Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-B-066 Durvalumab

Stand: Juli 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Durvalumab

als Monotherapie für die Behandlung des lokal fortgeschrittenen, nicht resezierbaren nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumor eine PD-L1-Expression ≥ 1% der Tumorzellen aufweist und deren Erkrankung nach Platin-basierter Radiochemotherapie nicht fortgeschritten ist

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 Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung: - für kleinzelliges Lungenkarzinom - für Erstlinientherapie beim lokal fortgeschrittenen NSCLC - für metastasiertes NSCLC
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht medikamentöse Behandlungen: - Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Nintedanib - Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35 a SGB V, Beschluss vom 18. Juni 2015 - Nivolumab und Crizotinib – derzeit im G-BA-Nutzenbewertungsverfahren - Carboplatin: Änderung der AM-RL in Anlage 9: Off-Label-Use vom 21. November 2006: Off-Label-Indikationserweiterung für Carboplatin zur Kombinationstherapie des NSCLC. - Protonentherapie bei der Indikation nicht-kleinzelliges Lungenkarzinom - Beschluss "Richtlinien Methoden Krankenhausbehandlung" , Beschluss vom 21. Oktober 2010
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:	
Durvalumab	Anwendungsgebiet laut Positive Opinion: (Anmerkung: inoffizielle Übersetzung) - Durvalumab ist indiziert als Monotherapie für die Behandlung des lokal fortgeschrittenen, nicht resezierbaren nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumor eine PD-L1-Expression ≥ 1% der Tumorzellen aufweist und deren Erkrankung nach Platin-basierter Radiochemotherapie nicht fortgeschritten ist.
Chemotherapeutika:	
Cisplatin L01XA01 Cisplatin-Lösung Ribosepharm 25 mg ®	- Zur Kombinationschemotherapie (auch in Verbindung mit Radiochemotherapie) beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom
Carboplatin L01XA02 Carboplatin gry ®	- Verordnungsfähigkeit für Off-Label-Indikation
Etoposid L01CB0 Etoposid 200 mg Hexal ®	- Palliative Therapie des fortgeschrittenen, nicht-kleinzelligen Bronchialkarzinoms bei Patienten in gutem Allgemeinzustand (Karnofsky-Index >80%)
Paclitaxel L01CD01 Aritaxel 6 mg / ml ®	- in Kombination mit Cisplatin ist für die Behandlung des nicht-kleinzelligen Bronchialkarzinoms (NSCLC) bei Patienten indiziert, für die potenziell kurative chirurgische Maßnahmen und/oder Strahlentherapie nicht angezeigt sind
Vinorelbin L01CA04 Navelbine 10 mg / 1 ml ®	- Zur Anwendung als Monotherapie oder in Kombination mit Cisplatin zur Behandlung des fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (Stadium III oder IV) bei Patienten mit gutem Allgemeinzustand
Vindesin L01CA03	- Kombinationschemotherapie: lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB oder IV).

II. Zugelassene Arzneimittel im Anwendungsgebiet

Eldisine ®	
EGFR-Blocker:	
Afatinib L01XE13 Giotrif 20 mg Filmtabletten®	- als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen
Gefitinib L01XE02 Iressa 250 mg Filmtabletten®	- angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK
Osimertinib L01XE35 Tagrisso ®	- ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) und einer positiven T790M-Mutation des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR)
Erlotinib L01XE03 Tarceva Filmtabeletten ®	- zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. - ist auch für eine Wechsel-Erhaltungstherapie (switch maintenance treatment) bei Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit aktivierenden EGFR-Mutationen und unverändertem Krankheitszustand nach First-Line-Chemotherapie angezeigt - zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Beim Verschreiben dieses Arzneimittels sollten Faktoren, die im Zusammenhang mit einer verlängerten Überlebenszeit stehen, berücksichtigt werden. Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere klinisch relevante Wirkungen durch die Behandlung gezeigt werden
Monoklonale Antikörper:	
Nivolumab L01XC17 Nivolumab BMS ®	- zur Behandlung des lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit plattenepithelialer Histologie nach vorheriger Chemotherapie bei Erwachsenen indiziert
Angiokinaseinhibitor:	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Nintedanib L01XE31 Vargatef Weichkapseln®	- Vargatef wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie
ALK-Rezeptor-Tyrosinkinasehemmer:	
Crizotinib L01XE16 Xalkori Hartkapseln ®	- XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (NSCLC) - XALKORI wird angewendet bei Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (NSCLC)
Folinsäureanaloga:	
Pemetrexed L01BA04 Alimta ®	- ALIMTA in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation nicht-kleinzelligen Lungenkarzinom (NSCLC) durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 03.06.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1157 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 7 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Behandlung von Patienten mit nicht-kleinzelligem Lungenkarzinom (NSCLC) Stadium III, das nach kombinierter Platin-basierter Radiochemotherapie in der Erstlinie nicht weiter fortgeschritten ist (Erhaltungstherapie).

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Weitere Hinweise:

- Publikationen, die „maintenance therapy“, „switch therapy“, continuation therapy“, “consolidation therapy” oder Behandlungen der “early second-line” untersucht haben, wurden generell berücksichtigt.
- Ausgeschlossen wurden jedoch Publikationen, in denen gänzlich unklar war, worin die Erstlinientherapie bestand.
- Weiterhin wurden Publikationen ausgeschlossen, in denen die Erstlinientherapie ausschließlich eine Platin-basierte Chemotherapie umfasste oder die Radiotherapie erst im Anschluss durchgeführt wurde.
- Publikationen zur Protonentherapie sind ebenso nicht berücksichtigt, da das Verfahren bis 31.12.2021 aufgrund bislang als nicht hinreichend belegtem Nutzen ist, ausgesetzt ist. (vgl. G-BA, Beschluss über eine Änderung der Richtlinie Methoden Krankenhausbehandlung: Protonentherapie beim inoperablen nicht - kleinzelligen Lungenkarzinom der UICC Stadien I bis III. 20.08.2015).

Abkürzungen:

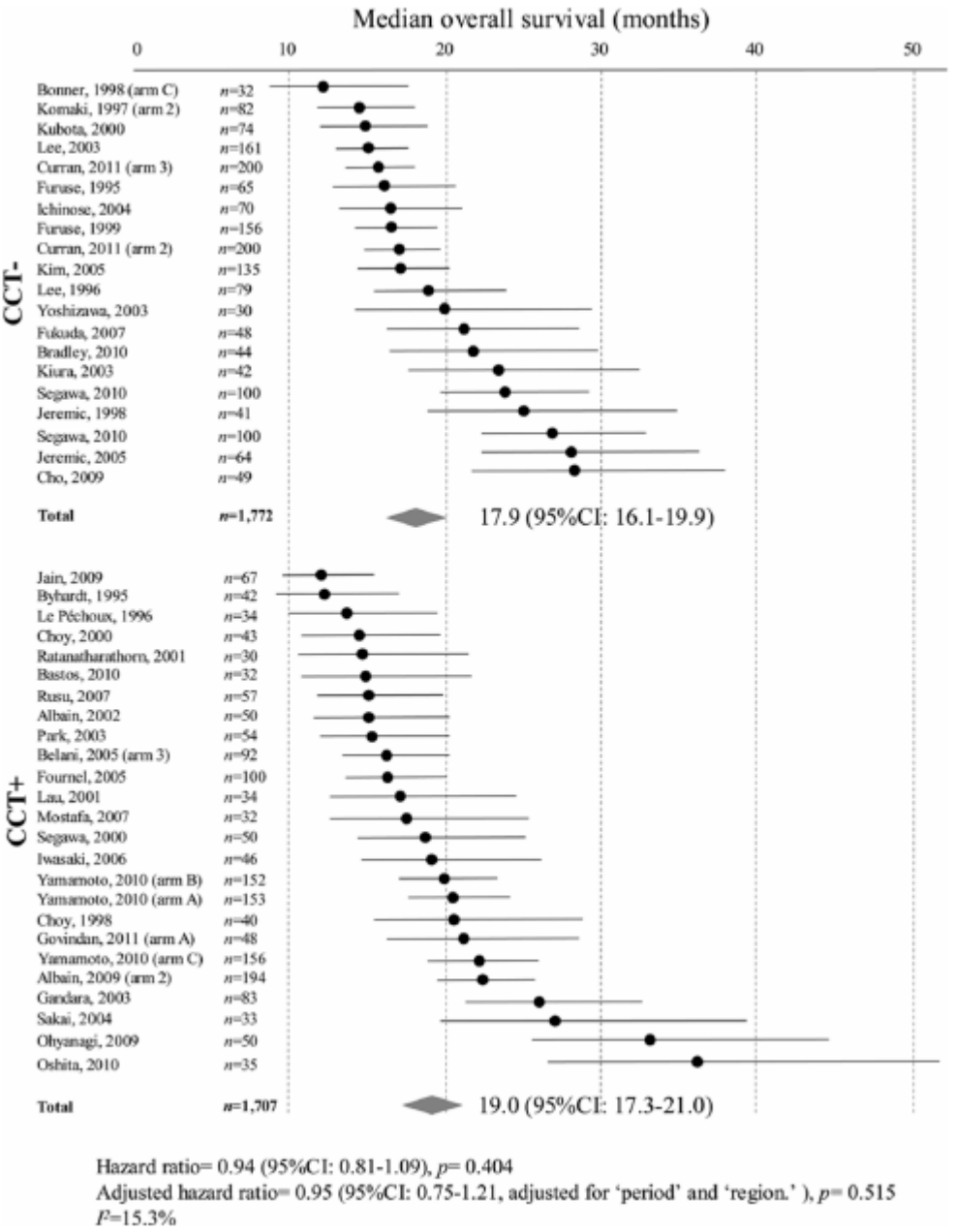
CCO	Cancer Care Ontario
CCT	concurrent chemo-radiotherapy
CCT+	consolidation chemo-radiotherapy
CCT-	no consolidation after concurrent chemo-radiotherapy
CCCT	continuous CCT
CF	Conventionally fractionated radiation therapy
EGFR TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
ESMO	European Society for Medical Oncology
HF	Hyperfractionated radiation therapy
HR	Hazard Ratio
ILD	Interstitial lung disease (Interstitielle Lungenerkrankung)
LA-NSCLC	locally advanced non-small cell lung cancer (lokal fortgeschrittenes nichtkleinzelliges Bronchialkarzionm)
NSCLC	non-small cell lung cancer (nichtkleinzelliges Bronchialkarzinom)
OS	Gesamtüberleben (Overall survival)
PFS	Progressionsfreies Überleben (progression free survival)
RR	Relatives Risiko
RT	radiotherapy
SCCT	switch CCT

Cochrane Reviews

Es konnten keine für die Indikation relevanten Cochrane Reviews identifiziert werden.

Systematische Reviews

Tsujino K et al., 2013 [6]. Is Consolidation Chemo-therapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer?	1. Fragestellung “The purpose of this study was to evaluate whether consolidation chemotherapy (CCT) after concurrent chemo-radiotherapy is beneficial for patients with locally advanced non–smallcell lung cancer (LA-NSCLC).”
	2. Methodik **Population:** Patients with stage III locally advanced non–small cell lung cancer disease (LA-NSCLC) treated with concurrent chemo-RT **Intervention:** consolidation chemotherapy after concurrent chemo-radiotherapy (CCT+) Hinweis: Arms, in which triweekly carboplatin plus paclitaxel were used after low-dose weekly carboplatin plus paclitaxel with concurrent thoracic radiotherapy (TRT), were included in CCT+ group in this analysis. CCT+ group was further divided into two patterns of CCT: continuous CCT (CCCT), which continues treatment with at least one of the agents given in the initial therapy and switch CCT (SCCT), which switches to a different agent. **Komparator:** concurrent chemo-radiotherapy (CCT-) **Endpunkte:** OS (median), toxicity **Suchzeitraum:** systematische Recherche bis Dezember 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** Insgesamt 41 davon 7 Phase III und 34 Phase II Studien (N=3479 Patienten). Weitere Studiencharakteristika s. Abbildungen 1 und 2 im Anhang. **Qualitätsbewertung der Studien:** keine systematische Bewertung **Heterogenitätsuntersuchung:** mittels I^2
	3. Ergebnisdarstellung Median OS „In random-effects models, pooled mOS was comparable between CCT+ (19.0 month; 95% CI, 17.3−21.0) and CCT− (17.9 month; 95% CI, 16.1−19.9), and predicted HR of CCT+ to CCT− was 0·94 (95% CI, 0.81−1.09; p = 0.40), suggesting that CCT did not significantly improve the mOS of LA-NSCLC patients.”



<u>Effect of study characteristics on median OS</u>

"CCT did not lead to significant survival benefit in any subgroups analyzed (period, region, trial phase, proportion of stage IIIA patients, use of third-generation drugs, or use of taxanes)."

<u>Toxicities</u>

"Toxicities throughout the treatment courses were comparable between CCT− and CCT+ arms. No significant differences were observed in neutropenia, leucopenia, esophagitis, pneumonitis, or treatment-related death."

4. Fazit der Autoren: […]

	• "The pooled analysis based on a publication basis failed to provide evidence that CCT yields significant survival benefit for LA-NSCLC." 5. Anmerkungen der Autoren: • "This study has several limitations. First, because of the nature of pooled analyses on a publication basis, our analyses included heterogeneous studies with different study designs and various patient populations. Although patient characteristics, trial phase, platinum regimens, study period, and region of the trials did not significantly differ between CCT+ and CCT−, and meta-regression analyses revealed similar results, we cannot exclude the possibility that some other differences might affect our conclusion." […]
Zhang C et al., 2015 [7]. Main-tenance or Conso-lidation Therapy for Non-Small-Cell Lung Cancer: A Meta-Analysis Involving 5841 Subjects	1. Fragestellung "To evaluate the significance of maintenance therapy, we performed a meta-analysis on randomized controlled trials (RCTs) with reference to maintenance or consolidation therapy for unresectable stage III/IV NSCLC."
	2. Methodik **Population:** "Patients at clinical stage III to IV, who achieve a non-progressive disease at the end of a defined number of induction chemotherapy cycles. **Intervention:** maintenance or consolidation therapy (siehe Ergebnisteil) **Komparator:** Placebo **Endpunkte:** OS, PFS, toxicity **Suchzeitraum:** Systematische Recherche bis August 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14 Studien (N=5841 Patienten) Studiencharakteristika s. Abbildung 3 im Anhang *Anmerkung FBMed: nur eine Studie mit Patienten mit Stadium III eingeschlossen, die eine parallele Radiochemotherapie in der Erstlinie* erhalten hatten → **Kelly et al. 2008** **Qualitätsbewertung der Studien:** mittels Jadad Score **Heterogenitätsuntersuchung:** mittels I^2
	3. Ergebnisdarstellung <u>OS</u> • "The total number of patients included in the meta-analysis was 5841, among whom 5752 were eligible for OS analysis. The results indicate that maintenance statistically therapy prolong OS (OR, 0.84; 95% CI,

	0.75-0.95; P= .005; I^2=42%)." • "The subgroup analysis revealed that overall OR was 0.80 (95% CI, 0.59-1.07; P = .13; I^2= 0%) for maintenance chemotherapy and 0.85 (95% CI, 0.75-0.97; P = .02; I^2=48%) for EGFR-TKI." • In der Studie von Kelly et al. zeigte sich kein statistisch signifikanter Effekt. (siehe auch: Abbildung 4 im Anhang) <u>PFS</u> • "Progression-free survival data were available in 12 trials with 4601 cases. A significant difference in PFS was found between the 2 arms (OR, 0.63; 95% CI, 0.54-0.73; P < .00001). Heterogeneity of effect among the 12 RCTs was significant (P < .00001, I^2 = 78%)." • "The results of our subgroup analysis for PFS show that OR was 0.43 (95% CI, 0.33-0.55; P < .00001; I^2=32%) in maintenance chemotherapy, and OR was 0.68 (95% CI, 0.56-0.83; P < .00001) in maintenance EGFR-TKI therapy. Heterogeneity of effect among the RCTs of EGFR-TKI therapy was significant (P = .0008; I^2 = 79%)." • In der Studie von Kelly et al. zeigte sich kein statistisch signifikanter Effekt. (siehe auch: Abbildung 5 im Anhang) <u>Toxicity</u> • "The main adverse effects of EGFR-TKI were rash and diarrhea." • In der Studie von Kelly et al. haben 2% der Patienten die Studienteilnahme aufgrund unerwünschter Ereignisse vorzeitig abgebrochen. Quelle: Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase iii trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage iii non-small-cell lung cancer: swog s0023. J Clin Oncol 2008;26:2450–6.
	4. Fazit der Autoren: […] • "The results of our meta-analysis suggest that maintenance therapy could prolong PFS and OS. We can conclude that maintenance therapy might be a beneficial strategy for advanced NSCLC patients who have benefited from the first-line treatment." • "Our subgroup analysis of maintenance therapy showed that EGFR-TKI can improve PFS and OS; chemotherapy improves PFS significantly without any OS benefit." 5. Anmerkungen der Autoren: • "Our meta-analysis has several limitations. First, significant heterogeneity existed among the valuable studies used to assess the effect of maintenance therapy on PFS, probably because of the existence of different combinations of platinum-based chemotherapy as

	first-line therapy, which led to different results (complete remission, partial remission, or stable disease) of the first-line treatment." [...]
Shi L et al., 2014 [5]. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials	1. Fragestellung "Performance of a meta-analysis to determine the risk of interstitial lung disease (ILD) events associated with gefitinib and erlotinib treatment."
	2. Methodik **Population:** Patients with advanced NSCLC **Intervention:** Behandlung mit Gefitinib oder Erlotinib; als Monotherapie oder in Kombination mit einer Chemotherapie **Komparator:** Placebo oder Chemotherapie **Endpunkt:** ILD events, fatal ILD events **Suchzeitraum:** systematische Suche bis Oktober 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 29; 17 Studien mit Gefitinib und 12 Studien mit Erlotinib (15,618, 9569 aus Studien mit Gefitinib und 6049 aus Studien mit Erlotinib) Studiencharakteristika siehe Abbildung 6 im Anhang *Anmerkung FB Med: nur eine Studie mit entsprechend vorbehandelten Patienten mit Stadium III NSCLC eingeschlossen →* ***Kelly et al. 2008*** **Qualitätsbewertung der Studien:** mittels Jadad score **Heterogenitätsuntersuchung:** mittels I^2
	3. Ergebnisdarstellung <u>Risk of ILD events</u> • All included randomized studies were available to calculate the RR of all-grade ILD events in patients assigned to gefitinib or erlotinib versus controls in the same trial. The overall RR of all-grade ILD events was 1.53 (95% CI, 1.13–2.08; P = 0.006; I^2=0%)." (siehe auch: Abbildung 7 im Anhang) • "When stratifying patients for their treatment line, we observed an RR of all-grade ILD events of 1.85 (95% CI, 1.13–3.00) for first-line patients and an RR of 1.36 (95% CI, 0.92–2.00) for non-first line patients. No significant difference was found between the groups stratified by treatment line." <u>Risk of fatal ILD events</u> • "Compared with controls, the relative risk of fatal ILD events associated

	with EGFR TKIs treatment was 1.96 (95% CI, 1.03–3.72, P = 0.041) using a fixed-effects model. Of note, among patients with EGFR TKIs-associated ILD events, the mortality of ILD events associated with EGFR TKIs was 22.8% (95% CI, 14.6–31.0%), whereas the mortality of ILD events associated with controls was 7.1% (95% CI, 0.0–14.9%)." Quelle: Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase iii trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage iii non-small-cell lung cancer: swog s0023. J Clin Oncol 2008;26:2450–6.
	4. Fazit der Autoren "Our study has shown that small-molecule EGFR TKIs gefitinib and erlotinib are associated with a significantly increased risk of developing both all-grade and fatal ILD events in advanced NSCLC." 5. Hinweise durch FB Med • Tumorklassifikation der eingeschlossenen Patienten unklar

Leitlinien

Ramnath N et al., 2013 [3]. **American College of Chest Physicians (ACCP)** Treatment of stage III non-small cell lung cancer: Diagnosis and	Zielsetzung "This review updates the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for stage III non-small cell lung cancer (NSCLC) patients."
	Methodik Grundlage der Leitlinie Update der Leitlinie von 2007, Repräsentatives Gremium, systematische Suche, Auswahl und Bewertung der Literatur, iterative Konsensusprozesse, externes Reviewboard, Erklärungen zu möglichen Interessenkonflikten liegen vor und wurden bei der Erstellung der Leitlinie berücksichtigt Suchzeitraum: Systematische Recherche bis Dezember 2011 LoE/GoR:

management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines

Table 1—*Strength of the Recommendations Grading System*

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

Sonstige methodische Hinweise

- Es wurden keine klinischen Fragestellungen formuliert
- Keine Patientenbeteiligung

Empfehlungen

2.3.2. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended ***(Grade 1A)*** .

Remark: Dose escalation of radiotherapy is not recommended (except in a clinical trial).

Remark: For patients with stage III NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended.

Quellen:

37. Liu HH , Wang X , Dong L , et al. Feasibility of sparing lung and other thoracic structures with intensity-modulated radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004 ;58(4):1268-1279.

38. Murshed H , Liu HH , Liao Z , et al. Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer [published correction in Int J Radiat Oncol Biol Phys . 2004;59(3):921]. Int J Radiat Oncol Biol Phys. 2004 ;58(4):1258-1267.

2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential

	*chemoradiotherapy **(Grade 1A)** .* *Remark: We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred to clinical trials to answer this question.* "The value of consolidation chemotherapy is unclear at this time. Initial phase 2 studies involving either docetaxel or cisplatin and etoposide consolidation after definitive chemoradiation were encouraging. [42] With regard to consolidation therapy, initial phase 2 data from the Southwestern Oncology Group (SWOG) were promising for docetaxel consolidation after definitive chemoradiation. SWOG enrolled 50 patients with stage IIIA NSCLC who received cisplatin and etoposide with concurrent radiotherapy (61 Gy) followed by two additional cycles of cisplatin and etoposide. [42] The 5-year survival of 15% was encouraging and led to the SWOG 9504 phase 2 trial of 83 patients receiving concurrent chemotherapy and radiotherapy, but the follow-up consolidation was accomplished by docetaxel. [43,44] The follow-up phase 3 study was stopped early because of increased toxicity in the consolidation docetaxel arm, with no difference in median overall survival found between the two arms. [45] The overall 5-year survival rate was 29% with docetaxel consolidation, which was much improved over the 15% rate with cisplatin and etoposide consolidation in the prior study. These encouraging results prompted the two ongoing phase 3 randomized trials: SWOG 0023, which has accrued 500 patients, and the Hoosier Oncology Group LUN 01-24, which is currently enrolling. These trials feature different designs intended to uncover, to varying degrees of confidence, the role of consolidation chemotherapy after definitive concurrent chemoradiation." Quellen: 42 . Albain KS , Crowley JJ , Turrisi AT III , et al . Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019 . J Clin Oncol . 2002 ; 20 (16): 3454 - 3460 . 43 . Gandara DR, Chansky K, Albain KS, et al; Southwest Oncology Group . Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504 . J Clin Oncol . 2003 ; 21 (10): 2004 - 2010 . 44 . Lara P, Chanski K, Gaspar L, Albain K, Crowley J, Gandara D. Consolidation doxetaxel following concurrent chemoradiotherapy in stage IIIB non-small cell lung cancer (NSCLC): updated fi ve-year survival results from Southwest Oncology Group trial S9504 [Abstract PD-075]. Lung Cancer . 2005 ; 49(supp 2):S89. 45 . Hanna N , Neubauer M , Yiannoutsos C , et al ; Hoosier Oncology Group ; US Oncology . Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology . J Clin Oncol . 2008 ; 26 (35): 5755 - 5760 .
Rodrigues G et al., 2015	Fragestellungen • KQ2: What is the ideal external beam dose fractionation for the curative-

[4]. **American Society for Radiation Oncology (ASTRO)** Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline	intent treatment of locally advanced non-small cell lung cancer with chemotherapy? • KQ3: What is the ideal timing of external beam radiation therapy in relation to systemic chemotherapy for the curative-intent treatment of locally advanced non-small cell lung cancer?
	Methodik Grundlage der Leitlinie: Repräsentatives Gremium, Formulierung klinischer Fragestellungen, systematische Suche, Auswahl und Bewertung der Literatur, formalisierte Konsensusprozesse mittels Delphi-Verfahren, externes Reviewboard und öffentliche Stellungnahmen, Erklärungen zu möglichen Interessenkonflikten liegen vor Suchzeitraum: Systematische Recherche (?) bis März 2013 LoE/GoR: <u>American College of Physicians (ACP) Process for Assigning Strength of Recommendation and Grading of Quality of Evidence</u> *Strong Recommendation* Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus. *Weak Recommendation* Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus. *High Quality Evidence (HQE)* Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect. *Moderate-Quality Evidence (MQE)* Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case– control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate.

	Low-Quality Evidence (LQE) Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose–response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.
	Empfehlungen <u>KQ2:</u> *B. Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be associated with any clinical benefits, including OS* ***(MQE, recommendation rated as "strong")****.* "Based on various phase 1/2 investigations, RTOG 0617 was a 2 × 2 factorial RCT with 2 objectives: (1) to determine if chemoradiation using 74 Gy led to superior OS compared with 60 Gy and (2) to determine if the addition of postradiation therapy cetuximab improved OS. This trial demonstrated that 74 Gy is not superior to standard 60 Gy of radiation therapy and was associated with worse OS. [21] The median survival times and 18-month OS rates are 28.7 months and 66.9% versus 19.5 months and 53.9%, for the 60-Gy and 74-Gy arms, respectively (P = .0007, 1-sided). Additionally, there was an increased rate of severe esophagitis on the 74-Gy arm. The addition of cetuximab had no effect on OS compared with chemoradiation alone. Prospective evidence related to intermediate doses between the RTOG 0617 treatment arms of 60 Gy to 74 Gy is currently of paramount importance to help define clinical benefits and risks of the delivery of such treatment." Quelle: 21. Bradley J, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617. J Clin Oncol. 2013:31. [abstract 7501]. *C. Hyperfractionated radiation therapy (HF) regimens that do not result in acceleration of the treatment course, even though the total nominal radiation therapy dose may be modestly increased, do not appear to improve outcomes compared with conventionally fractionated therapy (CF)* ***(MQE, recommendation rated as "strong")****.* "RTOG 9204 was a phase 2 RCT of standard dose (with CF, 63 Gy in 7 weeks) versus HF (69.6 Gy BID over 6 weeks, 1.2-Gy fractions) with concurrent chemotherapy for LA NSCLC.[22] The HF arm had a longer time

	to in-field progression (30% vs 49% at 4 years) with similar OS rates. In a follow-up RCT, RTOG 9410 used concurrent chemotherapy and HF to 69.6 Gy versus sequential and concurrent with once-daily radiation therapy.11 The survival rates in the HF arm were found to be inferior to the concurrent chemoradiation arm. Acute grade 3-5 nonhematologic toxicity was greater in the HF arm." Quelle: 22. Komaki R, Seiferheld W, Ettinger D, Lee JS, Movsas B, Sause W. Randomized phase II chemotherapy and radiotherapy trial for patients with locally advanced inoperable non-small-cell lung cancer: Long-term follow-up of RTOG 92-04. Int J Radiat Oncol Biol Phys. 2002;53:548-557. <u>KQ3:</u> *C. There are no phase 3 data specifically supporting the role for consolidation chemotherapy after chemoradiation therapy for the improvement of overall survival; however, this treatment is still routinely given to manage potential micrometastatic disease particularly if full systemic chemotherapy doses were not delivered during radiation therapy* ***(low quality of evidence, recommendation rated as "strong")****.* "Consolidation therapy following concurrent chemoradiation is routinely used in clinical practice to optimize the treatment of micrometastatic disease particularly when only 2 cycles of chemotherapy are used concurrently with radiation. When weekly radiosensitizing low-dose carboplatin and paclitaxel are administered concurrently with thoracic radiation therapy, consolidation therapy with full systemic doses is often given to address concern for systemic disease. Several studies have demonstrated improved survival outcomes for this approach. [27,28]." Quellen: 27. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: A randomized phase II locally advanced multi-modality protocol. J Clin Oncol. 2005;23:5883-5891. 28. Colin P, Jovenin N, Ganem G, et al. Effect of paclitaxel-carboplatin (PC) consolidation chemotherapy after weekly PC concurrent chemo-radiotherapy (CCR) for patients with locally advanced non-small cell lung cancer (LA NSCLC): 3-year definitive results of the B001-phase III GERCOR-study. J Clin Oncol. 2006:24. [abstract 7112].
Eberhardt WE et al., 2015 [1]. European Society for Medical Oncology (ESMO)	Fragestellungen • What is the optimal chemotherapy to be given to stage III disease patients? • What is the optimal radiation regimen given to stage III NSCLC patients? • Is there a place for targeted agents in the treatment of stage III NSCLC?
	Methodik Grundlage der Leitlinie:

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer	Konsensuskonferenz zur Ergänzung bestehender Leitlinien hinsichtlich spezifischer Fragestellungen; Repräsentatives Gremium; Formulierung klinisch relevanter Fragestellungen; systematische Auswahl und Bewertung der Literatur, informelle Konsensusprozesse; Erklärungen zu Interessenkonflikten liegen vor Suchzeitraum: unklar; jüngste Studie aus August 2014 LoE/GoR: **Table 1.** Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a]) Levels of evidence I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity III Prospective cohort studies IV Retrospective cohort studies or case–control studies V Studies without control group, case reports, experts opinions Grades of recommendation A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional D Moderate evidence against efficacy or for adverse outcome, generally not recommended E Strong evidence against efficacy or for adverse outcome, never recommended [a]By permission of the Infectious Diseases Society of America [1]. „Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty." Sonstige methodische Hinweise: • Systematik der Suche sowie der durchsuchten Datenbanken unklar • Charakteristika der eingeschlossenen Studien nicht dargestellt
	Empfehlungen <u>Number of chemotherapy cycles</u> *Recommendation 5.3.1: In the stage III disease chemoradiotherapy strategy, two to four cycles of concomitant chemotherapy should be delivered **[I, A]**. There is no evidence for further induction or consolidation*

chemotherapy.

„There is no evidence for extended induction or consolidation beyond these three to four cycles [99, 100]."

Quellen:

99. Hanna N, Neubauer M, Yiannoutsos C et al. Phase III study of cisplatin etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008; 26: 5755–5760.

100. Vokes EE, Herndon JE, II, Kelley MJ et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25: 1698–1704.

<u>Dose and fractionation in concurrent chemoradiotherapy</u>

*Recommendation 6.1.1: 60–66 Gy in 30–33 daily fractions is recommended for concurrent chemoradiotherapy **[I, A]**. Maximum overall treatment time should not exceed seven weeks **[III, B].** 'Biological intensification', such as treatment acceleration, is not standard practice in concurrent chemoradiotherapy schedules **[III, B].***

"The majority of clinical concurrent chemoradiotherapy regimens in stage III NSCLC have used 60–66 Gy cumulative radiotherapy doses in conventional daily fractions of 1.8–2.0 Gy [24, 84–86]. A detailed look at the relationship of overall treatment duration and outcome in these studies has confirmed that prolonged treatment time is a critical issue in this setting, as it is in other tumour types [92]."

Quellen:

92. Mauguen A, Le Péchoux C, Saunders MI et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol 2012; 30: 2788–2797.

<u>Targeted Agents</u>

Recommendation 9: There is currently no role for targeted agents in stage III NSCLC outside clinical trials [I, A].

"The large randomised SWOG trial in North America demonstrated an inferior OS in a patient group receiving an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (gefitinib) as consolidation therapy compared with placebo after chemoradiotherapy and consolidation docetaxel [107]. The reasons for this detrimental effect are still to be explored, looking at potential specific toxicities following chemoradiotherapy and/or docetaxel or underlying tumour-related adaptive biological mechanisms. […] Outside well-designed and closely monitored clinical trials in target-based selected populations, there is currently no role for targeted agents in stage III NSCLC."

107. Kelly K, Chansky K, Gaspar LE et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung

	cancer: SWOG S0023. J Clin Oncol 2008; 26: 2450–2456. *Anmerkung FB MED: Basierend auf gleicher Studie, die auch in den systematischen Reviews von Zhang und Shi eingeschlossen wurde* → ***Kelly et al. 2008***
PDQ® Adult Treatment Editorial Board, 2016 [2]. Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version	Zielsetzung This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of non-small cell lung cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions. Methodik Grundlage der Leitlinie Unabhängiges Gremium, monatliches Update relevanter Literatur, informelle Konsensusprozesse zur Bewertung der Literatur Suchzeitraum: letztes Update Mai 2016 LoE: <u>Strength of Study Design</u> The various types of study design are described below in descending order of strength: 1. Randomized, controlled, clinical trials (i) Double-blinded. (ii) Nonblinded treatment delivery. 2. Nonrandomized, controlled, clinical trials 3. Case series (i) Population-based, consecutive series. (ii) Consecutive cases (not population-based). (iii) Nonconsecutive cases <u>Strength of Endpoints</u> Commonly measured endpoints for adult and pediatric cancer treatment studies are listed below in descending order of strength: A. Total mortality (or overall survival from a defined time). B. Cause-specific mortality (or cause-specific mortality from a defined time). C. Carefully assessed quality of life D. Indirect surrogates. (i) Event-free survival (ii) Disease-free survival (iii) Progression-free survival

	(iv) Tumor response rate Sonstige methodische Hinweise: • Systematik der Suche sowie der durchsuchten Datenbanken unklar • keine Formulierung und Bewertung von Empfehlungen • Charakteristika der eingeschlossenen Studien nicht dargestellt
	Empfehlungen <u>Radiation therapy dose escalation for concurrent chemoradiation</u> "With improvement in radiation therapy–delivery technology in the 1990s, including tumor-motion management and image guidance, phase I/II trials demonstrated the feasibility of dose-escalation radiation therapy to 74 Gy with concurrent chemotherapy.[40-42] However, a phase III trial of a conventional dose of 60 Gy versus dose escalation to 74 Gy with concurrent weekly carboplatin/paclitaxel did not demonstrate improved local control or PFS, and OS was worse with dose escalation (HR, 1.38 [1.09–1.76]; P = .004). There was a nonsignificant increase in grade 5 events with dose escalation (10% vs. 2%) and higher incidence of grade 3 esophagitis (21% vs. 7%; P =.0003). Thus, there is no clear benefit in radiation dose escalation beyond 60 Gy for stage III NSCLC.[43]" **[Level of evidence: 1iiA]** Quellen: 40. Rosenman JG, Halle JS, Socinski MA, et al.: High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. Int J Radiat Oncol Biol Phys 54 (2): 348-56, 2002. 41. Socinski MA, Blackstock AW, Bogart JA, et al.: Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol 26 (15): 2457-63, 2008. 42. Bradley JD, Bae K, Graham MV, et al.: Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. J Clin Oncol 28 (14): 2475-80, 2010. 43. Bradley JD, Paulus R, Komaki R, et al.: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 16 (2): 187-99, 2015. <u>Additional systemic therapy before or after concurrent chemotherapy and radiation therapy</u> "The role of consolidation systemic therapy after concurrent chemotherapy and radiation therapy for unresectable NSCLC remains unclear. Randomized trials of consolidation systemic therapy including docetaxel,[45] gefitinib,[46] and tecemotide (MUC1 antigen-specific immunotherapy) [47]

	have not shown an improvement in OS." **[Level of evidence: 1iiA]** Quellen: 45. Hanna N, Neubauer M, Yiannoutsos C, et al.: Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 26 (35): 5755-60, 2008. 46. Kelly K, Chansky K, Gaspar LE, et al.: Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 26 (15): 2450-6, 2008. 47. Butts C, Socinski MA, Mitchell PL, et al.: Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 15 (1): 59-68, 2014. *Anmerkung FB MED: gleiche Studie, die auch in den Systematic reviews von Zhang und Shi eingeschlossen wurde →* ***Kelly et al. 2008***

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 02.06.2016**

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
2	MeSH descriptor: [Maintenance Chemotherapy] explode all trees
3	maintenance:ti,ab,kw
4	((non next small) or nonsmall) next cell next lung:ti,ab,kw
5	tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw
6	#4 and #5
7	#1 or #6 or (nsclc*:ti,ab,kw)
8	#7 and #2
9	#7 and #3
10	#8 or #9
11	#11 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 02.06.2016

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MesH]
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]
3	((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]
4	#2 AND #3
5	#1 OR #4
6	Maintenance Chemotherapy[MesH]
7	#5 AND #6
16	maintenanc*[Title/Abstract] OR maintain*[Title/Abstract]
17	#5 AND #16
18	#7 OR #17
19	#18 AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
20	(#19) AND ("2011/06/01"[PDAT] : "2016/06/02"[PDAT])
21	(((((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]) OR radiotherapy*[Title/Abstract]) OR chemotherap[Title/Abstract]
22	#5 AND #21
23	#22 AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR

	Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
24	(#23) AND ("2011/06/01"[PDAT] : "2016/06/02"[PDAT])

Leitlinien in Medline (PubMed) am 02.06.2016

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MesH]
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]
3	((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]
4	#2 AND #3
5	#1 OR #4
29	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
30	(#29) AND ("2011/06/01"[PDAT] : "2016/06/02"[PDAT])

Anhang:

Supplemental Table 1. Trials included in the analysis.

Trial	Phase	Region		Chemotherapy regimen		Dose of Radiation	No. of Patients
				Concurrent Phase	Consolidation Phase		
Curran WJ Jr et al, 2011 [4]	III	USA	arm 2	CDDP/Vinblastine	–	60	200
			arm 3	CDDP/Etoposide	–	69.6	200
Govindan R et al, 2011 [15]	II	USA	arm A	CBDCA/PEM	CBDCA/PEM	70	48
Oshita F et al, 2010 [16]	II	Japan		Nedaplatin/CPT-11	Nedaplatin/CPT-11	60	35
Yamamoto N et al, 2010 [17]	III	Japan	arm A	CDDP/VDS/MMC	CDDP/VDS/MMC	60	153
			arm B	CBDCA/CPT-11	CBDCA/CPT-11	60	152
			arm C	CBDCA/PTX	CBDCA/PTX	60	156
Segawa Y et al, 2010 [18]	III	Japan	DP arm	CDDP/DTX	–	60	100
			MVP arm	CDDP/VDS/MMC	–	60	100
Bradley JD et al, 2010 [19]	II	USA		CBDCA/PTX	–	74	44
Bastos BR et al, 2010 [20]	II	USA		CBDCA/CPT-11	DTX	63	32
Albain KS et al, 2009 [21]	III	USA	arm 2	CDDP/Etoposide	CDDP/Etoposide	61	194
Ohyanagi F et al, 2009 [22]	II	Japan		CDDP/S-1	CDDP/S-1	60	50
Jain AK et al, 2009 [23]	II	USA		CBDCA/DTX	CBDCA/DTX	63	67
Cho KH et al, 2009 [24]	II	Korea		CBDCA/PTX	–	60	49
Mostafa E et al, 2007 [25]	II	Egypt		CDDP/Etoposide	DTX	66	32
Fukuda M et al, 2007 [26]	II	Japan		CDDP/CPT-11	–	60	48
Rusu P et al, 2007 [27]	II	Romania		CDDP or CBDCA/VNR	CDDP or CBDCA/VNR	56-60	57
Iwasaki Y et al, 2006 [28]	II	Japan		CDDP/DTX	CDDP/DTX	60	46
Fournel P et al, 2005 [29]	III	France	Concurrent arm	CDDP/Etoposide	CDDP/VNR	66	100
Belani CP et al, 2005 [30]	II	USA	arm 3	CBDCA/PTX	CBDCA/PTX	63	92
Kim YS et al, 2005 [31]	II	Korea		CDDP/PTX	–	70.2	135
Jeremic B et al, 2005 [32]	II	Serbia		CBDCA/PTX	–	64	64
Ichinose Y et al, 2004 [33]	II	Japan		CDDP/ uracil+tegafur	–	60	70
Sakai H et al, 2004 [34]	II	Japan		CBDCA/DTX	CBDCA/DTX	60	33
Park J et al, 2003 [35]	II	Korea		CDDP/Etoposide	CDDP/Etoposide	63	54
Yoshizawa H et al, 2003 [36]	II	Japan		CBDCA/fluorouracil	–	60	30
Kiura K et al, 2003 [37]	II	Japan		CDDP/DTX	–	60	42
Lee SW et al, 2003 [38]	II	Korea		CDDP/Vinblastine	–	64.8-70	161
Gandara DR et al, 2003 [39]	II	USA		CDDP/Etoposide	DTX	61	83
Albain KS et al, 2002 [40]	II	USA		CDDP/Etoposide	CDDP/Etoposide	61	50
Lau D et al, 2001 [41]	II	USA		CBDCA/PTX	CBDCA/PTX	61	34
Ratanatharathorn V et al, 2001 [42]	II	Thailand		CBDCA/PTX	CBDCA/PTX	60	30
Kubota K et al, 2000 [43]	II	Japan		CDDP/VDS	–	50-60	74
Choy H et al, 2000 [44]	II	USA		CBDCA/PTX	CBDCA/PTX	69.6	43
Segawa Y et al, 2000 [45]	II	Japan		CDDP/fluorouracil	CDDP/fluorouracil	62.5-70	50
Furuse K et al, 1999 [2]	III	Japan	Concurrent arm	CDDP/VDS/MMC	–	56	156
Jeremic B et al, 1998 [46]	II	Yugoslavia		CBDCA/Etoposide	–	69.6	41
Choy H et al, 1998 [47]	II	USA		CBDCA/PTX	CBDCA/PTX	66	40
Bonner JA et al, 1998 [48]	III	USA	arm C	CDDP/Etoposide	–	60	32
Komaki R et al, 1997 [49]	II	USA	arm 2	CDDP/Etoposide	–	69.6	82
Le Péchoux C et al, 1996 [50]	II	France		CDDP/VDS	CDDP/VDS	60	34
Lee JS et al, 1996 [51]	II	USA		CDDP/Etoposide	–	69.6	79
Byhardt RW et al, 1995 [52]	II	USA		CDDP/Vinblastine	CDDP	69.6	42
Furuse K et al, 1995 [53]	II	Japan		CDDP/VDS/MMC	–	52	65

Abbreviation: CDDP, cisplatin; CBDCA, carboplatin; PEM, pemetrexed; CPT-11, irinotecan; VDS, vindesine; MMC, mitomicinC; PTX, paclitaxel; DTX, docetaxel; VNR, vinorelbine.

Abbildung 1: aus Tsujino et al. 2013 (eingeschlossene Studien)

TABLE 1. Differences of Patient Characteristics and Treatment Administrations between Study Arms with and without CCT

	Arms without CCT		Arms with CCT		
Patients Characteristics	**Mean**	**SD**	**Mean**	**SD**	***p*[a]**
Age					
Median age	61.71	2.72	60.58	3.24	0.22
Sex					
Female, %	21.96	12.54	23.79	12.92	0.63
Histology					
Squamous cell carcinoma, %	47.56	9.94	43.67	12.20	0.26
Adenocarcinoma, %	35.60	8.85	36.02	12.51	0.90
Stage					
IIIA, %	35.68	19.21	33.19	18.35	0.67
IIIB, %	63.27	19.29	66.31	18.61	0.52
PS, %[b]					
0	46.43	25.72	42.89	19.94	0.65
1	50.38	21.70	52.92	16.01	0.70
2	4.28	6.97	4.36	11.48	0.98
Treatment Administrations					
Concurrent phase					
Planned TRT dose (Gy)	62.85	5.99	62.70	3.50	0.96
Patients who completed TRT (%)	85.65	10.89	89.18	7.66	0.29
Patients who completed chemotherapies (%)	86.15	13.03	79.16	14.47	0.14
Consolidation phase					
No. of planned CCT cycles	—	—	2.32	0.90	—
Median no. of delivered CCT cycles	—	—	1.88	0.90	—
Mean no. of delivered CCT cycles	—	—	1.53	0.64	—

[a]Statistical differences were calculated using Student's *t* test across trial arms.
[b]KPS was converted to Eastern Cooperative Oncology Group PS as follows: KPS 90–100; PS 0, KPS 70–80; PS 1, KPS 60–70; PS 2.
TRT, thoracic radiotherapy; CCT, consolidation chemotherapy; PS, performance status; SD, standard deviation; KPS, Karnofsky performance score.

Abbildung 2: aus Tsujino et al. 2013 (Studiencharakteristika)

Table 1 Characteristics of RCTs Included in the Meta-Analysis

First Author	Induction Therapy	Maintenance Therapy	Patient n	Follow-Up Time, Months	PFS, Months[a]	OS, Months[a]
Butts[9]	Chemotherapy with or without RT	L-BLP25 with BSC versus BSC	88 and 83	26	NR	17.4 and 13; $P = .112$
Westeel[10]	MIC	Vinorelbine versus observation	91 and 90	10.4 and 11.9	5 and 3; $P = .32$	12.3 and 12.3; $P = .48$
Herbst[11]	Chemotherapy with or without EGFR-TKI	Erlotinib versus placebo	539 and 540	NR	5.1 and 4.9; $P = .36$	10.6 and 10.5; $P = .95$
Gatzemeier[12]	Chemotherapy with or without EGFR-TKI	Erlotinib versus placebo	580 and 579	NR	23.7 weeks and 24.6 weeks; $P = .74$	43 weeks and 44.1 weeks; $P = .49$
Kelly[13]	EP × 2 with RT and Docetaxel × 3	Gefitinib versus placebo	118 and 125	23 and 35	8.3 and 11.7; $P = .17$	23 and 35; $P = .013$
Hanna[14]	EP × 2 with RT	Docetaxel versus observation	73 and 74	41.6	NR and NR; $P = .960$	21.2 and 23.2; $P = .883$
Johnson[15]	Chemotherapy	CAI versus placebo	94 and 92	29.6 and 28.3	2.8 and 2.4; $P = .50$	11.4 and 10.5; $P = .54$
Ciuleanu[16]	Platinum-based chemotherapy × 4	Pemetrexed with BSC versus placebo with BSC	441 and 222	41.5 and 37.8	4.3 and 2.6; $P = .0001$	13.4 and 10.6; $P = .012$
Cappuzzo[17]	Platinum-based chemotherapy	Erlotinib versus placebo	438 and 451	11.4 and 11.5	12.3 weeks and 11.1 weeks; $P < .0001$	12.0 and 11.0; $P = .0088$
Gaafar[18]	Platinum-based chemotherapy × 4	Gefitinib versus placebo	86 and 87	41	4.1 and 2.9; $P = .0015$	10.9 and 9.4; $P = .2$
Paz-Ares[19,23,b]	Pemetrexed with cisplatin × 4	Pemetrexed with BSC versus placebo with BSC	359 and 180	23	4.1 and 2.8; $P < .0001$	13.9 and 11.0; $P = .0195$
Zhang[20]	Platinum-based chemotherapy × 4	Gefitinib versus placebo	148 and 148	19	4.8 and 2.6; $P < .0001$	18.7 and 16.9; $P = .26$
Mubarak[21]	Pemetrexed with cisplatin × 4	Pemetrexed with BSC versus BSC	28 and 27	NR	3.2 and 3.2; $P = .1815$	12.2 and 11.8; P, NR
Shi[22]	Platinum-based chemotherapy × 4	DC/CIK versus control	30 and 30	NR	3.20 and 2.56; $P < .05$	NR

Abbreviations: BSC = best supportive care; CAI = carboxyaminoimidazole; DC/CIK = dendritic cell/cytokine-induced killer cells; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; EP = etoposide with cisplatin; L-BLP25 = BLP25 liposome vaccine; MIC = mitomycin with ifosfamide and cisplatin; OS = overall survival; PFS = progression-free survival; RT = radiotherapy.
[a]Data are in months except where otherwise noted.
[b]PFS was extracted from Paz-Ares et al[19] and OS from Paz-Ares et al[23]

Abbildung 3: aus Zhang et al. 2015 (Studiencharakteristika)

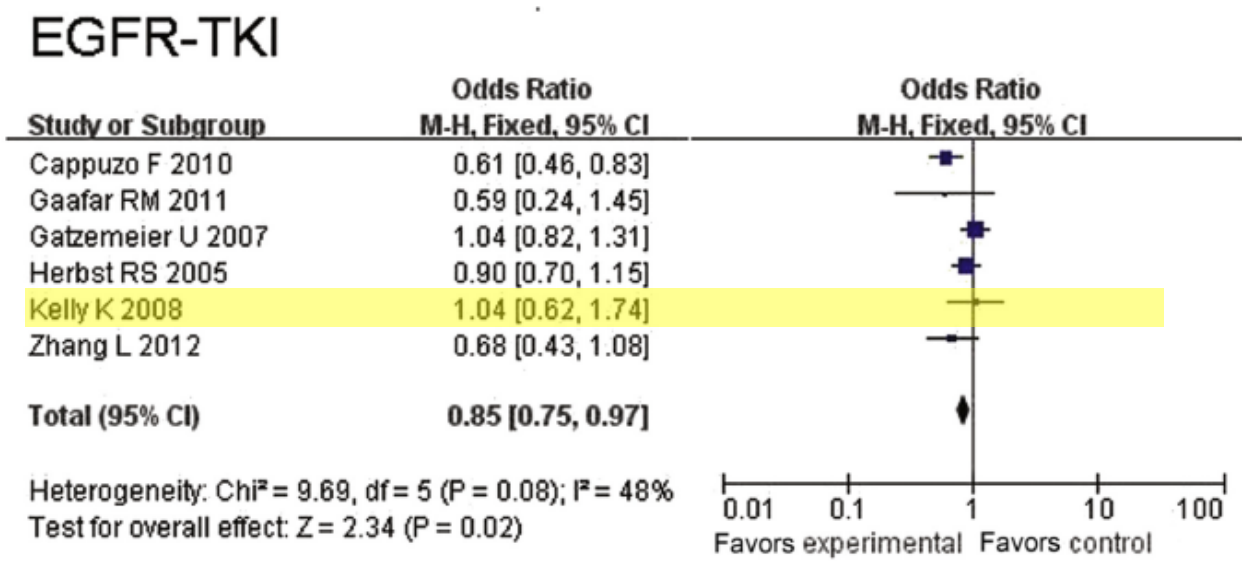


Abbildung 4: aus Zhang et al. 2015 (OS)

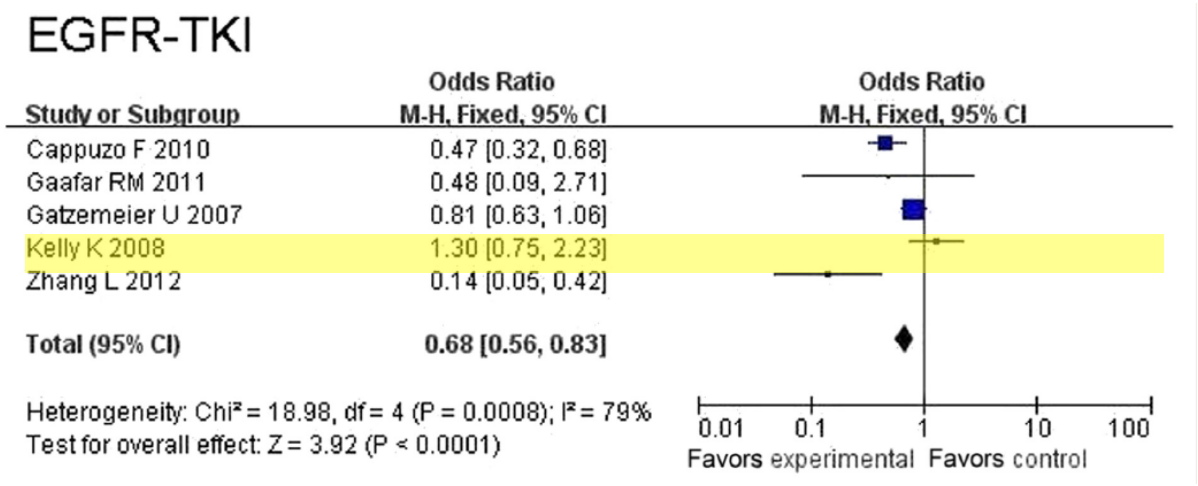


Abbildung 5: aus Zhang et al. 2015 (PFS)

Table 1
Characteristics of the trials included in the final analysis.

Author [reference]	Study location	Study phase	Treatment line	Treatment arms	No. for analysis	Median age (years)	Median treatment duration (months)	No. of ILD events	Death events	Reported events	Jadad score
Gefitinib											
Han et al. [20]	Korea	3	First	Gefitinib 250 mg/day	159	57	5.4	2	2	ILD	3
				Gemcitabine + cisplatin	150	56.5	6 cycles	0	0		
Zhang et al. [21]	China	3	Maintenance	Gefitinib 250 mg/day	147	55	4.9	2	1	ILD	5
				Placebo	148	55	2.4	0	0		
Sun et al. [22]	Korea	3	Second	Gefitinib 250 mg/day	68	58	NR	1	0	Interstitial	3
				Pemetrexed	67	64	NR	0	0	Pneumonitis	
Maemondo et al. [23]	Japan	3	First	Gefitinib 250 mg/day	114	63.9*	10.3	6	1	ILD	3
				Paclitaxel + carboplatin	113	62.6*	4 cycles	0	0		
Mitsudomi et al. [24]	Japan	3	First	Gefitinib 250 mg/day	87	64	5.5	2	1	ILD	3
				Docetaxel + cisplatin	88	64	2.1	0	0		
Takeda et al. [25]	Japan	3	Maintenance	Gefitinib 250 mg/day after chemotherapy	300	62	2.3	4	0	ILD	3
				Platinum-doublet chemotherapy	298	63	3 cycles	2	0		
Lee et al. [26]	Korea	3	Second	Gefitinib 250 mg/day	81	57	NR	3	2	ILD-type	3
				Docetaxel	76	58	NR	3	0		
Mok et al. [35]	Asian	3	First	Gefitinib 250 mg/day	607	57	5.6	16	3	ILD	3
				Paclitaxel + carboplatin	589	57	4.1	8	1		
Goss et al. [28]	Global	2	First	Gefitinib 250 mg/day	100	74	1.7	0	0	ILD-type	5
				Placebo	101	76	1.5	1	0		
Kim et al. [29]	Global	3	Second or Third	Gefitinib 250 mg/day	729	61	4.4	10	NR	ILD	3
				Docetaxel	715	60	3.0	8	NR		
Maruyama et al. [30]	Japan	3	Second or third	Gefitinib 250 mg/day	244	NR	2.0	14	3	ILD	3
				Docetaxel	239	NR	3 cycles	7	0		
Crino et al. [31]	Global	2	First	Gefitinib 250 mg/day	94	74	NR	2	0	ILD-type	3
				Vinorelbine	96	74	NR	0	0		
Kelly et al. [32]	United States Canada	3	Maintenance	Gefitinib 250 mg/day after chemoradiotherapy	107	62	NR	3	0	Interstitial pneumonitis	3
				Placebo after chemoradiotherapy	125	61	NR	0	0		
Cufer et al. [33]	Global	2	Second	Gefitinib 250 mg/day	68	63	3.0	0	0	ILD-type	3
				Docetaxel	71	59.5	2.8	2	0		
Thatcher et al. [34]	Global	3	Second or Third	Gefitinib 250 mg/day	1126	62	2.9	11	NR	ILD	5
				Placebo	562	61	2.7	6	NR		
Herbst et al. [15]	United States	3	First	Gefitinib 250 mg/day plus paclitaxel + carboplatin	342	61	4.3	7	0	ILD-type	5
				Gefitinib 500 mg/day plus	342	62	3.3	5	0		

Abbildung 6: aus Shi et al. 2013 (Studiencharakteristika, Ausschnitt)

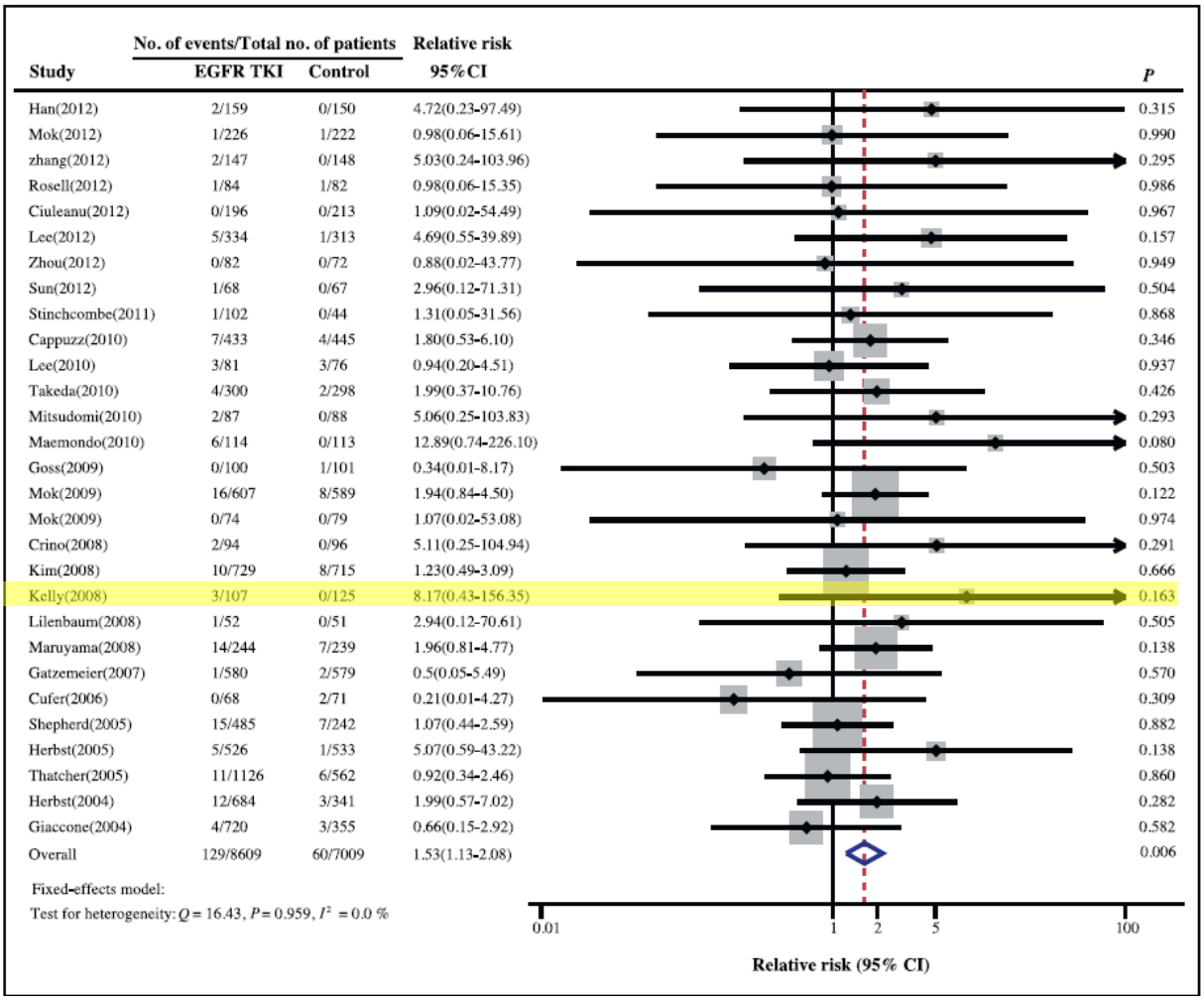


Abbildung 7: aus Shi et al. 2013 (Risk of Interstitial lung disease)

Literatur

1. **Eberhardt WE, De Ruysscher D, Weder W, Le Pechoux C, De Leyn P, Hoffmann H, et al.** 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol 2015;26(8):1573-1588.
2. **PDQ® Adult Treatment Editorial Board.** Non-Small Cell Lung Cancer Treatment (PDQ) [online]. Updated: 05.2016. Bethesda (USA): National Cancer Institute (NCI),; 2016. [Zugriff: 30.05.2016]. URL: http://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#section/all.
3. **Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, et al.** Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e314S-e340S.
4. **Rodrigues G, Choy H, Bradley J, Rosenzweig KE, Bogart J, Curran WJ, Jr., et al.** Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. Pract Radiat Oncol 2015;5(3):141-148.
5. **Shi L, Tang J, Tong L, Liu Z.** Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials. Lung Cancer 2014;83(2):231-239.
6. **Tsujino K, Kurata T, Yamamoto S, Kawaguchi T, Kubo A, Isa S, et al.** Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. J Thorac Oncol 2013;8(9):1181-1189.
7. **Zhang C, Huang C, Wang J, Wang X, Li K.** Maintenance or Consolidation Therapy for Non--Small-Cell Lung Cancer: A Meta-Analysis Involving 5841 Subjects. Clin Lung Cancer 2015;16(5):e15-23.