Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-10-01-D-383 Dabrafenib

Stand: Oktober 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Dabrafenib **[in Kombination mit Trametinib zur adjuvanten Behandlung des BRAF-V600-Mutation-positiven Melanoms]**	
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.	Adjuvante Radiotherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Es liegen keine Beschlüsse vor.*
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:	
Dabrafenib/ Trametinib	Dabrafenib in Kombination mit Trametinib ist angezeigt zur adjuvanten Behandlung von erwachsenen Melanom-Patienten im Stadium III mit einer BRAF-V600-Mutation nach vollständiger Resektion.
Interferon alfa-2b L03AB05 IntronA®	Malignes Melanom Als adjuvante Therapie bei Patienten, die nach einem chirurgischen Eingriff tumorfrei, aber in hohem Maß rezidivgefährdet sind, z. B. Patienten mit primärem oder rezidivierendem (klinischem oder pathologischem) Befall der Lymphknoten. (Stand: Dezember 2015)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2016-B-130 Dabrafenib/Trametinib

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	11.10.2016

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 metastasiertes Melanom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 07.09.2016 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, CADTH, Clinical Evidence, CCO, DAHTA, ESMO, G-BA, GIN, IQWiG, NCI, NGC, NICE, NCCN, 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 830 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:

Dabrafenib in Kombination mit Trametinib ist angezeigt zur adjuvanten Behandlung von erwachsenen Melanom-Patienten im Stadium III mit einer BRAF-V600-Mutation nach vollständiger Resektion.

Berücksichtigte Wirkstoffe/Therapien:

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

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

keine

Cochrane Reviews

Mocellin S et al., 2013 [3]. (assessed as up-to-date 22.8.2012) **Interferon alpha for the adjuvant treatment of cutaneous melanoma**	1. Fragestellung *"To assess the disease-free survival and overall survival effects of interferon alpha as adjuvant treatment for people with high-risk cutaneous melanoma*." 2. Methodik Population "*We included people with high-risk skin melanoma, that is, those with regional lymph node metastasis undergoing radical lymph node dissection (AJCC stage III), or people without nodal disease but with primary tumour thickness greater than 1 mm (AJCC stage II).*" Intervention *"We included adjuvant (i.e. postoperative) interferon (experimental arm) versus observation or any treatment other than interferon (control arm)."* *"Interferon regimens varied in terms of dosage (high-dose (20 megaunits (MU)/m²), intermediate-dose (10MU/m²), and low-dose (1 to 3MU/m²)), administration route (subcutaneously (s.c.), intramuscularly (i.m.), and intravenously (i.v.)), and duration of treatment (4 months to 5 years)"* Endpunkt "*The primary outcomes considered were disease-free survival and overall survival*." Suchzeitraum (Aktualität der Recherche): August 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 18 RCTs (n=10.499), davon 16 RCTs Interferon vs. abwartendes Beobachten und 2 RCTs Interferon vs. GMK Melanomvakzine Qualitätsbewertung der Studien: *"We assessed risk of bias according to The Cochrane Collaboration checklist:* *(a) the method of generation of the randomisation sequence;* *(b) the method of allocation concealment;* *(c) the blinding of participants, clinicians, and outcome assessors;* *(d) the presence of incomplete outcome data; and* *(e) selective outcome reporting.* *This information was recorded in a 'Risk of bias' table"* *"The main outcome measure was the hazard ratio (HR), defined*

	as the ratio between the risk of event in the treatment arm (adjuvant interferon) and the same risk in the control arm (no adjuvant interferon). Hazard ratios were reported with their 95% confidence intervals (CIs). Survival data (HR) were either entered directly in RevMan or extrapolated from Kaplan-Meier plots using dedicated methods" *"We assessed the consistency of results (effect sizes) among studies using the two standard heterogeneity tests: the Chi²-based Cochran Q-test and the I² statistic"* *"We used the 'leave-one-out' sensitivity analysis to systematically ascertain the impact of individual randomised studies on the overall effect."*
	3. Ergebnisdarstellung Risk of Bias insgesamt niedrig **Ergebnisse für Gesamtüberleben:** - 15 RCTs mit 9.927 Patienten: HR 0,91 [95%-CI 0,85;0,97], p=0,0029, I^2=6% (Interferon signifikant überlegen), Ergebnisse robust in der Sensitivitätsanalyse - Ergebnisse für Subgruppenanalyse: „*According to subgroup analysis, interferon is not associated with an OS benefit in participants with AJCC TNM stage III melanoma (that is, in participants with regional lymph node metastasis), whereas the OS advantage is maintained in trials including both participants with stage III and those with stage II disease (that is, without lymph node metastasis)*." o TNM Stage II: 1 RCT (N=489), HR 0,70 [95%-CI 0,50;0,98], p=0,046, Interferon signifikant überlegen o TNM Stage III: 5 RCTs, HR 0,95 [95%-CI 0,85;1,05], p=0,32, I^2=43% o TNM stage II/III: 9 RCTs, HR 0,90 [95%-CI 0,83; 0,98], p=0,01, I^2=0%, Interferon signifikant überlegen. **Ergebnisse für krankheitsfreies Überleben** - 17 RCTs mit 10.345 Patienten: HR 0,83 [95%-CI 0,78;0,87], p<0,00001, I^2=16% (Interferon signifikant überlegen), Ergebnisse robust in der Sensitivitätsanalyse - Ergebnisse für Subgruppenanalyse: "*Overall, we found that none of the assessable factors we considered (interferon dose, TNM stage, year of publication, and treatment duration) significantly affected the impact of interferon on participants' DFS."*

	4. Anmerkungen/Fazit der Autoren "*Our findings support the efficacy of adjuvant interferon alpha (interferon) for the treatment of participants with high-risk (AJCC TNM stage II-III) cutaneous melanoma in terms of both disease-free survival and, to a lesser extent, overall survival. High-grade toxicity was observed in a minority of participants, who reported impairment in their quality of life. Nevertheless, participants reported relief from symptoms and improvement in quality of life after treatment discontinuation*."

Systematische Reviews

keine

Leitlinien

NICE, 2015 [5]. **Melanoma: assessment and management** **Nice guideline 14**	Leitlinie von NICE, erstellt durch das National Collaborating Centre for Cancer
	Methodik *Critical Appraisal and Evidence Grading* *"Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness."* Grundlage der Leitlinie Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informell) - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations." – Formulierung der Empfehlungen durch Guideline Development Group (GDG) auf der Basis systematischer klinischer und ggf. ökonomischer Evidenzaufbereitung – Suchzeitraum: Oktober 2014
	Empfehlung 1 "*Do not offer adjuvant radiotherapy to people with stage IIIA melanoma.* *Do not offer adjuvant radiotherapy to people with stage IIIB or IIIC melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of significant adverse effects*." (S. 148) "*For stage IIIB-IIIC the GDG considered that the evidence of a significant reduction in local recurrence did not justify recommending routine use of adjuvant radiotherapy for these*

	patients. The reasons for this were the absence of any evidence of an overall survival benefit of using adjuvant radiotherapy in stage IIIB-IIIC melanoma patients, and the evidence of increased risk of grade 3 lymphoedema after radiotherapy. *(…)* *For stage IIIA patients no evidence was identified during the evidence review for this topic. The GDG considered the low risk of loco-regional recurrence after completion lymphadenectomy for stage IIIA disease, and the lack of a survival benefit from adjuvant therapy for stage IIIB and stage IIIC melanoma. As a result the GDG agreed that adjuvant radiotherapy for stage IIIA disease should be avoided in view of the possible harmful effects of the adverse events (lymphoedema and late effects of radiation)*." (S. 149) NB: adjuvante Therapie mit Interferon in der LL nicht adressiert
NCCN, 2016 [4]. NCCN Clinical Practice Guidelines in Oncology. Melanoma Version 3.2016	*Leitlinie des National Comprehensive Cancer Network (USA)* – *Update 3.2016*
	Grundlage der Leitlinie Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - eigenes Graduierungssystem - industriefinanziert - Angaben zu CoI in zugehörigen Publikationen des JNCCN zu finden Suchzeitraum: März 2015 Grades of Recommendation: Category 1 Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Category 3 Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.
	Empfehlungen (ab S. MS-26)

	"For all patients with stage III melanoma, postoperative management options include participation in a clinical trial and observation. For those with completely resected stage III melanoma, additional postoperative management options may include high-dose or pegylated IFN, biochemotherapy, or high-dose ipilimumab. Selection of an active adjuvant treatment for these patients depends on many factors, including patient preference, patient age and comorbidities, and risk of recurrence." Empfehlung 1 *"Interferon* *Due to the inconsistency of results, NCCN does not recommend use of low-dose or intermediate-dose IFN. Adjuvant high-dose and pegylated IFN are both appropriate options for patients with completely resected stage III disease. This recommendation is category 2A for patients with either positive sentinel nodes or clinically positive nodes. There is panel consensus that high-level evidence supports IFN therapy for improving relapse-free survival in these patients, but that the effect of IFN on OS did not achieve statistical significance with long-term follow-up. Adjuvant high-dose IFN is a potentially toxic therapy that is not being used in all institutions, but panelists agree that it still may have a role in certain settings. The clinical trials cited above included very few patients with in-transit disease. Hence, adjuvant IFN is a category 2B recommendation for patients with completely resected stage III in-transit disease. Decisions about adjuvant IFN treatment should be made on an individual basis, after a thorough discussion with the patient about the potential benefits and side effects of therapy. If the decision is made to use adjuvant IFN, the best available evidence suggests that options include using either high-dose IFN with a planned duration of up to a year, or pegylated IFN with a planned duration of up to five years."* Empfehlung 2 *"Adjuvant Radiation Therapy* *Most patients with in situ or early-stage melanoma will be cured by primary excision alone. However, patients with desmoplastic melanomas, especially those with extensive neurotropism, are at high risk for local recurrence, especially if margins are suboptimal. Adjuvant radiation following surgery may be considered to improve local control. Adjuvant RT may be considered for select patients with clinically positive nodes and features predicting a high risk of nodal basin relapse. The NCCN panel discussed at length the value of adjuvant RT in patients at high risk of recurrence. Panelists agreed that high-level evidence indicates that adjuvant RT is useful in delaying or preventing nodal relapse. However,*

	some institutions argued that the increased incidence of late RT-related toxicity could potentially outweigh the benefit of reducing nodal basin recurrence. This, coupled with the statistically insignificant trend towards worse OS in the RT arm resulted in substantial heterogeneity of opinion among panel members as to the role of adjuvant nodal basin RT. Patient characteristics that suggest potential use of radiation are those used as entry criteria in the phase III trial described above.396 The use of adjuvant RT for these patients is a category 2B recommendation, reflecting nonuniform panel consensus on its value. Careful patient selection based on location, size, number of positive nodes, and gross (instead of histologic) extranodal extension is critical. The benefits of adjuvant RT must be weighed against the increased likelihood of long-term skin and regional toxicities that can affect quality of life. Consideration should be given to potential interactions between radiation and systemic therapy. The current data regarding adjuvant RT, either WBRT or SRS, for resected brain metastases are insufficient to formulate a specific recommendation. Adjuvant RT should be considered for these patients on a case-by-case basis. With the advent of more effective systemic therapy, melanoma patients are living longer than in the past, and may be more susceptible to the long-term neurocognitive toxicity of WBRT." (MS-26-30).
Dummer R et al. 2015 [1]. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Leitlinie der European Society for Medical Oncology (ESMO)
	Grundlage der Leitlinie Methodenreport hier verfügbar: http://www.esmo.org/content/download/77789/1426712/file/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf Details zu Literaturrecherche, -auswahl und –bewertung fehlen Update vom Juli 2015 *"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"*
	Empfehlung: "*Patients with resected stage III melanomas should be evaluated for adjuvant interferon therapy [II, B]. Subgroup analyses suggest patients with microscopic regional nodal involvement and/or ulcerated primaries are most likely to benefit from adjuvant IFN. In stage IIIB and higher, participation in clinical trials should be encouraged*." (S. v131)
Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe **AWMF), 2016 [2].** Diagnostik, Therapie und Nachsorge des Melanoms	S3-Leitlinie zum Melanom Version 2, 2016
	Grundlage der Leitlinie „Die Empfehlungen wurden auf Basis von Schlüsselfragen erarbeitet, die zu Beginn im Kick-off-Meeting durch die Mandatsträger konsentiert wurden. **Evidenzbasierte Empfehlungen**: Angabe von Evidenzlevel (Qualitätsstufe der Evidenz) sowie Empfehlungsgrad (Einbeziehung der klinischen Bewertung) und Konsensstärke. Grundlage: Adaptation der Quell-Leitlinien oder De-novo-Recherche **Konsensbasierte Empfehlungen**: Ein kleinerer Anteil der Empfehlungen wurde nicht evidenzbasiert durch Konsens beantwortet: Angabe von EK (Expertenkonsens) und Konsensstärke, kein Evidenzlevel, kein ausgewiesener Empfehlungsgrad (A/B/0)." (S. 24)

	Level of Evidence: 1a = Systematischer Review (SR) (mit Homogenität von randomisiert-kontrollierten Studien (RCTs) 1b = Einzelne RCT (mit engem Konfidenzintervall) 1c = Alle oder keiner 2a = SR (mit Homogenität) von Kohortenstudien 2b = Einzelne Kohorten-Studie (eingeschlossen RCT mit schlechter Qualität; z. B. < 80 % Nachbeobachtungsrate) 2c = Ergebnisforschung; Ökologische Studien 3a = SR (mit Homogenität) von Fall-Kontroll-Studien 3b = Einzelne Fall-Kontroll-Studie 4 = Fall-Serie (und qualitative schlechte Kohorten- und Fall-Kontroll-Studien) 5 = Expertenmeinung ohne kritische Analyse oder basiert auf physiologischer oder experimenteller Forschung oder „Grundprinzipien“ Empfehlungsgrade: A = Starke Empfehlung B = Empfehlung 0 = Empfehlung offen
	Empfehlungen zur adjuvanten Therapie: a) Interferontherapie: • „Patienten im AJCC-2009-Tumorstadium IIB/C und IIIA-C soll eine adjuvante Interferontherapie angeboten werden.“ (S. 100) (Empfehlungsgrad A, Level of Evidence 1a-) • „Patienten im AJCC-2009-Tumorstadium IIA kann eine niedrig dosierte adjuvante Interferontherapie angeboten werden.“ (S. 100) (Empfehlungsgrad 0, Level of Evidence 1b) • „Patienten mit hohem Metastasierungsrisiko können ausschließlich nachbeobachtet werden, sofern zuvor eine adjuvante Therapie mit IFN-alpha diskutiert wurde.“ (Evidenzbasiertes Statement, Level of Evidence 1b) b) Radiotherapie nach Lymphadenektomie: • „Zur Verbesserung der Tumorkontrolle der

	Lymphknotenstation sollte eine postoperative adjuvante Radiotherapie bei Vorliegen mindestens eines der folgenden Kriterien durchgeführt werden: - 3 befallene Lymphknoten, - Kapseldurchbruch, - Lymphknotenmetastase > 3 cm. (S. 91) (Empfehlungsgrad B, Level of Evidence 1b) • „Zur Verbesserung der Tumorkontrolle der Lymphknotenstationen sollte nach Resektion eines lymphogenen Rezidivs eine postoperative Bestrahlung durchgeführt werden.“ (S. 91) (Expertenkonsens) • „Falls die Indikation zur Bestrahlung des Lymphabflussgebietes gestellt wird, soll die Strahlentherapie mit 50–60 Gy in konventioneller Fraktionierung (5 x 1,8–2,5 Gy/Woche) erfolgen.“ (S. 91) (Empfehlungsgrad A, Level of Evidence 2b) • „Ein positiver Einfluss einer postoperativen adjuvanten Radiotherapie des regionalen Lymphabflussgebietes auf die Überlebenszeit ist bisher nicht belegt worden.“ (S. 92) (Evidenzbasiertes Statement, Level of Evidence 2b) Evidenz aus 2 RCTs und mehreren retrospektiven Beobachtungsstudien; kein nachgewiesener Einfluss auf Überleben oder progressionsfreies Überleben, sondern lediglich auf regionale Tumorkontrolle.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Sun A et al., 2016 [7]. The use of adjuvant radiation therapy for curatively resected melanoma.	Leitlinie von Cancer Care Ontario *"Recommendation 1* *For patients at high risk for recurrence at the primary site following curative resection, adjuvant RT may be a reasonable option if adequate clear margins are unachievable."* *"Recommendation 2* *No evidence-based recommendation for adjuvant RT can be made for patients following curative resection for primary melanoma with satellites, or for recurrence at the primary melanoma site; however, based on expert opinion of the Working Group, adjuvant RT may be a reasonable option for these patients if adequate clear margins are unachievable."* *"Recommendation 3* *For patients diagnosed with desmoplastic melanoma, adjuvant RT following curative resection for the primary tumour is a reasonable option to improve local control."* *"Recommendation 4* *No evidence-based recommendation can be made for patients following curative resection for in-transit primary melanoma or in-transit recurrences; however, based on the expert opinion of the Working Group, adjuvant RT may be considered on a case-by-case basis."* *"Recommendation 5* *Following lymphadenectomy either for stage III melanoma patients at high risk for lymph node relapse, or for all patients with nodal recurrence, adjuvant RT to the regional nodal basin is a reasonable option to improve local regional control."*
Petrella T et al., 2013 [6]. Systemic Adjuvant Therapy for Patient at High Risk for Recurrent Melanoma Version 4	Leitlinie von Cancer Care Ontario "*RECOMMENDATIONS* • *Patients with high-risk melanoma should be encouraged to participate in appropriate clinical trials exploring novel therapeutics, given that at most a small OS benefit exists with currently available therapies.* • *The Melanoma Disease Site Group recommends that high dose interferon alpha 2b therapy (20 x106 U/m^2/d intravenously five days/week for four weeks, then 10X106 U/m^2 subcutaneously three times weekly for 48 weeks) be discussed and offered to the high-risk group defined above to increase DFS. It may be used as adjuvant treatment, provided that each patient has been made aware of the relative risks, benefits, and costs of this therapy and wishes to proceed.* • *The Melanoma Disease Site Group recommends that pegylated interferon (6µg/kg subcutaneously per week for 8 weeks followed by 3µg/kg subcutaneously per week for a duration of 5 years) be considered as a reasonable alternative to high dose interferon in high-risk melanoma patients. It may be used as adjuvant*

	treatment, provided that each patient has been made aware of the relative risks, benefits, and costs of this therapy and wishes to proceed. • *At this time, there is insufficient evidence to recommend one month of high dose interferon alone.*"

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 06.09.2016**

#	Suchfrage
#1	MeSH descriptor: [Melanoma] explode all trees
#2	melanom*:ti,ab,kw (Word variations have been searched)
#3	(skin* or cutaneous):ti,ab,kw (Word variations have been searched)
#4	(neoplasm* or sarcoma* or tumor* or tumour* or cancer*):ti,ab,kw (Word variations have been searched)
#5	#3 and #4
#6	#1 or #2 or #5
#7	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#8	(metastatic* or metastas* or advanced or unresectable* or malignant* or maligne*):ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	#6 and #9
#11	#10 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 07.09.2016

#	Suchfrage
1	melanoma[MeSH Terms]
2	melanom*[Title/Abstract]
3	(skin*[Title/Abstract]) OR cutaneous[Title/Abstract]
4	((((neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR cancer*[Title/Abstract]
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	metastatic*[Title/Abstract] OR metastas*[Title/Abstract] OR advanced[Title/Abstract] OR unresectable*[Title/Abstract] OR malignant*[Title/Abstract] OR maligne*[Title/Abstract] OR Neoplasm Metastasis[MeSH Terms]
8	(#6 AND #7)
9	(#8) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
10	(#8) AND (((((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]))))
11	(#9 OR #10)
12	(#11) AND ("2011/09/01"[PDAT] : "2016/09/07"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 07.09.2016

#	Suchfrage
1	(melanoma[MeSH Terms]) OR melanoma*[Title]
2	(skin[Title] OR cutaneous[Title])
3	(neoplasm*[Title] OR sarcoma*[Title] OR tumor*[Title] OR tumour*[Title] OR cancer*[Title])
4	#2 AND #3
5	#1 OR #4
6	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
7	#5 AND #6
8	(#7) AND ("2011/09/01"[PDAT] : "2016/09/07"[PDAT])

Literatur:

1. **Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U.** Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v126-132.
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