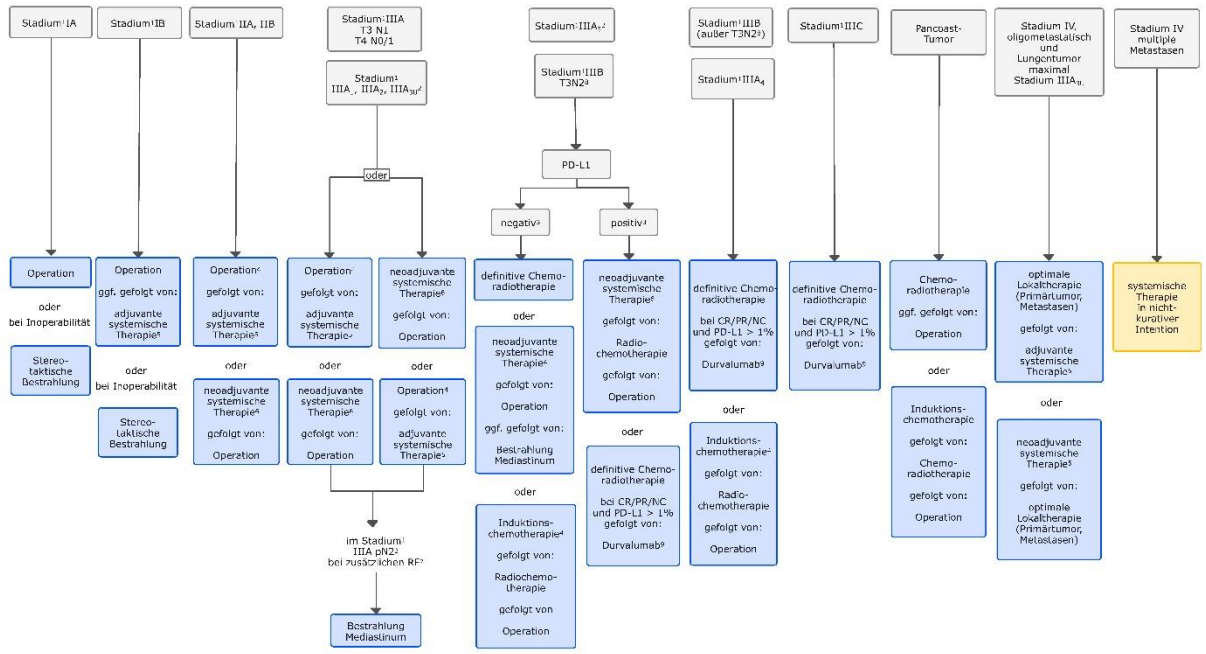
Bei der Indikationsstellung sollen Komorbidität und Therapieziele berücksichtigt werden.

Fragestellung

Stand des Wissens

Die Behandlung des NSCLC erfolgt stadienabhängig [1, 2], siehe Abbildung. Basis der ersten Therapieentscheidung ist die klinische Stadieneinteilung unter Berücksichtigung des Allgemeinzustandes, der lungenfunktionellen Reserve und Komorbiditäten. Nach einer Operation wird die weitere Therapie durch die Ergebnisse der pathologischen Untersuchungen und des Lymphknotenstatus bestimmt.

Abbildung: Therapiestruktur für das nicht-kleinzellige Lungenkarzinom (NSCLC)



[1] klinische Stadien;
[2] Die Festlegung der individuellen Therapie soll in einem interdisziplinären Tumorboard unter Beteiligung aller diagnostisch und therapeutisch tätigen Disziplinen erfolgen;
[3] negativ: PD-L1 <1%; positiv: PD-L1 ≥1%;
[4] Operation – Überbegriff für alle Formen der Tumorresektion bzw. -ablation;
[5] die adjuvante systemische Therapie nach Resektion umfasst
- *Platin-haltige Chemotherapie in den Stadien IIA – IIIA und*
- *bei EGFRmut (del 19, L858R) in den Stadien IB – IIIA: Osimertinib (zur Klassifikationsänderung von UICC 7. Edition bzw. nach UICC 8. Edition und*
- *bei PD-L1-Expression auf Tumorzellen ≥50% in den Stadien IIA – IIIA bei EGFR/ALK Wildtyp: Atezolizumab;*
- *oder eine Kombination aus diesen Optionen*

[6] Platin-haltige Kombinationschemotherapie + Nivolumab, für abweichende Zulassungen in den jeweiligen Ländern siehe Arzneimittel Zulassungsstatus.
[7] zusätzliche Risikofaktoren: multipler N2-Befall und Kapselüberschreitung;
[8] pT3 Kriterium aufgrund der Tumorgröße, Brustwandinfiltration oder einer Größe zwischen 5 -7 cm erfüllt;
[9] siehe die aktuell gültigen Zulassungsinformationen; Zulassung in der Schweiz unabhängig vom PD-L1-Status

Zahlreiche randomisierte Studien wurden in den vergangenen 35 Jahren zur Verbesserung der Überlebensraten nach chirurgischer Resektion durchgeführt. Einschlusskriterien, Zusammensetzung der Kollektive, Therapieprotokolle und Nachbeobachtungszeiten variieren. Aus den Ergebnissen der

einzelnen Studien, aus Metaanalysen und aus Subgruppenanalysen können folgende Schlussfolgerungen gezogen werden:

Indikation nach pathohistologischem Stadium

Es ist anzumerken, dass die Studien in der Regel nach TNM, Version 7 dargestellt werden. Seit 2017 ist allerdings die Stadieneinteilung nach TNM, Version 8 anzuwenden.

- Stadium IB (TNM, Version 7): Bei Pat. im Stadium IB (T2 ≥4cm) kann eine adjuvante Chemotherapie in Betracht gezogen werden. Die aus den Daten abgeleiteten Empfehlungen verschiedener Leitlinien sind nicht einheitlich [1-3]. Retrospektive Analysen deuten darauf hin, dass möglicherweise Pat. im Stadium IB (TNM, Version 7) mit zusätzlichen Risikofaktoren wie mikropapilläre oder solide Subtypisierung der Adenokarzinome, Pleurainfiltration, lymphatische (L1) oder vaskuläre (V1) Infiltration auch von einer adjuvanten Chemotherapie profitieren [4]. Diese zusätzlichen Parameter sind nicht prospektiv validiert. In diesem Zusammenhang ist besonders auf potenzielle Kontraindikationen und Komorbiditäten zu achten.
- Stadium II: Adjuvante, Cisplatin-basierte Chemotherapie führte zu einer signifikanten Steigerung der 5-Jahresüberlebensrate [5].
- Stadium IIIA: Das Stadium IIIA ist heterogen. In den Stadien IIIA T3 N1, T4 N0, T4 N1 sowie in den Stadien $IIIA_1$ und $IIIA_2$ entsprechen die Empfehlungen zur adjuvanten Therapie dem Stadium II.
- Der Vorteil einer adjuvanten Chemotherapie ist nicht auf bestimmte Altersgruppen beschränkt. Es liegen jedoch keine ausreichenden Daten für Pat. >75 Jahre vor.
- Die adjuvante Chemotherapie sollte 4 – 8 Wochen nach der Operation beginnen. Ein Vorteil ist nur belegt, wenn die Chemotherapie innerhalb von 60 Tagen nach der Operation begonnen wird.
- Die adjuvante Chemotherapie sollte aus einer Cisplatin-haltigen Kombination bestehen. Bei Kontraindikationen gegen Cisplatin kann auf eine Carboplatin-haltige Kombination ausgewichen werden, Daten hierzu liegen nur für das Stadium IB (UICC7) mit einer Studie vor.
- Die meisten Daten liegen für die Kombination von Cisplatin und Vinorelbin vor, gegeben über 3-4 Behandlungskurse. Abhängig von Komorbidität, Nebenwirkungen und Zulassungsstatus können andere Cisplatin-haltige Kombinationen gewählt werden, z. B. mit Docetaxel, Etoposid, Gemcitabin oder Pemetrexed.
- Eine adjuvante Bestrahlung ist nur indiziert nach inkompletter Resektion (R1, R2), wenn eine Nachresektion nicht möglich ist. In der postoperativen Situation nach R0 Resektion hat sie einen negativen Einfluss auf die Prognose und ist nicht indiziert [6]. Auch im Stadium IIIA N2 sollte eine adjuvante mediastinale Strahlentherapie nur in Einzelfällen (bulky N2, kapselüberschreitendes N2) erwogen werden.

Ergänzende Indikation nach PD-L1-Expression

- In der IMpower 010-Studie bei Pat. mit NSCLC in den Stadien IB-IIIA (TNM 7) nach adjuvanter Cisplatin-haltiger Chemotherapie führte eine anschließende Immuntherapie mit Atezolizumab über 16 Zyklen (1 Jahr) zu einer signifikanten Verlängerung des progressionsfreien Überlebens (HR 0,81). Die Unterschiede waren deutlicher bei Pat. in den höheren Erkrankungsstadien und zeigten einen Trend zur Verlängerung der Gesamtüberlebenszeit bei Expression von PD-L1. Die Zulassung beschränkt die Indikation auf Pat. mit einer PD-L1-Expression ≥50%, hohem Rezidivrisiko und Ausschluss einer *EGFR*- bzw. *ALK*-Alteration). Daten zum Einfluss von Atezolizumab auf die Gesamtüberlebenszeit sind noch unreif [7], zeigen jedoch in der Interim-Analyse einen statistisch hoch signifikanten Unterschied mit einer HR von 0,42.

Indikation nach *EGRF*-Mutation

- In der ADAURA-Studie führte die adjuvante Therapie mit Osimertinib über 3 Jahre bei Pat. mit einer *EGFR* common mutation (*del19, L858R*) in den Stadien IB, II und IIIA (UICC7) nach einer R0 Resektion gegenüber Placebo zur signifikanten Verlängerung des krankheitsfreien Überlebens (HR 0,17; p<0,001) und zur Reduktion des Risikos einer ZNS-Metastasierung um 90% [8]. 76% der Pat. hatten zusätzlich eine adjuvante Chemotherapie erhalten. Reife Daten zum Einfluss von adjuvantem Osimertinib auf die Gesamtüberlebenszeit liegen noch nicht vor, werden aber Anfang Juni 2023 auf dem ASCO Jahreskongress vorgestellt.

Grundsätzlich ist zu berücksichtigen, dass das Stadium IIIA sehr heterogen ist [1-3].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Ja, diese betreffen vor allem das Stadium und die Biologie des NSCLC, siehe oben.

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