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: 2025-B-072-z Pembrolizumab

Stand: April 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab [in Kombination mit Pemetrexed mit Platin-Chemotherapie zur Erstlinienbehandlung des malignen Pleuramesothelioms] 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.	Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Nivolumab: Beschluss vom 16.12.2021
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	Pembrolizumab in Kombination mit Pemetrexed und Platin-Chemotherapie ist für die Erstlinientherapie bei Erwachsenen mit einem nicht-resezierbaren, nicht-epitheloiden malignen Pleuramesotheliom angezeigt.
Ipilimumab L01XC11 Yervoy	Malignes Pleuramesotheliom (MPM) Yervoy ist in Kombination mit Nivolumab für die Erstlinientherapie des nicht-resezierbaren malignen Pleuramesothelioms bei Erwachsenen indiziert.
Nivolumab L01XC17 Opdivo	Malignes Pleuramesotheliom (MPM) Opdivo ist in Kombination mit Ipilimumab für die Erstlinientherapie des nicht-resezierbaren malignen Pleuramesothelioms bei Erwachsenen indiziert.
Pemetrexed L01LA04 generisch	Malignes Pleuramesotheliom Pemetrexed in Kombination mit Cisplatin ist angezeigt zur Behandlung von chemonaiven Patienten mit inoperablem malignem Pleuramesotheliom.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-072-z (Beratung nach § 35a SGB V) Pembrolizumab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. April 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CP	Cisplatin plus Pemetrexed
CPP	Cisplatin and Pemetrexed plus Pembrolizumab
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MPM	Malignant pleural mesothelioma
MSI	microsatellite instability
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progressionsfreies Überleben
PM	Pleural Mesothelioma
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TMB	Tumor Mutational Burden
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erstlinientherapie des nicht resezierbaren, nicht epitheloiden malignen Pleuramesothelioms.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind 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 Pleuramesotheliom 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.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 18.03.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 512 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. 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, wurde insgesamt 1 Referenz eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine relevanten CR identifiziert werden.

3.2 Systematische Reviews

Es konnten keine relevanten systematischen Reviews identifiziert werden.

3.3 Leitlinien

Kindler HL et al., 2025 [1].

American Society of Clinical Oncology

Treatment of Pleural Mesothelioma: ASCO Guideline Update

Zielsetzung/Fragestellung

This guideline update focuses on four key areas: the role of surgery, new systemic treatments, pathologic insights, and germline testing.

Methodik

Grundlage der Leitlinie

Update der Leitlinie aus dem Jahr 2018

- Repräsentatives Gremium: multidisziplinäres Expertengremium + Patientenvertretung
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu

Recherche/Suchzeitraum:

- Systematic review of PubMed (January 2016-June 2024)

LoE

- Cochrane risk of bias

GoR

- GRADE

Sonstige methodische Hinweise

Hinweis: Die Empfehlungen 4.13 bis 4.16 bestanden bereits in der originalen Leitlinie von 2018. Alle weiteren Empfehlungen sind neu mit dem Update von 2025 hinzugekommen.

How do clinicians integrate immunotherapy into the treatment paradigm?

3.1. In patients with newly diagnosed pleural mesothelioma, ipilimumab plus nivolumab immunotherapy should be offered as a first-line systemic treatment option. (Evidence quality: High; Strength of recommendation: Strong)

On the basis of the results of the CheckMate 743 trial, this regimen became only the second regimen approved by the US Food and Drug Administration (FDA) for PM.[28] This global open-label phase III study randomly assigned 605 patients with previously untreated, unresectable PM to either 2 years of immunotherapy with nivolumab plus ipilimumab or six cycles of chemotherapy with pemetrexed plus either cisplatin or carboplatin. The primary end point was OS.

At a median follow-up of 29.7 months, nivolumab plus ipilimumab significantly improved median OS compared with chemotherapy (18.1 months v 14.1 months; HR, 0.74; P 5 .0020). The 2-year OS rates were also superior for immunotherapy (41% v 27%). OS was improved with nivolumab plus ipilimumab versus chemotherapy across histologic subtypes. Patient-reported outcome data assessed using EuroQol 5-dimensional (EQ-5D) and Lung Cancer Symptom Scale- Mesothelioma (LCSS-Meso) measures further support the use of immunotherapy over chemotherapy in patients with previously untreated

mesothelioma. In the CheckMate 743 trial, treatment with nivolumab plus ipilimumab delayed the time to definitive deterioration in health-related quality of life, HR 0.52, and showed a trend in symptom delay when compared with chemotherapy.[27]

27. Scherpereel A, Antonia S, Bautista Y, et al: First-line nivolumab plus ipilimumab versus chemotherapy for the treatment of unresectable malignant pleural mesothelioma: Patient-reported outcomes in CheckMate 743. Lung Cancer 167:8-16, 2022
28. Baas P, Scherpereel A, Nowak AK, et al: First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): A multicentre, randomised, open-label, phase 3 trial. Lancet 397:375-386, 2021

3.2. In patients with newly diagnosed nonepithelioid mesothelioma, ipilimumab plus nivolumab immunotherapy should be offered as the recommended first-line treatment. (Evidence quality: High; Strength of recommendation: Strong)

As discussed in the 2018 guideline, and in the Pathology section of the current update, the three principal histologic subtypes of mesothelioma, epithelioid, biphasic, and sarcomatoid, have prognostic significance. The results of the CheckMate 743 trial demonstrate that histologic subtype also has treatment implications regarding the choice of systemic therapy. While CheckMate 743 demonstrated an OS benefit across histology favoring ipilimumab plus nivolumab versus platinum pemetrexed, the findings by histologic subtype were striking. Patients with epithelioid tumors had a median survival of 18.7 months when treated with ipilimumab plus nivolumab and 16.5 months (HR, 0.86) when treated with chemotherapy. Patients with nonepithelioid (sarcomatoid or biphasic) tumors had a median survival of 18.1 months when treated with ipilimumab plus nivolumab versus 8.8 months when treated with chemotherapy (HR, 0.46).[28]

Thus, for patients with previously untreated nonepithelioid mesothelioma, first-line ipilimumab nivolumab is recommended as the preferred treatment option for patients without contraindications to immunotherapy, because of the marked improvement in OS with immunotherapy observed in the CheckMate 743 trial.

28. Baas P, Scherpereel A, Nowak AK, et al: First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): A multicentre, randomised, open-label, phase 3 trial. Lancet 397:375-386, 2021

3.4. In patients with newly diagnosed pleural mesothelioma (epithelioid or nonepithelioid), chemoimmunotherapy with pembrolizumab and pemetrexed plus platinum-based chemotherapy may be offered as a first-line systemic treatment option. (Evidence quality: High; Strength of recommendation: Strong)

Three multicenter, single-arm phase II trials have assessed chemoimmunotherapy in patients with treatment-naive mesothelioma.[34,43,44] The US phase II PrE0505 trial evaluated the combination of platinum-pemetrexed with the anti– PD-L1 antibody durvalumab in 55 patients with previously untreated PM. Patients received four to six cycles of chemotherapy plus durvalumab, followed by durvalumab maintenance for up to 1 year of total treatment or until disease progression. The primary end point of OS was met, achieving a median OS of 20.1 months. The ORR was 56.4%. All adverse events because of immunotherapy were grade 2 or less. There was no correlation between tumor PD-L1 expression and treatment outcome. In an exploratory analysis, a significant difference in response rate, PFS, and OS by histology was observed, favoring the epithelioid subtype.[34] The Australian phase II DREAM trial evaluated the same regimen in 55 patients. The study met its primary end point, PFS at 6 months, with 57% of patients progression-free at 6 months.[44] The phase II Japanese JME-001 trial assessed the combination of pemetrexed plus cisplatin plus nivolumab for four to six cycles, followed by nivolumab maintenance until disease progression in 18 patients. The primary end point, ORR, was met, with an ORR of 77.8%. The median OS was 20.8 months, and the 6-month PFS was 69%.[43]

In the phase II Canadian Cancer Trials Group IND.227 trial, 60 patients with previously untreated PM were stratified by histology and randomly assigned 1:1:1 to cisplatin plus pemetrexed (CP), cisplatin and pemetrexed plus pembrolizumab (CPP), or pembrolizumab (P) alone. The primary end point was PFS. Accrual to the single-agent arm was halted after it failed to meet the 16-week disease control rate specified by the interim analysis. PFS was similar between arms (6.7, 6.8, and 5.26 months, for CP, CPP, and P, respectively, P 5 .29). Grade 3 or higher toxicity was greater in the chemotherapy-containing arms. ORRs

(19%, 47%, and 13% for CP, CPP, and P, respectively) and median OS (8.9, 19.8, and 17.5 months for CP, CPP, and P, respectively) favored the chemoimmunotherapy arm.[26]

This study was subsequently amended to become a phase III, open-label international trial in 440 patients. Patients were randomly assigned to receive pemetrexed plus cisplatin or carboplatin for up to six cycles, with or without pembrolizumab given for up to 2 years. The primary end point was OS. The addition of pembrolizumab to pemetrexed + platinum chemotherapy resulted in an improvement in median OS when compared with chemotherapy alone (17.3 v 16.1 months; HR, 0.79; two-sided P 5 .0324). This was observed in patients with both epithelioid (19.8 v 18.2 months; HR, 0.89) and nonepithelioid histology (12.3 v 8.2 months; HR, 0.57). The 3-year OS rate was also superior for chemoimmunotherapy (25% v 17%), as well as among patients with both epithelioid (26% v 20%) and nonepithelioid histologic subtypes (23% v 7%). Although there was no difference in median PFS between arms (7.13 v 7.16 months), the HR for progression or death favored the chemoimmunotherapy arm (HR, 0.80, stratified log rank P 5 .0372). The triplet regimen also yielded a much higher ORR (62% v 38%; odds ratio, 2.70; P < .0001). Grade 3 or higher treatment-related toxicity were more frequent in the combination arm (27% v 15%, respectively).[33]

In September 2024, the FDA approved the regimen of pembrolizumab with pemetrexed plus platinum-based chemotherapy as a first-line treatment option for patients with unresectable advanced or metastatic PM. The openlabel, randomized phase III ETOP BEAT-meso trial similarly compared pemetrexed, carboplatin, and bevacizumab with or without the addition of atezolizumab in 400 patients with previously untreated PM. Although there was a significant improvement in PFS and response duration in the experimental arm, this did not translate into a statistically significant improvement in the primary end point of OS. Patients with nonepithelioid histology in the experimental arm also experienced an improvement in PFS and OS. Further details should become available on publication of this trial.[121]

26. Piccirillo MC, Chu Q, Bradbury P, et al: Brief report: Canadian Cancer Trials Group IND.227: A phase 2 randomized study of pembrolizumab in patients with advanced malignant pleural mesothelioma (NCT02784171). J Thorac Oncol 18:813-819, 2023
33. Chu Q, Perrone F, Greillier L, et al: Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: A phase 3, open-label, randomised controlled trial. Lancet 402:2295-2306, 2023
34. Forde PM, Anagnostou V, Sun Z, et al: Durvalumab with platinum-pemetrexed for unresectable pleural mesothelioma: Survival, genomic and immunologic analyses from the phase 2 PrE0505 trial. Nat Med 27:1910-1920, 2021
43. Miyamoto Y, Kozuki T, Aoe K, et al: JME-001 phase II trial of first-line combination chemotherapy with cisplatin, pemetrexed, and nivolumab for unresectable malignant pleural mesothelioma. J Immunother Cancer 9:e003288, 2021
44. Nowak AK, Lesterhuis WJ, Kok PS, et al: Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): A multicentre, single-arm, phase 2 trial with a safety run-in. Lancet Oncol 21:1213-1223, 2020
121. Popat S, Felip E, Dafni U, et al: BEAT-meso: A randomized phase III study of bevacizumab (B) and standard chemotherapy (C) with or without atezolizumab (A), as first-line treatment (TX) for advanced pleural mesothelioma (PM)—Results from the ETOP 13-18 trial. J Clin Oncol 42, 2024 (suppl 17; abstr LBA8002)

3.5. PD-L1, TMB, or MSI should not be used to determine choice of chemotherapy or immunotherapy in patients with pleural mesothelioma. (Evidence quality: Moderate; Strength of recommendation: Conditional)

In contrast to many other tumor types, the impact of tumor PD-L1 status on prognosis and response to anti–PD-1 immunotherapy in mesothelioma is unclear. A systematic review of clinical trials in mesothelioma reported that PD-L1–positive tumors might have a poorer prognosis when treated with nonimmunotherapy treatments.[117] In the CheckMate 743 trial, PD-L1 status was not a stratification variable. The magnitude of benefit from immunotherapy (versus chemotherapy) was greater in those patients with tumor PD-L1 expression of 1% or higher (HR, 0.69) compared with patients whose tumor expression was <1% (HR, 0.94). Median OS, however, was similar among patients treated with ipilimumab plus nivolumab regardless of the tumor PD-L1 expression level.[28]

PD-L1 expression also does not appear to predict clinical benefit from the combination of immunotherapy and chemotherapy. In the PrE0505 and DREAM trials (both examining the use of platinum pemetrexed plus durvalumab), PD-L1 expression did not appear to predict benefit from immunotherapy.[34,44] Similarly,

in the phase III IND227 trial (platinum pemetrexed with or without pembrolizumab), there was also no indication that PD-L1 expression was predictive of benefit from immunotherapy.[33]

Mesothelioma usually has a very low mutational burden, and the prognostic or predictive value of tumor mutational burden (TMB) in mesothelioma is yet to be shown. In the PrE0505 study, while overall TMB was not predictive of benefit from chemotherapy plus durvalumab, there was a suggestion that persistent mutation burden (higher numbers of mutations that led to neoantigens less likely to be recognized and eliminated by the host immune system) may predict benefit from immunotherapy; however, this finding requires further validation.[34,118] Anti–PD-(L)1 immunotherapy has demonstrated efficacy in tumors with high levels of microsatellite instability (MSI); however, few (eg, 4 of 233, 1.7%) patients with mesothelioma have been included in prospective studies.[119] Conversely, large retrospective analyses have reported that MSI is very rare in mesothelioma.[120]

Thus, at present, there is insufficient evidence to support the use of PD-L1 status or TMB in the selection of patients with mesothelioma for treatment with immunotherapy. In the rare situation of mesothelioma with MSI, such patients should be considered for treatment with immunotherapy in the absence of any contraindication.

28. Baas P, Scherpereel A, Nowak AK, et al: First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): A multicentre, randomised, open-label, phase 3 trial. Lancet 397:375-386, 2021
33. Chu Q, Perrone F, Greillier L, et al: Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: A phase 3, open-label, randomised controlled trial. Lancet 402:2295-2306, 2023
34. Forde PM, Anagnostou V, Sun Z, et al: Durvalumab with platinum-pemetrexed for unresectable pleural mesothelioma: Survival, genomic and immunologic analyses from the phase 2 PrE0505 trial. Nat Med 27:1910-1920, 2021
117. Mansfield AS, Brown RJ, Sammon C, et al: The predictive and prognostic nature of programmed death-ligand 1 in malignant pleural mesothelioma: A systematic literature review. JTO Clin Res Rep 3:100315, 2022
118. Niknafs N, Balan A, Cherry C, et al: Persistent mutation burden drives sustained anti-tumor immune responses. Nat Med 29:440-449, 2023
119. Marabelle A, Le DT, Ascierto PA, et al: Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol 38:1-10, 2020
120. Arulananda S, Thapa B, Walkiewicz M, et al: Mismatch repair protein defects and microsatellite instability in malignant pleural mesothelioma. J Thorac Oncol 13:1588-1594, 2018

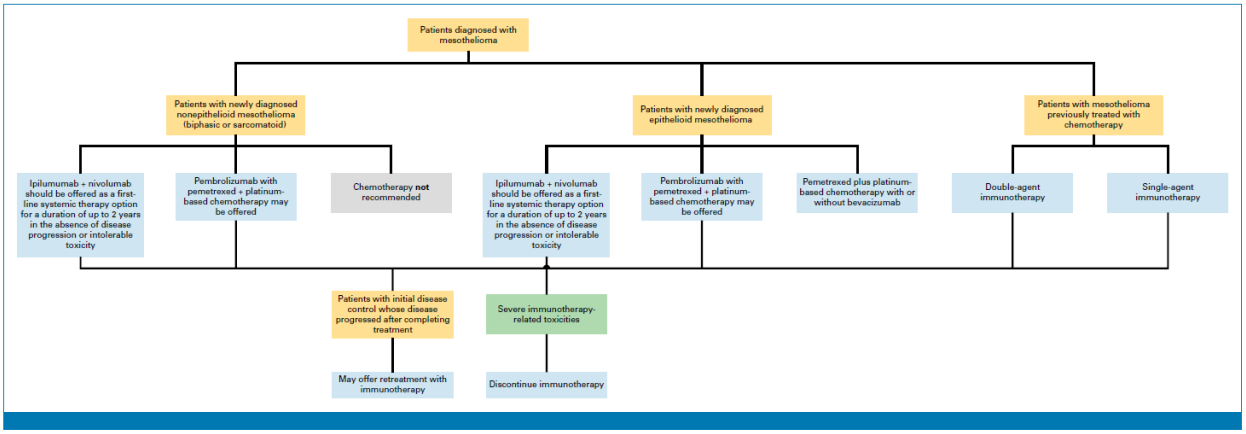

FIG 4. Integration of immunotherapy in treatment paradigm.

How do clinicians integrate chemotherapy into the treatment paradigm?

4.2. In patients with nonepithelioid histology who have not received any prior systemic therapy, chemotherapy should not be offered unless there are medical contraindications to immunotherapy. (Evidence quality: High; Strength of recommendation: Strong)

4.3. In patients with newly diagnosed pleural mesothelioma (epithelioid or nonepithelioid), chemoimmunotherapy with pembrolizumab and pemetrexed plus platinum-based chemotherapy may be offered as a first-line systemic treatment option. (Evidence quality: High; Strength of recommendation: Strong)

4.4. In patients with nonepithelioid histology who have not received any prior systemic therapy and are not candidates for immunotherapy, the addition of pegargiminase to pemetrexed plus platinum chemotherapy may be offered as a treatment option. (Evidence quality: Moderate; Strength of recommendation: Conditional)

Pemetrexed+cisplatin chemotherapy improves OS (HR, 0.77; P 5 .20), compared with single-agent cisplatin in patients with PM who have not received previous systemic therapy.[57] The addition of bevacizumab to pemetrexed + cisplatin further improves OS (HR, 0.77 [95% CI, 0.62 to 0.95]; P 5 .0167).[58] The CheckMate 743 trial demonstrated that ipilimumab + nivolumab immunotherapy increased OS compared with pemetrexed + platinum chemotherapy, but with a differential effect by histology.[28] The magnitude of the OS benefit was greater for patients with nonepithelioid mesothelioma (epithelioid: HR, 0.86 [95% CI, 0.69 to 1.08]; nonepithelioid HR, 0.46 [95% CI, 0.31 to 0.68]). This benefit was driven by the poor outcome from chemotherapy in nonepithelioid mesothelioma, with a median OS of 8.8 months for patients with nonepithelioid histology who received chemotherapy compared with 16.5 months for patients with epithelioid histology.

On the basis of these data, in patients with epithelioid histology, pemetrexed + platinum-based chemotherapy with or without bevacizumab may be offered as a first-line systemic treatment option. In patients with nonepithelioid histology who have not received any previous systemic therapy, chemotherapy should not be offered unless there are medical contraindications to immunotherapy. In patients with nonepithelioid histology who have not received any previous systemic therapy and are not candidates for immunotherapy, the addition of pegargiminase to pemetrexed + platinum chemotherapy may be offered as a treatment option. This is based on the rationale that tumors that have loss of arginosuccinate synthetase 1 (ASS1) are dependent on arginine for survival and may be sensitive to strategies that result in amino acid deprivation. In preclinical models, pegargiminase, which degrades arginine into ammonia and citrulline, is cytotoxic in ASS1-deficient cancers such as mesothelioma. Pegargiminase is thought to sensitize mesothelioma to pemetrexed by suppressing de novo synthesis and salvage of thymidine.[53]

In the phase II/III ATOMIC-Meso trial, 249 patients with previously untreated nonepithelioid PM were randomly assigned to receive four to six cycles of pemetrexed and cisplatin or carboplatin, given with intramuscular pegylated arginine deiminase (ADI-PEG20, pegargiminase) or placebo, followed by maintenance pegargiminase or placebo for up to 2 years until progression. The primary end point was OS.[53] When compared with chemotherapy plus placebo, the addition of pegargiminase to pemetrexed + platinum led to an improvement in median OS (7.7 v 9.3 months; HR for death, 0.71; P 5 .02) and PFS (5.6 v 6.2 months; HR, 0.64; P 5 .02). Three-year survival was also superior in the pegargiminase arm (3.3 v 11.9%). Response rates were similar between arms. Treatment-related grade 3 or higher toxicity was greater in the combination arm (16.9% v 28.8%), primarily because of myelosuppression.

No trials which compare pegargiminase plus pemetrexed + platinum with ipilimumab + nivolumab in patients with nonepithelioid PM have been performed.

53. Szlosarek PW, Creelan BC, Sarkodie T, et al: Pegargiminase plus first-line chemotherapy in patients with nonepithelioid pleural mesothelioma: The ATOMIC-meso randomized clinical trial. JAMA Oncol 10:475-483, 2024

57. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 41:2125-2133, 2023

58. Zalcman G, Mazieres J, Margery J, et al: Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): A randomised, controlled, open-label, phase 3 trial. Lancet 387:1405-1414, 2016

28. Baas P, Scherpereel A, Nowak AK, et al: First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): A multicentre, randomised, open-label, phase 3 trial. Lancet 397:375-386, 2021

4.5. There is insufficient evidence to make a recommendation on the addition of TTFields to pemetrexed plus platinum-based chemotherapy. (Evidence quality: Very Low; Strength of recommendation: NA)

4.13. Systemic therapy (chemotherapy and/or immunotherapy) should be offered to patients with mesothelioma because it improves survival and quality of life. (Evidence quality: Moderate; Strength of recommendation: Strong)

4.15. Selected patients with a poor PS (2) may be offered single-agent palliative chemotherapy or palliative care alone. Patients with a PS of 3 or greater should receive palliative care. (Evidence quality: Low; Strength of recommendation: Strong)

4.16. Bevacizumab is not recommended for patients with PS ≥2, substantial cardiovascular comorbidity, uncontrolled hypertension, age >75 years, bleeding or clotting risk, or other contraindications to bevacizumab. (Evidence quality: Moderate; Strength of recommendation: Strong)

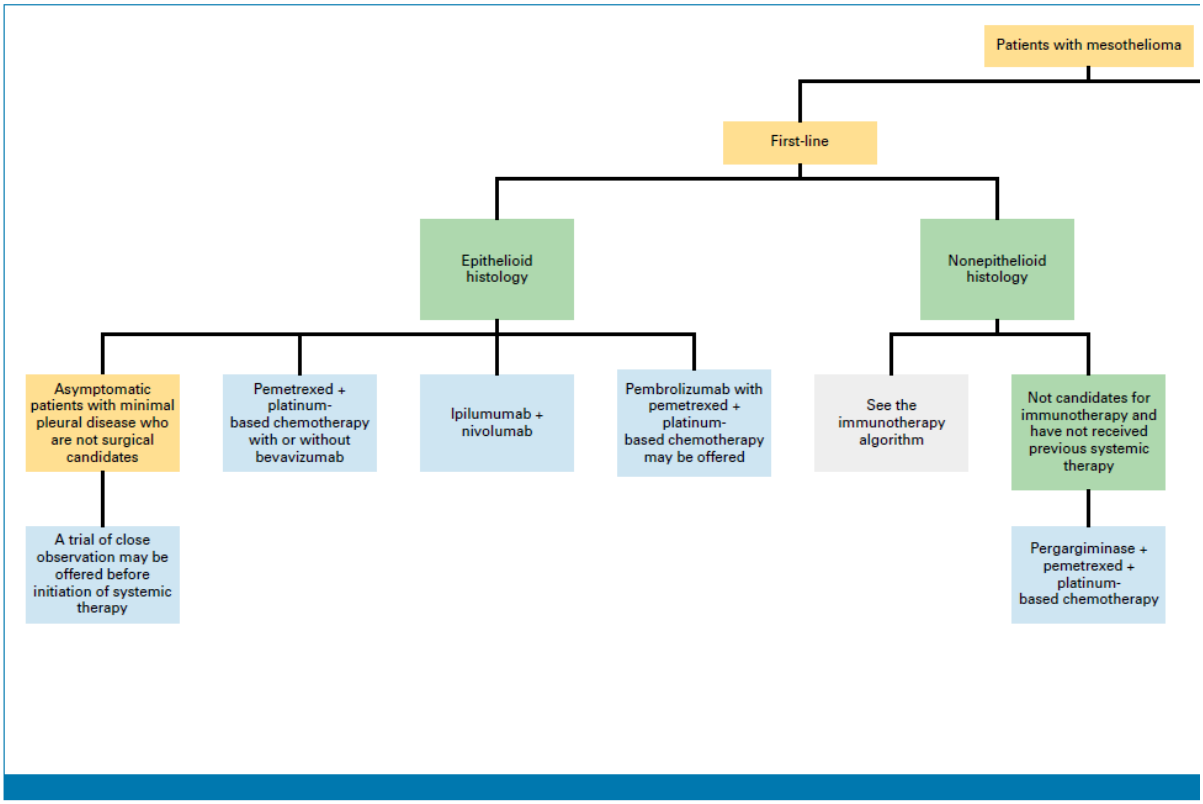

FIG 5. Integration of chemotherapy in treatment paradigm.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2025) am 13.03.2025

#	Suchschritt
1	[mh "Mesothelioma"]
2	[mh "Pleural Neoplasms"]
3	Mesothel*:ti,ab,kw
4	Pleura*: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	#1 OR #2 OR #3 OR #6
8	#7 with Cochrane Library publication date from Mar 2020 to present, in Cochrane Reviews
9	#7 with Cochrane Library publication date from Mar 2023 to present, in Cochrane Reviews
10	#8 NOT #9

Leitlinien und systematische Reviews in PubMed am 13.03.2025

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

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	"Mesothelioma" [mh]
2	"Pleural Neoplasms" [mh]
3	Mesothel*[tiab]
4	Pleura*[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	#4 AND #5
7	#1 OR #2 OR #3 OR #6

#	Suchschritt
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
9	(#8) AND ("2020/03/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
11	(#7) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
12	(#11) AND ("2020/03/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
15	(#14) NOT (#10)
16	(#15) AND ("2023/03/01"[PDAT] : "3000"[PDAT])
17	#15 NOT #16

Iterative Handsuche nach grauer Literatur, abgeschlossen am 18.03.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- 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)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Kindler HL, Ismaila N, Bazhenova L, Chu Q, Churpek JE, Dagogo-Jack I, et al.** Treatment of pleural mesothelioma: ASCO guideline update. J Clin Oncol 2025;43(8):1006-1038.

[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.2016.01.021

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.: 2025-B-072-z

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	8. April 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Zur Erstlinientherapie des nicht-resezierbaren, nicht-epitheloiden malignen Pleuramesothelioms.
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.)*
Der Behandlungsstandard in dieser Indikation in Deutschland ist eine primäre Immuncheckpoint-Inhibitor-Therapie mit Nivolumab in Kombination mit Ipililumab bis zum Progress oder toxizitätsbedingtem Abbruch. Grundlage dieser auch in Deutschland gängigen Praxis sind die Ergebnisse der randomisierten Phase-III-Studie CheckMate 743 (1) zum Vergleich alleiniger Immuncheckpoint-Inhibitor-Therapie mit Nivolumab in Kombination mit Ipililumab bis maximal zwei Jahre versus Platin (Cis- oder Carboplatin) plus Pemetrexed über sechs Zyklen. Nach einem medianen Follow-up von 30 Monaten war das mediane Überleben in der Immuncheckpoint-Inhibitor-Gruppe mit 18,1 Monaten signifikant besser gegenüber der Kontrollgruppe mit 14,1 Monaten (HR 0,74; p = 0,002). Auch die 2-Jahres-Überlebensraten waren mit 41 % versus 27 % gebessert. Der Überlebensvorteil war in allen histologischen Subgruppen nachweisbar. Am ausgeprägtesten war der Überlebensvorteil in der Gruppe mit nichtepithelialer Histologie mit einem medianen Überleben von 18,1 Monaten unter Immuncheckpoint-Inhibitor-Therapie versus 8,8 Monaten unter Chemotherapie (HR 0,46). Auch in Bezug auf PROM (patient reported outcome measures) wie krankheitsassoziierte Symptome und Lebensqualitätsdaten war unter der Immuncheckpoint-Inhibitor-Therapie ein Vorteil gegenüber der Chemotherapie zu verzeichnen mit einer in der Regel verbesserten Verträglichkeit. Die Ergebnisse haben entsprechende Berücksichtigung in den aktuellen Leitlinien gefunden (2, 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.)*

Lediglich bei Kontraindikationen gegen eine primäre Immuncheckpoint-Inhibitor-Therapie, was selten der Fall ist, wäre als Alternativoption die Kombination aus Platin (Cis- oder Carboplatin) mit Pemetrexed in Erwägung zu ziehen.

Referenzliste:

1. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet (London, England) 2021; 397(10272):375–86. doi: 10.1016/S0140-6736(20)32714-8.
2. Kindler HL, Ismaila N, Bazhenova L, Chu Q, Churpek JE, Dagogo-Jack I et al. Treatment of Pleural Mesothelioma: ASCO Guideline Update. JCO 2025; 43(8):1006–38. doi: 10.1200/JCO-24-02425.
3. Metzenmacher M, Aigner C, Curioni-Fontecedro A, Grohé C, Gütz S, Hagemeyer O et al. DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (Hrsg.) Pleuramesotheliom. Onkopedia-Leitlinie; November 2023. Verfügbar unter: https://www.onkopedia.com/de/onkopedia/guidelines/pleuramesotheliom/@@guideline/html/index.html.