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: 2022-B-131-z Pembrolizumab

Stand: Juli 2022

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

Pembrolizumab **[adjuvante Behandlung des 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.	Radiotherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: − Nivolumab: Beschluss vom 16. September 2021 − Pembrolizumab: Beschluss vom 19. September 2019 − Dabrafenib: Beschluss vom 22. März 2019 − Trametinib: Beschluss vom 22. März 2019 − Nivolumab: Beschluss vom 21. Februar 2019
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 L01FF02 Keytruda	<u>Anwendungsgebiet laut Fachinformation:</u> „KEYTRUDA ist als Monotherapie zur adjuvanten Behandlung des Melanoms in den Tumorstadien IIB, IIC oder III nach vollständiger Resektion bei Kindern und Jugendlichen ab 12 Jahren und Erwachsenen angezeigt (siehe Abschnitt 5.1). “
Dabrafenib L01XE23 Tafinlar	<u>Adjuvante Melanom-Behandlung</u> 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[1] L03AB05 IntronA	<u>Malignes Melanom</u> 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.
Interferon alfa-2a[1] L03AB04 Roferon-A	Malignes Melanom des AJCC-Stadiums II (Breslow-Tumordicke > 1,5 mm, ohne Lymphknotenbeteiligung oder Hautausbreitung) bei Patienten, die nach einer Tumorresektion krankheitsfrei sind.
Nivolumab L01XC17 OPDIVO	<u>Adjuvante Behandlung des Melanoms</u> OPDIVO ist als Monotherapie bei Erwachsenen zur adjuvanten Behandlung des Melanoms mit Lymphknotenbeteiligung oder Metastasierung nach vollständiger Resektion indiziert (siehe Abschnitt 5.1).
Trametinib L01XE2 Mekinist	<u>Adjuvante Melanom-Behandlung</u> Trametinib in Kombination mit Dabrafenib ist angezeigt zur adjuvanten Behandlung von erwachsenen Melanom-Patienten im Stadium III mit einer BRAF-V600-Mutation nach vollständiger Resektion.

Quellen: AMIce-Datenbank, Fachinformationen

[1] außer Vertrieb

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2022-B-131 (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	16. Juni 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	‘Adverse Events / Unerwünschtes Ereignis
AJCC	American Joint Committee on Cancer
AM-RL	Arzneimittel-Richtlinie
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best-Supportive-Care
CHEM	Chemotherapie
CI	Konfidenzintervall
CrI	Glaubwürdigkeitsintervall
DAB	Dabrafenib
DFS	Krankheitsfreies Überleben
DKG	Deutsche Krebsgesellschaft
DKH	Deutsche Krebshilfe
DMFS	Metastasenfreies Überleben
ECOG	Eastern Cooperative Oncology Group
ECRI	ECRI Guidelines Trust
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
Gy	Gray
HR	Hazard Ratio
IFN	Interferon
IPI	Ipilimumab
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LN	Lymphknoten
LoE	Level of Evidence
MM	Malignant Melanoma
NED	Kein nachweisbarer Tumor
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab

NMA	Netzwerk-Metaanalyse
NR	Not reported
OBS	Observation
OS	Gesamtüberleben
PBO	Placebo
PBS	Pharmaceutical Benefits Scheme
PEM	Pembrolizumab
RCT	Randomisierte kontrollierte Studie
RFS	Rezidivfreies Überleben
RT	Radiotherapie
SGB V	Sozialgesetzbuch V
SIGN	Scottish Intercollegiate Guidelines Network
SITC	Society for Immunotherapy of Cancer
SLR	Systematische Literaturrecherche
SMR	Society for Melanoma Research
SR	Systematischer Review
TGA	Therapeutic Goods Administration
TRAM	Trametinib
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Adjuvante Behandlung des Melanoms im Tumorstadium IIB, IIC oder III nach vollständiger Resektion bei Erwachsenen und Jugendlichen ab 12 Jahren.

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 *Melanom* 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), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 04.06.2021 durchgeführt, die folgende am 08.02.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 1963 Referenzen.

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

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine CR für das vorliegende AWG identifiziert.

3.2 Systematische Reviews

Toor K et al., 2021 [9].

Comparative efficacy and safety of adjuvant nivolumab versus other treatments in adults with resected melanoma: a systematic literature review and network meta-analysis

siehe auch: Sharma R et al., 2019 [8].

Zielsetzung

[…] to assess the efficacy and safety of nivolumab versus other treatment options in patients with resected melanoma by using both constant and time-varying treatment-effect assumptions.

Methodik

Population:

adults (aged 18 years and older) with non-metastatic stage III/IV melanoma

Intervention/Komparator:

pharmacological interventions for the adjuvant treatment

Endpunkte:

- recurrence-free survival (RFS)
- disease-free survival (DFS)
- distant metastasis-free survival (DMFS)
- all-cause grade 3/4 adverse events (AE)
- overall discontinuations
- discontinuations due to AEs

Recherche/Suchzeitraum:

A comprehensive systematic literature search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted. The original searches were executed on October 12, 2017 with predefined search strategies and was updated on May 8, 2018. Additionally, manual searches of four conference proceedings were conducted: International Society for Quality of Life Research 2017, Society for Melanoma Research 2017, Society for Immunotherapy of Cancer 2017, and American Academy of Cancer Research 2015 to 2018.

Laut Appendix A wurde am 1. Mai 2019 eine weitere systematische Recherche in MEDLINE, EMBASE und im Cochrane Register of Controlled Trials durchgeführt.

Qualitätsbewertung der Studien:

Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- An SLR conducted through May 2019 identified 11 new studies in addition to the 41 studies identified in an earlier SLR, generating an evidence base of 52 studies. These studies represent 26 RCTs.
- A feasibility assessment excluded seven trials […].
- Overall, 19 trials were included in the NMA.

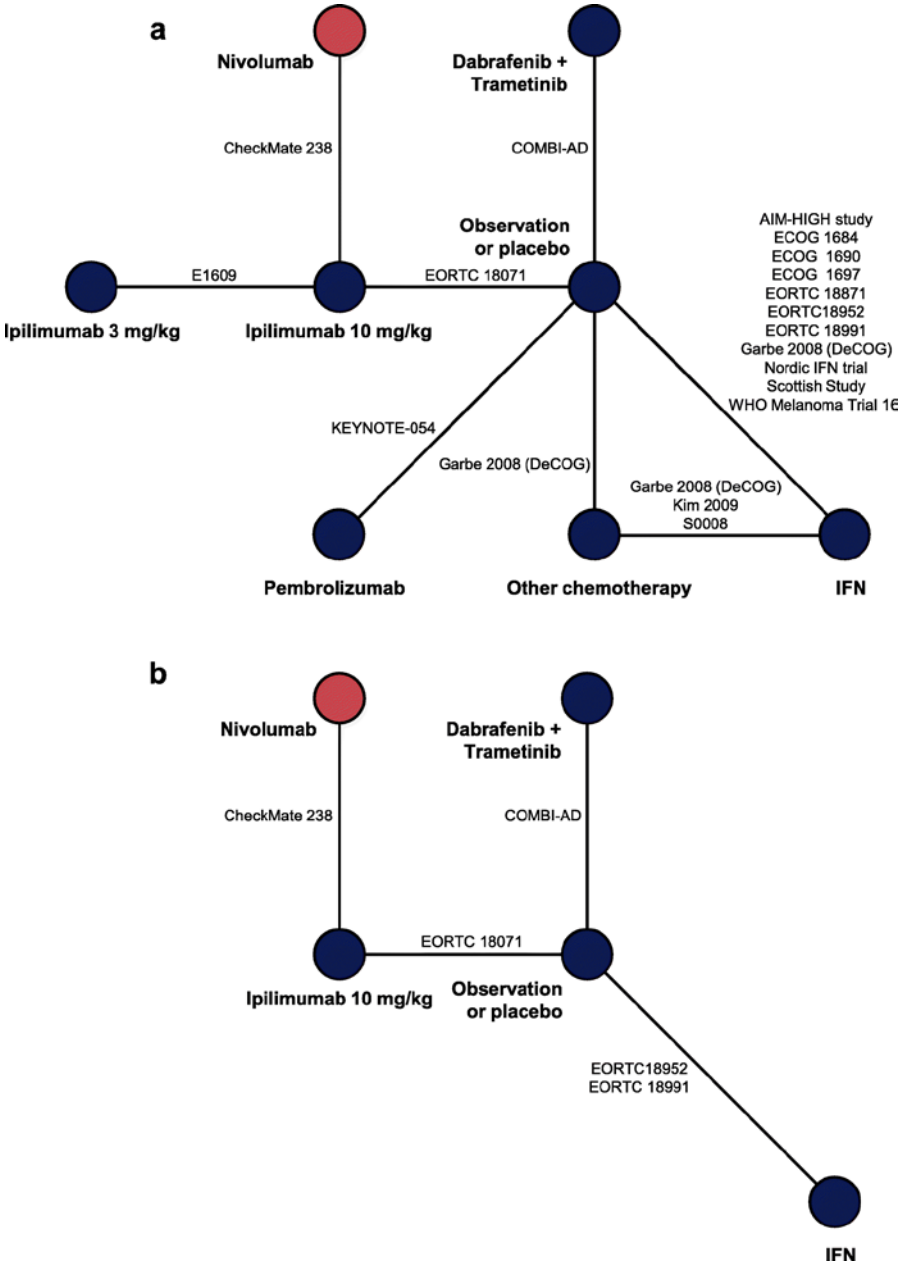

Abbildung 1: Network diagrams of randomized controlled trials for base-case efficacy outcomes in patients with stage II-IV melanoma for (a) RFS/DFS and (b) DMFS

Charakteristika der Population: ⇨ siehe Anhang Tabelle 1

Qualität der Studien: ⇨ siehe Anhang Tabelle 2

Studienergebnisse:

Efficacy

RFS/DFS

Based on HRs for RFS/DFS, the risk of recurrence was similar between nivolumab and dabrafenib plus trametinib (HR 1.06, 95% CrI 0.77-1.45), and between nivolumab and pembrolizumab (HR 0.92, 95% CrI 0.67-1.29) when the HR was constant over time. Risk of recurrence was lower with nivolumab than with ipilimumab 3 mg/kg, ipilimumab 10 mg/kg, or IFN.

Tabelle 1: Constant HR estimates[a] from a fixed-effects NMA or RFS/DFS in patients with resected stage II-IV melanoma

Observation or placebo	**1.93 (1.50–2.48)**	**2.04 (1.68–2.48)**	**1.79 (1.45–2.20)**	**1.32 (1.11–1.55)**	1.32 (1.00–1.73)	1.17 (0.97–1.41)	**1.13 (1.06–1.21)**
0.52 (0.40–0.67)	Nivolumab	1.06 (0.77–1.45)	0.92 (0.67–1.29)	**0.68 (0.56–0.82)**	**0.68 (0.51–0.90)**	**0.61 (0.44–0.83)**	**0.59 (0.45–0.76)**
0.49 (0.40–0.59)	0.95 (0.69–1.30)	Dabrafenib + trametinib	0.88 (0.66–1.17)	**0.64 (0.50–0.83)**	**0.64 (0.46–0.91)**	**0.58 (0.44–0.75)**	**0.55 (0.45–0.68)**
0.56 (0.45–0.69)	1.08 (0.78–1.49)	1.14 (0.86–1.52)	Pembrolizumab	**0.74 (0.56–0.95)**	0.73 (0.52–1.03)	**0.66 (0.49–0.87)**	**0.63 (0.51–0.79)**
0.76 (0.65–0.90)	**1.47 (1.22–1.78)**	**1.55 (1.20–2.01)**	**1.36 (1.05–1.77)**	Ipilimumab 10 mg/kg	1.00 (0.81–1.24)	0.89 (0.70–1.15)	0.86 (0.72–1.03)
0.76 (0.58–1.00)	**1.47 (1.11–1.95)**	**1.55 (1.10–2.19)**	1.36 (0.97–1.92)	1.00 (0.81–1.24)	Ipilimumab 3 mg/kg	0.89 (0.64–1.25)	0.86 (0.65–1.15)
0.85 (0.71–1.03)	**1.65 (1.20–2.25)**	**1.74 (1.33–2.30)**	**1.53 (1.15–2.03)**	1.12 (0.87–1.44)	1.12 (0.80–1.57)	Other chemotherapy	0.97 (0.81–1.16)
0.88 (0.83–0.94)	**1.70 (1.32–2.21)**	**1.80 (1.47–2.21)**	**1.58 (1.27–1.96)**	1.16 (0.97–1.38)	1.16 (0.87–1.54)	1.04 (0.86–1.24)	IFN pooled

[a] The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level

As the assumption of proportional hazards did not hold, a subsequent analysis was conducted in which HR varied over time. In this analysis, the risk of recurrence with nivolumab was similar to that with dabrafenib plus trametinib at 12 months (HR 1.02, 95% CrI 0.71-1.47), but was lower at later time points (HR at 24 months 0.46, 95% CrI 0.27-0.78; HR at 36 months 0.28, 95% CrI 0.14-0.59).

Tabelle 2: Time-varying HR estimates[a] from a fixed-effects NMA of RFS/DFS (p1 = 0, p2 = -1, scale, shape x1) in patients with resected stage II-IV melanoma

Treatment	Time points			
	12 months	24 months	36 months	48 months
NIVO vs. OBS/PBO	**0.58 (0.43–0.77)**	**0.51 (0.33–0.80)**	**0.46 (0.26–0.86)**	**0.43 (0.21–0.91)**
NIVO vs. DAB+TRAM	1.02 (0.71–1.47)	**0.46 (0.27–0.78)**	**0.28 (0.14–0.59)**	**0.20 (0.08–0.49)**
NIVO vs. PEM	1.19 (0.81–1.76)	1.06 (0.56–2.05)	0.96 (0.40–2.29)	0.88 (0.30–2.51)
NIVO vs. IPI (10 mg/kg)	**0.69 (0.55–0.86)**	**0.66 (0.46–0.96)**	0.65 (0.40–1.07)	0.64 (0.35–1.17)
NIVO vs. IPI (3 mg/kg)	0.75 (0.54–1.04)	0.93 (0.58–1.48)	1.06 (0.57–2.01)	1.16 (0.54–2.55)
NIVO vs. CHEM	**0.63 (0.44–0.89)**	**0.53 (0.32–0.86)**	**0.47 (0.24–0.91)**	**0.42 (0.19–0.95)**
NIVO vs. IFN	**0.64 (0.48–0.86)**	**0.55 (0.36–0.88)**	**0.49 (0.27–0.93)**	**0.46 (0.22–0.97)**

[a] The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment; bolded values are statistically significant at the 0.05 significance level

DMFS

Pembrolizumab was not included in the DMFS analysis due to a lack of publicly available data.

Based on HRs for DMFS, the risk of developing distant metastases was lower with nivolumab than with ipilimumab 10 mg/kg or IFN but was similar to that of dabrafenib plus trametinib.

Tabelle 3: Constant HR estimates[a] from a fixed-effects NMA or DMFS in patients with stage II-IV melanoma

Observation or placebo	**1.69 (1.25–2.25)**	**1.89 (1.50–2.39)**	**1.32 (1.10–1.57)**	1.09 (0.98–1.22)
0.59 (0.44–0.80)	**Nivolumab**	1.12 (0.77–1.62)	**0.78 (0.62–0.99)**	**0.64 (0.47–0.88)**
0.53 (0.42–0.67)	0.89 (0.62–1.29)	**Dabrafenib + trametinib**	**0.70 (0.53–0.93)**	**0.58 (0.44–0.75)**
0.76 (0.64–0.91)	**1.28 (1.01–1.62)**	**1.44 (1.08–1.90)**	**Ipilimumab 10 mg/kg**	0.83 (0.68–1.02)
0.92 (0.82–1.02)	**1.55 (1.13–2.11)**	**1.73 (1.34–2.26)**	1.21 (0.98–1.48)	**IFN pooled**

[a] The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level

In the analysis with time-varying HR, the risk of developing distant metastases was lower for nivolumab compared with observation/placebo at 12 months (HR 0.67, 95% CrI 0.48-0.93), but was not different at later time points or compared with other treatments.

Tabelle 4: Time-varying HR estimates[a] from a fixed-effects NMA for DMFS (p1 = 0, p2 = - 0,5, scale, shape x1) in patients with stage II-IV melanoma

Treatment	Time points			
	12 months	24 months	36 months	48 months
NIVO vs. OBS/PBO	**0.67 (0.48–0.93)**	0.77 (0.50–1.20)	0.83 (0.46–1.49)	0.87 (0.42–1.76)
NIVO vs. DAB+TRAM	1.06 (0.68–1.63)	0.65 (0.37–1.14)	0.51 (0.24–1.07)	0.44 (0.17–1.08)
NIVO vs. IPI (10 mg/kg)	0.80 (0.61–1.06)	0.88 (0.60–1.28)	0.93 (0.55–1.56)	0.96 (0.50–1.84)
NIVO vs. IFN	0.73 (0.51–1.05)	0.80 (0.51–1.27)	0.84 (0.47–1.53)	0.86 (0.42–1.78)

[a] The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment; bolded values are statistically significant at the 0.05 significance level

Subgroup analyses

Results for RFS/DFS and DMFS were consistent between subgroup analyses that included patients with stage III/IV disease and overall analyses that included patients with stage II-IV disease.

Safety

Based on odds ratios estimated in the safety analyses, nivolumab was associated with lower rates of grade 3/4 AEs than the other active interventions and lower rates of discontinuations due to AEs than the other active interventions, with the exception of pembrolizumab.

Tabelle 5: Odds ratio estimates[a] from a fixed-effects network meta-analysis of grade 3/4 adverse events in patients with stage II-IV melanoma

Observation or placebo	1.08 (0.73, 1.60)	**0.23 (0.16, 0.32)**	**0.30 (0.23, 0.39)**	**0.50 (0.34, 0.72)**	**0.05 (0.03, 0.08)**	**0.09 (0.07, 0.11)**	**0.49 (0.37, 0.66)**
0.92 (0.63, 1.37)	Nivolumab	**0.21 (0.13, 0.36)**	**0.28 (0.21, 0.36)**	**0.46 (0.32, 0.66)**	**0.05 (0.03, 0.08)**	**0.08 (0.05, 0.13)**	**0.45 (0.28, 0.74)**
4.32 (3.12, 6.06)	**4.68 (2.79, 7.86)**	Dabrafenib + trametinib	1.30 (0.84, 1.99)	**2.15 (1.31, 3.54)**	**0.21 (0.12, 0.37)**	**0.40 (0.27, 0.59)**	**2.13 (1.37, 3.30)**
3.34 (2.55, 4.41)	**3.62 (2.74, 4.79)**	0.77 (0.50, 1.18)	Ipilimumab 10 mg/kg	**1.66 (1.29, 2.13)**	**0.16 (0.10, 0.27)**	**0.31 (0.22, 0.43)**	**1.64 (1.10, 2.46)**
2.01 (1.40, 2.92)	**2.18 (1.50, 3.17)**	**0.47 (0.28, 0.76)**	**0.60 (0.47, 0.77)**	Ipilimumab 3 mg/kg	**0.10 (0.06, 0.17)**	**0.18 (0.12, 0.28)**	0.99 (0.62, 1.59)
20.46 (13.30, 31.55)	**22.15 (12.44, 39.52)**	**4.73 (2.72, 8.13)**	**6.12 (3.69, 10.18)**	**10.16 (5.74, 17.93)**	Other chemotherapy	**1.88 (1.28, 2.75)**	**10.05 (5.97, 17.04)**
10.91 (8.90, 13.40)	**11.81 (7.61, 18.32)**	**2.52 (1.70, 3.69)**	**3.26 (2.33, 4.57)**	**5.41 (3.56, 8.23)**	**0.53 (0.36, 0.78)**	IFN	**5.36 (3.75, 7.66)**
2.03 (1.52, 2.73)	**2.20 (1.34, 3.59)**	**0.47 (0.30, 0.73)**	**0.61 (0.41, 0.91)**	1.01 (0.63, 1.62)	**0.10 (0.06, 0.17)**	**0.19 (0.13, 0.27)**	Pembrolizumab

[a] The value in each cell represents the odds ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level

Tabelle 6: Odds ratio estimates[a] from a fixed-effects network meta-analysis of discontinuations due to adverse events in patients with stage II-IV melanoma

Observation or placebo	**0.28 (0.15, 0.51)**	**0.08 (0.04, 0.14)**	**0.04 (0.02, 0.07)**	**0.09 (0.05, 0.15)**	**0.07 (0.04, 0.10)**	**0.04 (0.03, 0.06)**	**0.14 (0.07, 0.25)**
3.52 (1.95, 6.48)	Nivolumab	**0.28 (0.11, 0.65)**	**0.14 (0.10, 0.21)**	**0.31 (0.20, 0.49)**	**0.23 (0.11, 0.49)**	**0.15 (0.08, 0.30)**	0.48 (0.19, 1.15)
12.65 (7.16, 24.76)	**3.62 (1.53, 8.82)**	Dabrafenib + trametinib	0.52 (0.24, 1.18)	1.12 (0.50, 2.67)	0.83 (0.39, 1.83)	0.55 (0.29, 1.12)	1.72 (0.70, 4.26)
24.49 (15.38, 40.49)	**6.96 (4.86, 10.08)**	1.93 (0.85, 4.15)	Ipilimumab 10 mg/kg	**2.17 (1.68, 2.80)**	1.60 (0.85, 3.09)	1.06 (0.62, 1.86)	**3.31 (1.45, 7.41)**
11.25 (6.65, 19.84)	**3.21 (2.06, 4.97)**	0.89 (0.37, 2.00)	**0.46 (0.36, 0.59)**	Ipilimumab 3 mg/kg	0.74 (0.37, 1.49)	**0.49 (0.27, 0.90)**	1.52 (0.65, 3.55)
15.38 (9.78, 23.67)	**4.36 (2.04, 9.08)**	1.20 (0.55, 2.54)	0.63 (0.32, 1.18)	1.36 (0.67, 2.70)	Other chemotherapy	**0.66 (0.45, 0.96)**	2.08 (0.89, 4.50)
23.25 (17.61, 29.80)	**6.57 (3.36, 12.56)**	1.83 (0.89, 3.47)	0.94 (0.54, 1.61)	**2.05 (1.11, 3.69)**	**1.51 (1.04, 2.21)**	IFN pooled	**3.15 (1.45, 6.20)**
7.37 (3.95, 14.93)	2.10 (0.87, 5.15)	0.58 (0.23, 1.44)	**0.30 (0.14, 0.69)**	0.66 (0.28, 1.55)	0.48 (0.22, 1.12)	**0.32 (0.16, 0.69)**	Pembrolizumab

[a] The value in each cell represents the odds ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level

Overall discontinuation rates with nivolumab were lower than those with ipilimumab 10 mg/kg or IFN and similar to those with the other treatment options.

Tabelle 7: Odds ratio estimates[a] from a fixed-effects network meta-analysis of discontinuation in patients with stage II-IV melanoma

Observation or placebo	1.46 (0.82, 2.56)	**0.35 (0.21, 0.56)**	1.79 (0.92, 3.58)	**0.32 (0.20, 0.53)**	0.97 (0.76, 1.25)
0.68 (0.39, 1.22)	Nivolumab	**0.24 (0.18, 0.31)**	1.23 (0.52, 3.01)	**0.22 (0.11, 0.48)**	0.67 (0.36, 1.25)
2.89 (1.78, 4.84)	**4.23 (3.20, 5.61)**	Ipilimumab 10 mg/kg	**5.20 (2.29, 12.20)**	0.93 (0.47, 1.92)	**2.81 (1.64, 4.97)**
0.56 (0.28, 1.09)	0.81 (0.33, 1.94)	**0.19 (0.08, 0.44)**	Other chemotherapy	**0.18 (0.11, 0.29)**	0.54 (0.26, 1.11)
3.11 (1.88, 5.08)	**4.54 (2.08, 9.52)**	1.07 (0.52, 2.11)	**5.56 (3.51, 9.02)**	IFN pooled	**3.02 (1.73, 5.22)**
1.03 (0.80, 1.32)	1.50 (0.80, 2.77)	**0.36 (0.20, 0.61)**	1.84 (0.90, 3.82)	**0.33 (0.19, 0.58)**	Pembrolizumab

[a] The value in each cell represents the odds ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level

Anmerkung/Fazit der Autoren

In summary, nivolumab is an adjuvant treatment option with a promising risk-benefit profile indicated for the treatment of patients with resected melanoma. […] The efficacy assessment reported here may support patient preferences and clinician choices for short-term versus long-term effectiveness. The current analysis is consistent with the established safety profile of nivolumab. Due to the potential occurrence of immune-

mediated AEs, additional analyses may be warranted, such as long-term follow-up of safety data.

Kommentare zum Review

[…] a lack of available data and network connectivity precluded a subgroup analysis based on BRAF status, as only three trials reported this information.

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Adjuvant therapy of high-risk (stages IIC-IV) malignant melanoma in the post interferon-alpha era: a systematic review and meta-analysis

Fragestellung

Adjuvant Therapy of High-Risk (Stages IIC-IV) Malignant Melanoma in the Post Interferon-Alpha Era: A Systematic Review and Meta-Analysis.

Methodik

Population:

- high-risk MM (stages IIC-IV) with no evidence of disease (NED) after excision

Intervention:

- adjuvant treatment

Komparator:

- placebo or an FDA- or EMA approved agent

Endpunkte:

- recurrence-free survival (RFS)

Recherche/Suchzeitraum:

- PubMed and Cochrane Library databases were searched without restriction in year of publication in June and 14th September 2020

Qualitätsbewertung der Studien:

- Cochrane tool for assessing risk of bias (RoB2 tool)

Ergebnisse

Anzahl eingeschlossener Studien:

- Five prospective randomized placebo-controlled trials
- Regimens included ipilimumab, pembrolizumab, nivolumab, nivolumab/ ipilimumab, vemurafenib, and dabrafenib/trametinib.

Charakteristika der Population: ⇨ siehe Anhang Tabelle 3

- In total, data from 3505 patients were evaluated.
- Staging was performed according to the 7th edition of the American Joint Committee on Cancer (AJCC) in the COMBI-AD, EORTC-1325 and BRIM8 trials.
- The EORTC-18071 trial included only patients with stage III disease according to the 6th AJCC edition.
- The IMMUNED trial included only patients with stage IV with NED, whose distinction from stage III does not differ between the 7th and 8th editions.

- Taken together, all trials enrolled patients with completely resected stage IIC to IV cutaneous MM.

TABLE 1 | Overview of the characteristics of the included studies.

Trial	Comparison	Randomised patients (n)	Dose schedule	Duration of treatment	Median follow up	Primary endpoint HR, (95% CI)
EORC-18071	Ipilimumab versus placebo	951	10 mg/kg i.v. q3w for four doses, then every 3 months for 3 years	3 years	2.74 years	RFS, 0.76 (0.64–0.89)
COMBI-AD	Dabrafenib plus Trametinib versus placebo	870	Dabrafenib 150 mg 2× day + trametinib 2 mg 1× day	1 year	2.9 years	RFS, 0.49 (0.40–0.59)
BRIM8	Vemurafenib versus placebo	Cohort 1: 314	Vemurafenib tablets (960 mg 2× day for 52 weeks [13 × 28-day cycles])	52 weeks	33.5 months	DFS, 0.55 (0.38–0.80)
		Cohort 2: 184	as Cohort 1	52 weeks	30.8 months	DFS, 0.81 (0.55–1.19)
EORTC-1325	Pembrolizumab versus placebo	1019	200 mg i.v. q3w for a total of 18 doses	Approximately 1 year	15 months	RFS, 0.57 (0.43–0.74)
IMMUNED	Nivolumab versus placebo	167	3 mg/kg nivolumab q3w	Up to 1 year	28.4 months	RFS, 0.56 (0.33–0.94)
	Nivolumab plus Ipilimumab versus placebo		1 mg/kg i.v. nivolumab q3w plus 3 mg/kg i.v. ipilimumab q3w for four doses, followed by 3 mg/kg i.v. nivolumab q2w			RFS, 0.23 (0.12–0.45)*

** 97.5% CI.*

Abbildung 1: Overview of characteristics of the included studies

Qualität der Studien:

- Overall, the trials were deemed to be at low risk for bias, except for "deviation of intended intervention" bias, for which it was unclear, whether participants with missing outcome data were excluded. In the COMBI-AD trial RFS was the prespecified outcome measurement however its estimation at 3 years was not prespecified.

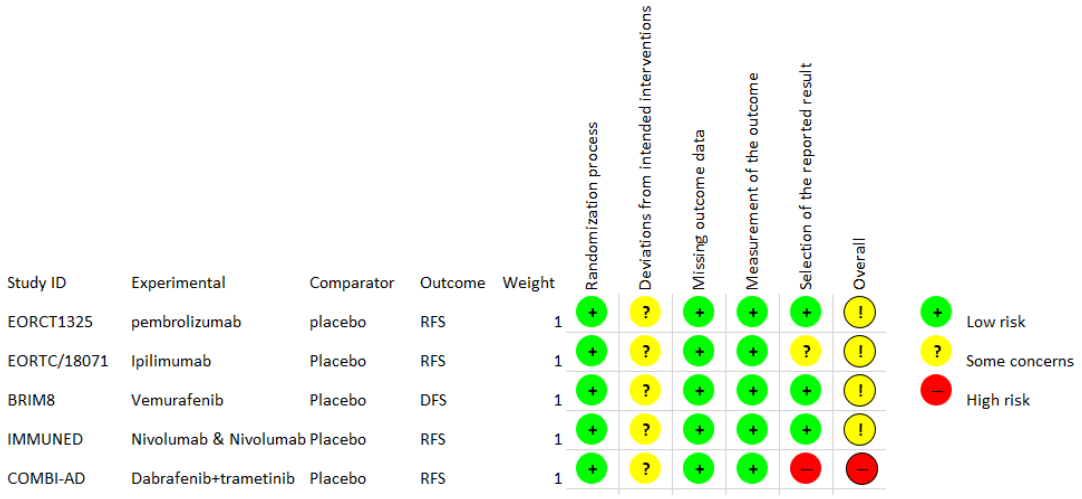

Abbildung 2: Risk of bias graph. Author's judgements about each risk of bias category presented as percentages across all included trials

Studienergebnisse:

- Allgemein:
  - Adjuvant treatment resulted consistently in longer RFS compared to placebo (HR 0.57; 95% CI= 0.45–0.7).

- Patients in stage IV treated with nivolumab/ipilimumab derived the highest benefit (HR 0.23; 97.5% CI= 0.12–0.45).
- Pembrolizumab and nivolumab demonstrated similar efficacy, (HR 0.57; 95% CI= 0.43–0.74 and HR 0.56; 95% CI= 0.33–0.94 respectively).
- Patients with stage III BRAFmut MM treated with dabrafenib/trametinib had a 51% lower risk of relapse (HR 0.49; 95% CI= 0.40–0.59).
- Adjuvant therapy with ipilimumab was less effective (HR 0.76; 95% CI= 0.64– 0.89).
- BRIM8 did not reach its primary endpoint in cohort 2 (stage IIIC MM, HR 0.81; 95%CI= 0.55–1.19). In cohort 1 however, treatment with vemurafenib resulted in longer RFS (stages IIC– IIIA, HR 0.55; 95% CI= 0.38–0.80).

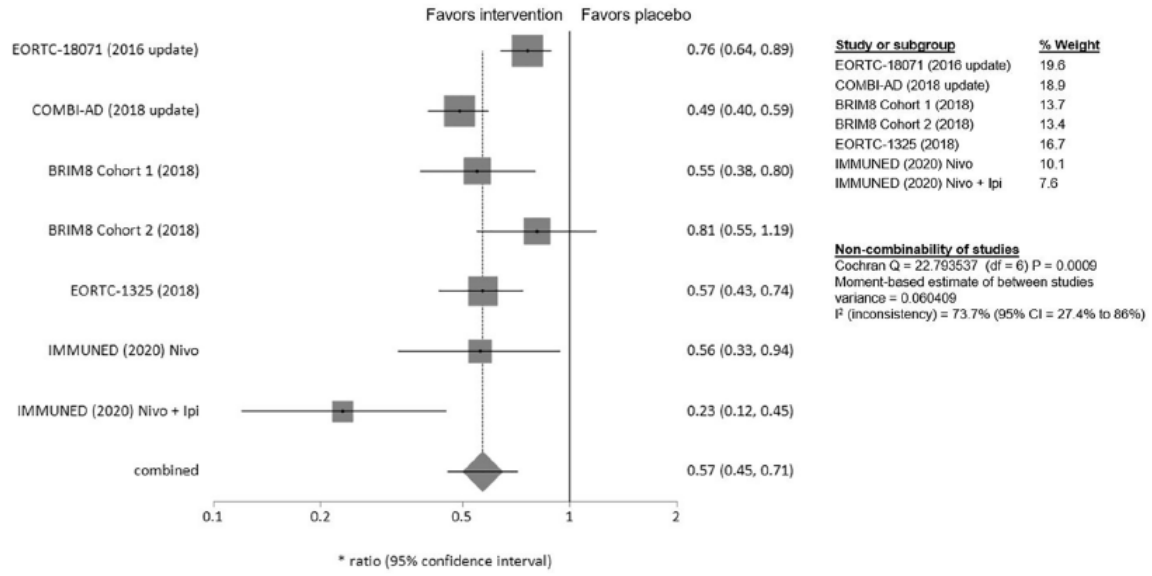

Abbildung 3: Forest plot for primary outcome analysis on relapse free survival

- Subgroup analysis of Stage
  - In stage IIIA, while none of the examined substances alone reach statistical significance in the corresponding trials, our metaanalysis demonstrates a clear RFS-benefit for treatment versus placebo in stage IIIA, which in fact is numerically equivalent to that shown for stages IIIB/C.
  - Dabrafenib/trametinib were associated with a consistent improvement in RFS, apart from stage IIIA where the upper confidence interval is marginally crossed (HR 0.58; 95% CI= 0.32–1.06).
  - In contrast, ipilimumab had limited efficacy in patients with stage IIIA/B whereas a clear benefit with treatment was seen only in stage IIIC with >4 LN (HR 0.48; 95%CI= 0.28–0.81).
  - Consistently, pembrolizumab also demonstrated a non-statistically significant benefit in stage IIIA (HR 0.38; 95%CI= 0.11–1.31) while higher stages (IIIB/C) clearly profit from adjuvant pembrolizumab treatment.

- The BRIM8 trial was the only to include patients with stage IIC. Here, median RFS was not reached in the vemurafenib arm.

- Adverse Events ⇨ siehe Anhang Tabelle 4
  - The highest rate of grades 3-4 adverse events (AE) was observed with the nivolumab/ipilimumab combination (82%) with a treatment discontinuation rate of up to 62%.
  - Ipilimumab monotherapy and vemurafenib were also associated with high grade 3-4 AE rates (54% and 59%, respectively) and discontinuation rates of 52% and 20%, respectively. Five deaths were attributed to ipilimumab monotherapy.
  - 26% of patients treated with dabrafenib/trametinib went off study due to AE. One fatal serious AE (pneumonia) was reported in the combination-therapy group.
  - In the EORTC-1325 trial, 13.8% of the patients discontinued pembrolizumab due to AE, which were equal to or higher than grade 3 in 31.6% of cases.
  - Similar AE rates were observed with nivolumab monotherapy, with grades 3-4 toxicity up to 41% and 13% treatment discontinuation rate

Anmerkung/Fazit der Autoren

Adjuvant therapy should not be withheld on account of advanced age or stage IIIA alone. The presence of a BRAF mutation is prognostically favorable in terms of RFS. BRAF/MEK inhibitors should be preferred in the adjuvant treatment of BRAF-mutant non-ulcerated melanoma.

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Lorenzi M et al., 2019 [3].

An indirect treatment comparison of the efficacy of pembrolizumab versus competing regimens for the adjuvant treatment of stage III melanoma

Fragestellung

[…] to compare the relative efficacy, specifically RFS, […] of pembrolizumab to additional competing interventions for the adjuvant treatment of high-risk stage III melanoma patients […].

Methodik

Population:

stage III melanoma patients

Intervention:

- Pembrolizumab, Interferon (IFN)-α2a
- IFN-α2b
- Pegylated IFN-α2b
- Nivolumab
- Ipilimumab
- Dabrafenib in combination with trametinib
- Temozolomide in combination with cisplatin
- Vemurafenib

Komparator:

- Placebo or best supportive care (BSC)
- Any intervention of interest as monotherapy or in combination
- Any treatment that facilitates an indirect treatment comparison

Endpunkte:

Recurrence-free (or relapse-free) survival (RFS)

Recherche/Suchzeitraum:

A systematic literature review (SLR) was performed using OVID MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The final date for the literature searches was February 8, 2018.

In addition, 2016 and 2017 conference proceedings from the European Society of Medical Oncology (ESMO), The Society of Melanoma Research (SMR), Society of Immunotherapy of Cancer (SITC), American Association for Cancer Research (AACR), and the American Society of Clinical Oncology (ASCO) were searched. A hand search of the US National Institutes of Health Clinical Trials Registry was also performed.

Qualitätsbewertung der Studien:

Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- […] 23 included publications corresponded to 12 unique trials.
- Included studies formed a connected network of evidence composed of eight trials.

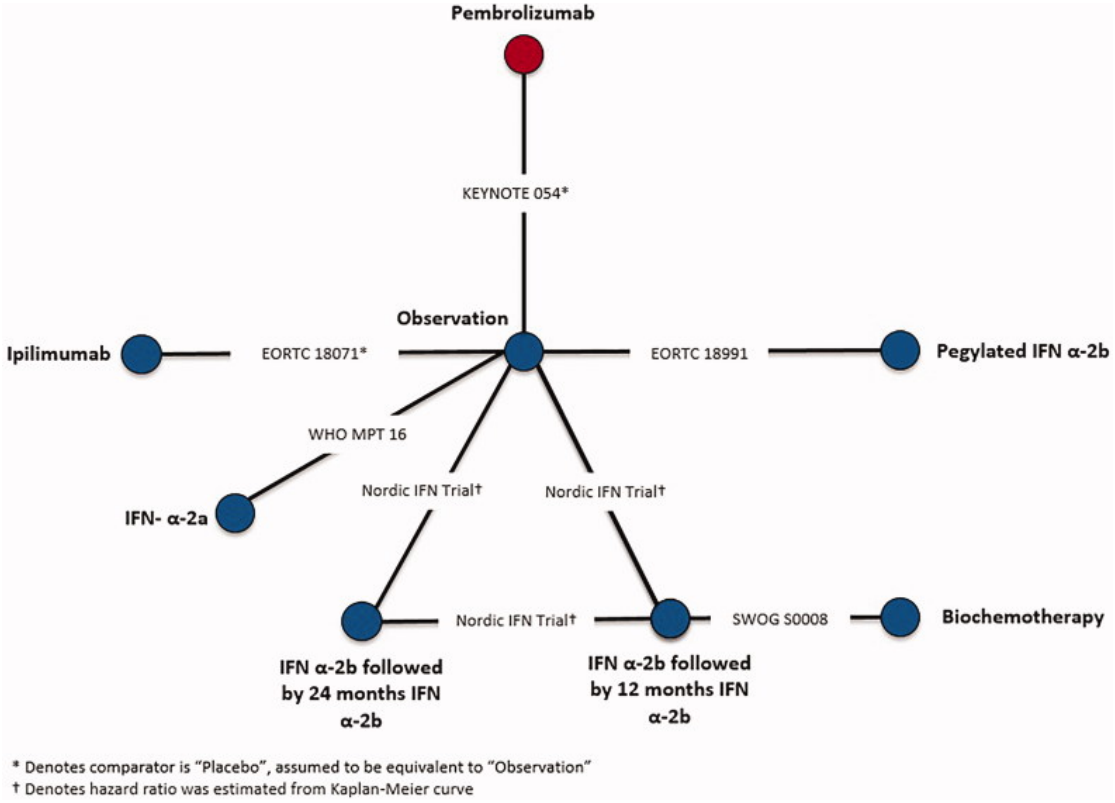

Abbildung 1: Network of evidence for recurrence-free survival, stage III

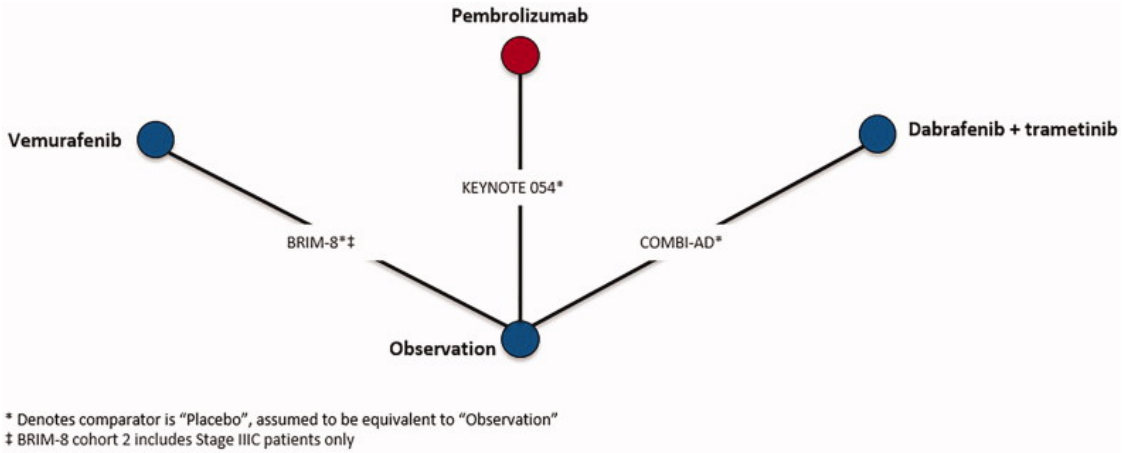

Abbildung 2: Network of evidence for recurrence-free survival, BRAF+ subgroup

Charakteristika der Population: ⇨ siehe Anhang Tabelle 5

Qualität der Studien: ⇨ siehe Anhang Tabelle 6

Studienergebnisse:

- For RFS in stage III melanoma patients, the HR for pembrolizumab vs observation decreased significantly over time. The superiority of pembrolizumab vs observation became statistically meaningful by 3 months.
- The HRs for biochemotherapy and IFN-α2b (12 months) vs observation increased significantly over time […].

- After 9 months of follow-up, pembrolizumab vs observation was statistically differentiated from all regimens in the network except biochemotherapy and ipilimumab as evidenced by no longer overlapping 95% CrIs.
- Although pembrolizumab was not statistically differentiated from ipilimumab, due to overlapping 95% CrIs throughout all follow-up, and point estimate HRs for both pembrolizumab and ipilimumab are statistically significant after 15 months, pembrolizumab had much lower HR point estimates compared with ipilimumab vs observation.
- Furthermore, all IFN-containing regimens are no longer statistically significantly better than observation after 12 months as shown by their associated 95% CrIs […].

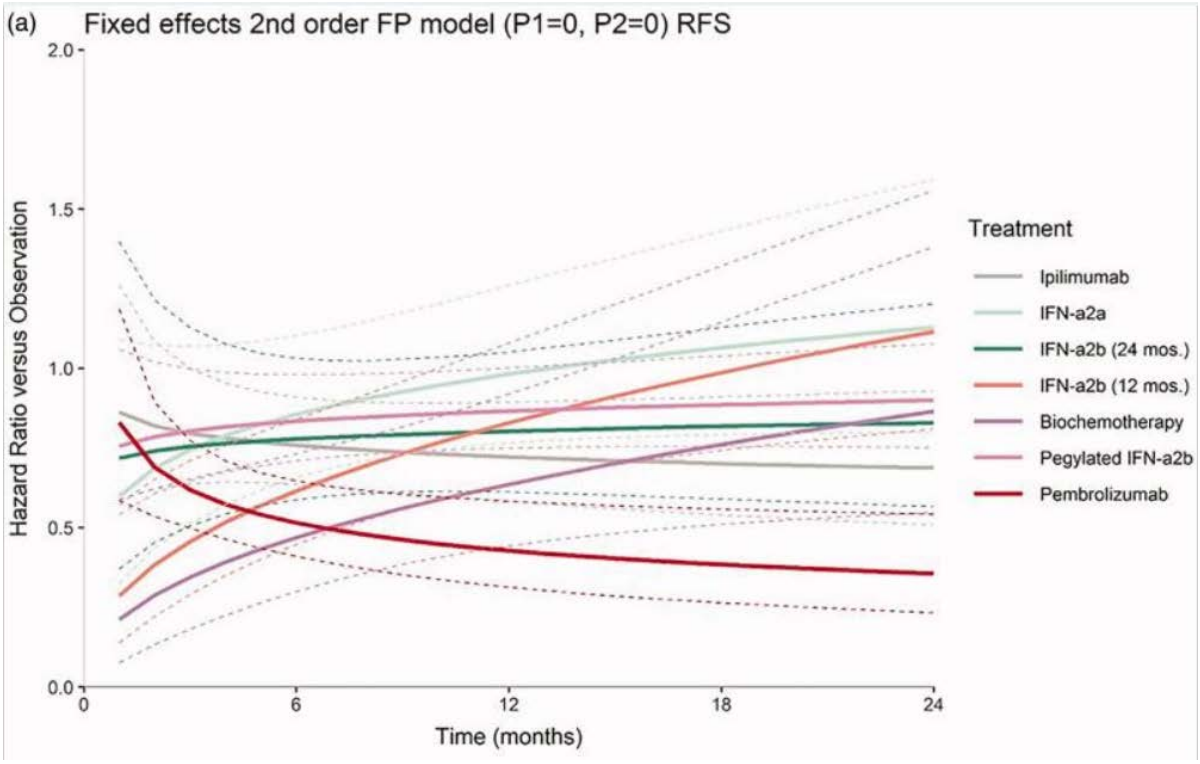

Abbildung 3: Results of fixed-effects time-varying hazards network meta-analyses for recurrence-free survival in Stage III melanoma patients with treatment effects as hazard ratio over time relative to observation under the best-fitting second order fractional polynomial model, (p1 = 0, p2 = 0)

Tabelle 1: Time-varying hazard ratios of recurrence-free survival at select follow-up times for competing interventions vs observation, Stage III

Months	HR vs observation (95% CrI)						
	Pembrolizumab	Ipilimumab	Biochemotherapy	Interferon-α2a	Interferon-α2b (12 months)	Interferon-α2b (24 months)	Pegylated Interferon-α2b
3	0.62 (0.50–0.77)*	0.80 (0.64–1.00)	0.34 (0.18–0.65)*	0.74 (0.51–1.07)	0.46 (0.29–0.71)*	0.75 (0.51–1.13)	0.80 (0.65–1.00)
6	0.51 (0.41–0.65)*	0.76 (0.63–0.91)*	0.47 (0.30–0.73)*	0.85 (0.66–1.10)	0.61 (0.45–0.84)*	0.78 (0.59–1.03)	0.83 (0.71–0.98)*
9	0.46 (0.35–0.61)*	0.74 (0.61–0.89)*	0.56 (0.38–0.82)*	0.93 (0.73–1.17)	0.73 (0.56–0.96)*	0.79 (0.61–1.03)	0.85 (0.74–0.98)*
12	0.43 (0.32–0.58)*	0.72 (0.58–0.89)*	0.64 (0.44–0.92)*	0.98 (0.76–1.26)	0.83 (0.64–1.08)	0.80 (0.61–1.05)	0.87 (0.75–1.00)
15	0.40 (0.29–0.57)*	0.71 (0.56–0.90)*	0.70 (0.48–1.03)	1.03 (0.78–1.34)	0.91 (0.70–1.20)	0.81 (0.60–1.09)	0.88 (0.75–1.02)
18	0.39 (0.27–0.56)*	0.70 (0.54–0.91)*	0.76 (0.51–1.14)	1.06 (0.79–1.43)	0.99 (0.74–1.32)	0.82 (0.59–1.13)	0.88 (0.75–1.04)
21	0.37 (0.25–0.55)*	0.69 (0.52–0.92)*	0.81 (0.53–1.26)	1.10 (0.80–1.51)	1.05 (0.78–1.44)	0.82 (0.58–1.17)	0.89 (0.75–1.06)
24	0.36 (0.23–0.54)*	0.69 (0.51–0.93)*	0.86 (0.55–1.38)	1.13 (0.80–1.59)	1.12 (0.81–1.56)	0.83 (0.57–1.20)	0.90 (0.75–1.08)

*Statistically significant results.

- In BRAF+ patients, HR point estimates for pembrolizumab were statistically superior to observation for the follow-up months […].
- […] HRs for pembrolizumab vs observation did not statistically vary over time in BRAF+ patients. Therefore, pembrolizumab vs observation does not violate the proportional hazards assumption.
- […] the increase in HRs of both BRAF-inhibitors vs observation over time was statistically important […]. Because the HRs of both BRAF inhibitors increased significantly across all follow-up time, there was a statistical advantage for pembrolizumab vs the BRAF inhibitors after 15 months, as determined by no longer overlapping 95% CrIs between pembrolizumab and BRAF inhibitors vs observation.
- Additionally, […] pembrolizumab offers improved RFS compared to both BRAF inhibitors. Specifically, HRs at time-points after 12 months show that pembrolizumab offers statistically significantly better RFS than observation, whereas both BRAF-inhibitors do not.
- By 24 months, both BRAF inhibitors are statistically inferior to observation […].

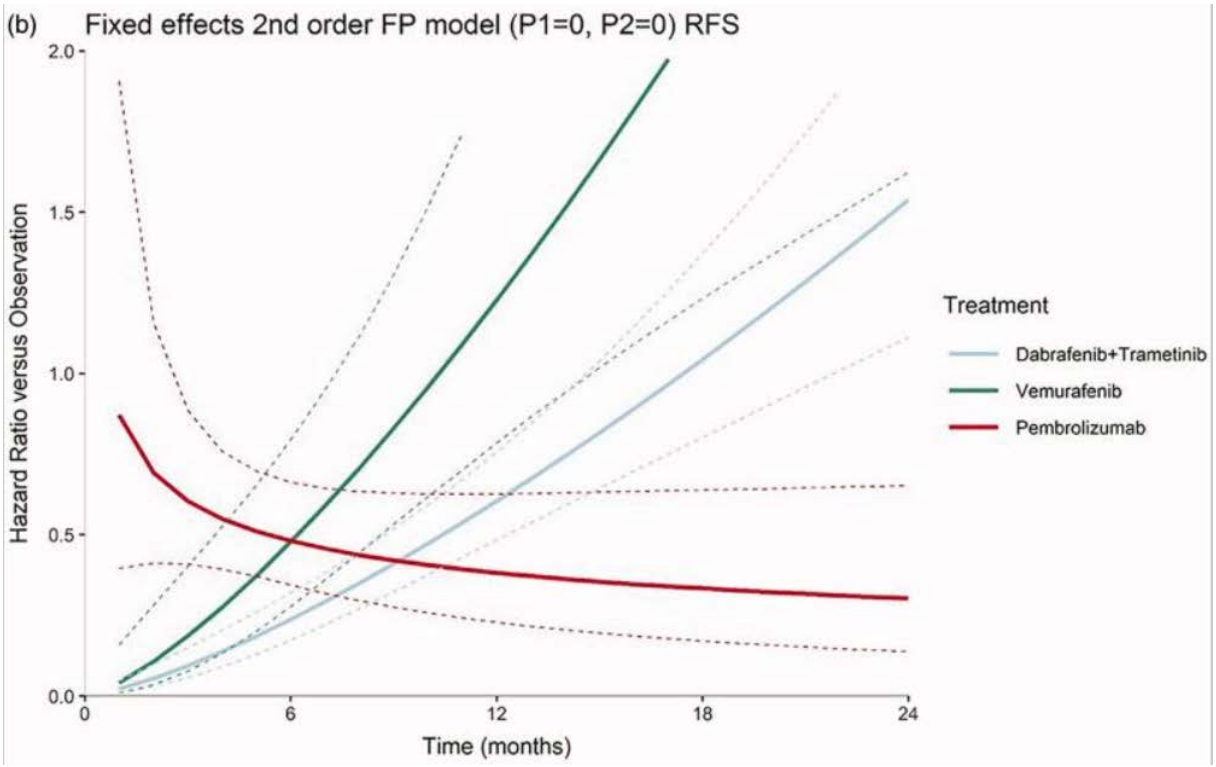

Abbildung 4: Results of fixed-effects time-varying hazards network meta-analyses for recurrence-free survival in BRAF+ melanoma patients with treatment effects as hazard ratio over time relative to observation under the best-fitting 2nd order fractional polynomial model (p1 = 0, p2 = 0)

Tabelle 2: Time-varying hazard ratios of recurrence-free survival at select follow-up times for competing interventions vs observation, BRAF+ subgroup analysis

Months	HR vs observation (95% CrI)		
	Pembrolizumab	Dabrafenib + trametinib	Vemurafenib
3	0.60 (0.41–0.89)*	0.09 (0.06–0.15)*	0.19 (0.08–0.40)*
6	0.48 (0.34–0.66)*	0.24 (0.17–0.32)*	0.48 (0.28–0.79)*
9	0.42 (0.28–0.63)*	0.41 (0.32–0.52)*	0.83 (0.53–1.31)
12	0.38 (0.23–0.63)*	0.60 (0.48–0.76)*	1.23 (0.78–2.00)
15	0.35 (0.19–0.63)*	0.82 (0.64–1.04)	1.66 (1.02–2.90)*
18	0.33 (0.17–0.64)*	1.04 (0.80–1.37)	2.13 (1.23–4.00)*
21	0.32 (0.15–0.65)*	1.28 (0.96–1.74)	2.63 (1.43–5.28)*
24	0.30 (0.14–0.65)*	1.54 (1.11–2.16)*	3.16 (1.62–6.77)*

*Statistically significant results.

Anmerkung/Fazit der Autoren

Standard treatment for patients with primary melanoma with or without regional metastases to lymph nodes is surgery followed by adjuvant therapy, but lack of direct evidence comparing standard of care treatment options with newer treatment options, such as immunotherapy, prevents adequate assessment of relative treatment efficacy in patients with higher-risk of recurrent melanoma.

This analysis shows RFS benefit provided by pembrolizumab monotherapy over standard of care agents for the adjuvant treatment of stage III melanoma, overall, and for BRAF+, with the benefit over competing interventions increasing over time.

Kommentare zum Review

Four trials were removed after the feasibility assessment, to ensure a homogeneous evidence base: Caraceni 1998, CheckMate 238, Lian 2013, and EORTC 18952.

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Sharma R et al., 2019 [8].

Comparative efficacy and safety of dabrafenib in combination with trametinib versus competing adjuvant therapies for high-risk melanoma.

Fragestellung

To conduct a systematic literature review of high-risk resectable cutaneous melanoma adjuvant therapeutics and compare safety and efficacy.

Methodik

Population:

- patients with completely resected, BRAFV600E/K mutation-positive, high-risk cutaneous melanoma. High-risk cutaneous melanoma was defined a priori as patients with stage IIB, IIC and IIIA–C cutaneous melanoma

Intervention/Komparator:

- dabrafenib plus trametinib (DAB + TRAM), nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy and interferons

Endpunkte:

- overall survival (OS), relapse-free survival, distant metastasis-free survival and safety

Recherche/Suchzeitraum:

- from inception until 13 July 2017, and were later updated on 27 July 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 37 studies that met the study eligibility criteria. 13 studies included patients with stage II–III disease, seven studies included patients with stage III disease only, three studies included patients with stage III–IV disease and one study included patients with stage II–IV disease.
- Of the 37 included studies, nine studies included a mix of stage II–IV patients and did not report on results for the study defined high-risk melanoma subgroup (matched AJCC-7 IIB–C and IIIA–C) and hence, were excluded from the dataset.

Charakteristika der Population:

- Performance score was required to be ECOG 0-2, ECOG 0-1, Karnofsky ≥70% and Karnofsky ≥80%, in one, 16, two and one studies, respectively. The median age across trials ranged from 38 to 56 years with proportion of males between 50 and 65%.

Qualität der Studien:

- Overall, the trials were considered to have low risk of bias

Studienergebnisse:

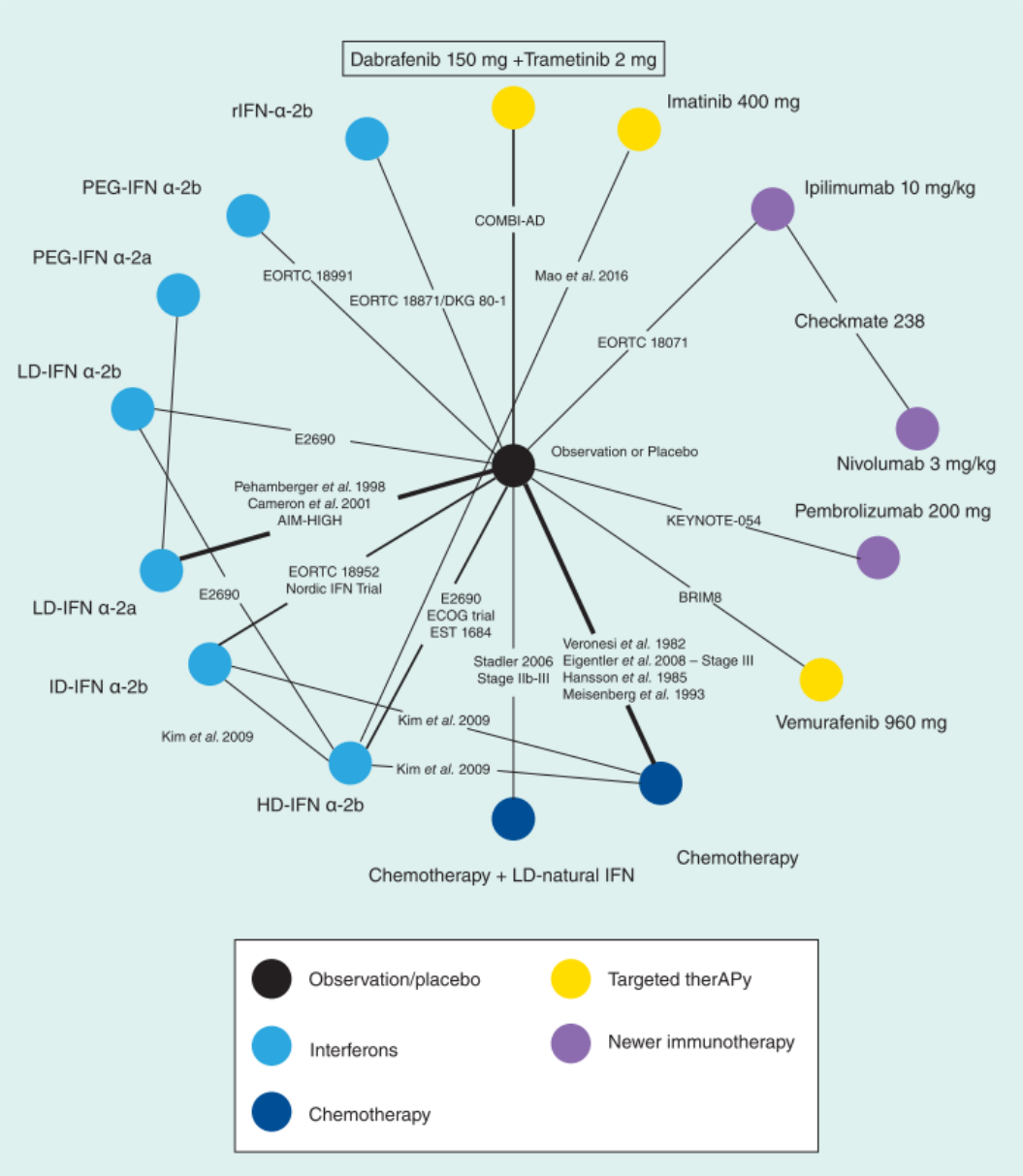

Figure 2. Network of evidence for high-risk melanoma (American Joint Committee on Cancer-7 IIB–C and IIIA–C) independent of *BRAF* mutation status, irrespective of outcomes of interest. The details of interferon dose categories are presented in Supplementary Data.
HD: High dose; ID: Intermediate dose; IFN: Interferon; LD: Low-dose; PEG: Pegylated; rIFN: Recombinant interferon.

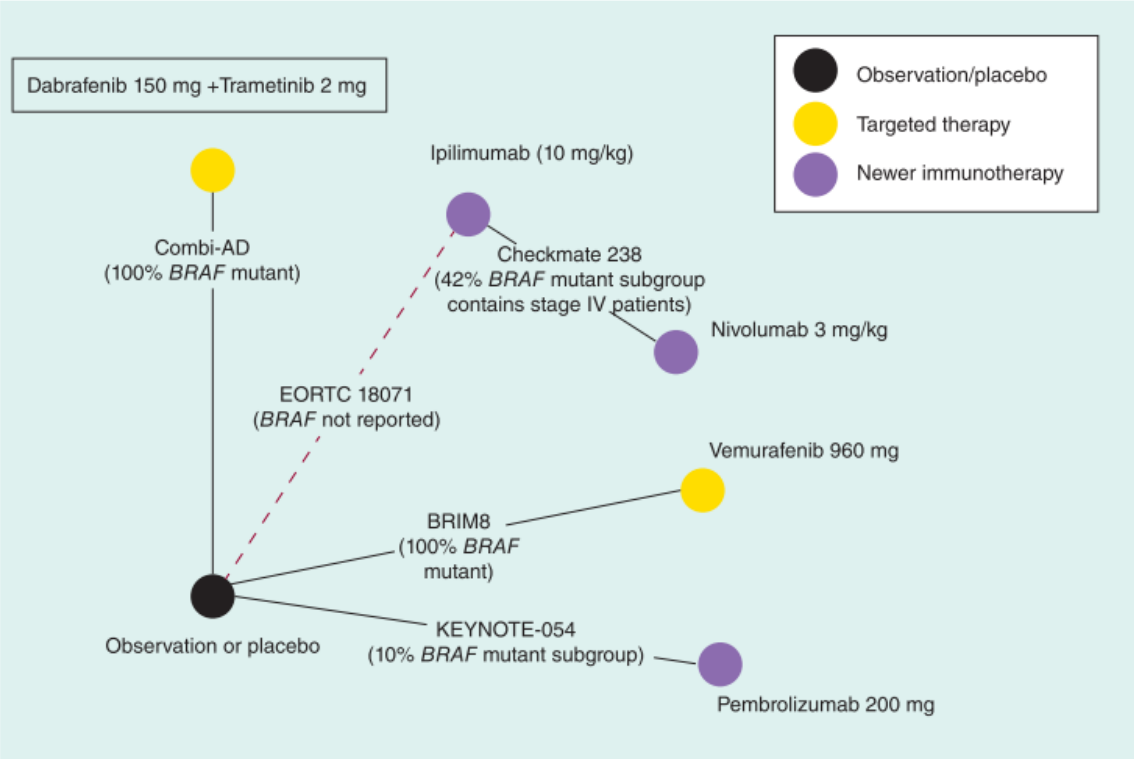

Figure 3. High-risk (American Joint Committee on Cancer-7 IIB–C and IIIA–C) melanoma *BRAF* mutation positive status – network of randomized controlled trials for relapse-free survival/disease-free survival; subgroup analysis.
The dotted line in red represents connection via EORTC 18071 study comparing ipilimumab and placebo; however, *BRAF* mutation status was unknown in these patients.

- Across relapse-free survival, distant metastasis-free survival and OS, DAB + TRAM had the lowest estimated hazards of respective events relative to all other treatments (exception relative to nivolumab in OS).
- Differences were significant relative to placebo, chemotherapy, interferons and ipilimumab.
- AE/SAE: The odds of experiencing any AE were statistically significantly higher with dabrafenib plus trametinib relative to placebo (OR: 4.52; 95% credible interval [CrI]: 2.47–8.93) and pembrolizumab (OR: 3.00; 95% CrI: 1.39–6.73) while being statistically significantly lower than with vemurafenib (OR: 0.11; 95% CrI: 0.01–0.68). It was comparable with nivolumab and ipilimumab. There were also higher odds of SAEs with dabrafenib plus trametinib when compared with placebo (OR: 4.92; 95% CrI: 3.44–7.21) and nivolumab (OR: 4.51; 95% CrI: 2.61–7.89).

Anmerkung/Fazit der Autoren

The results from NMA suggested that adjuvant therapy with dabrafenib plus trametinib significantly prolongs the survival outcomes in high-risk resected cutaneous melanoma compared with interferon, ipilimumab and chemotherapy while the combination is comparable in efficacy to nivolumab and pembrolizumab. Further investigations from direct head-to head trials will be needed to confirm the results.

3.3 Leitlinien

Seth R et al., 2020 [7].

American Society of Clinical Oncology

Systemic Therapy for Melanoma: ASCO Guideline

Zielsetzung/Fragestellung

To provide guidance to clinicians regarding the use of systemic therapy for melanoma:

(1) What neoadjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with cutaneous melanoma eligible for resection?

(2) What adjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with resected (stage II, III, IV) cutaneous melanoma?

(3) What systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with unresectable/metastatic cutaneous melanoma?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium (Expert Panel of medical, radiation, surgical and community oncologists as well as two patient representatives and an ASCO guidelines staff member with health research methodology expertise);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Erstellung der Empfehlungen zum Teil auf Basis der Guidelines Into Decision Support (GLIDES) methodology,
- je nach Fragestellung, vorliegender Evidenz werden formale und informale Konsensusprozesse genutzt
- externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed and the Cochrane Trial Registry were searched in October 2018, Update of Pubmed search in June 2019

LoE

Rating	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.

GoR

Type of Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement.
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Sonstige Hinweise

- All references to stage in these recommendations refer to stage determined by the eighth edition American Joint Committee on Cancer (AJCC) criteria unless otherwise noted.

Empfehlungen

What adjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with resected (stage II, III, IV) cutaneous melanoma? Are there subpopulations of patients (eg, clinical features, biomarker status, lymph node dissection v sentinel lymph nodes) who benefit more or less from those options?

Recommendation 2.1

- Adjuvant pembrolizumab, nivolumab, or combination dabrafenib and trametinib therapy should not be offered to patients with resected stage II melanoma outside of enrollment in a clinical trial (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).
  - Literature review and analysis. No positive trials (notably, BRIM8 included patients with stage IIC BRAF-mutant melanoma) were identified that inform treatment in stage II disease.
  - Clinical interpretation. In the absence of data, therapy with these agents cannot be recommended. Participation in a suitable clinical trial is favored.
- Recommendation 2.2
  - For patients with resected stage IIIA/B/C/D disease that is BRAF wild type, the following options should be offered (in no particular order): nivolumab x 52 weeks OR pembrolizumab x 52 weeks. Ipilimumab and high-dose interferon are not recommended for routine use in adjuvant therapy. See Table 2 for recommended dosing and scheduling details (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).
  - Clinical interpretation: While the Suciu et al. (13) metaanalysis did demonstrate significant benefits in terms of RFS and OS for IFN compared with observation, these benefits were limited when compared with more recently available agents, and the Expert Panel believes that the benefits are outweighed by the known toxicity of IFN (Data Supplement Table 5). The results of trials of different forms of IFN (eg, high dose) were not interpretable and did not lead to any new recommendation. Therefore, the Expert Panel determined that IFN could not be recommended. The EORTC 18071 study found ipilimumab to be superior to placebo in terms of RFS and OS. However, Checkmate 238 found nivolumab superior to ipilimumab with regard to RFS and with lower toxicity. Given these data, adjuvant ipilimumab can no longer be recommended as the preferred form of adjuvant immunotherapy. Nivolumab is recommended on the basis of the Checkmate 238 trial results. EORTC 1325/Keynote 054 found that pembrolizumab was superior to placebo in RFS. In addition, the Expert Panel believes that the RFS benefit and toxicity found in that trial are comparable to those found with nivolumab in the Checkmate 238 trial. Given this assessment, because there is no head-to-head comparison of nivolumab versus pembrolizumab, pembrolizumab is a valid treatment option. In both adjuvant trials of pembrolizumab/nivolumab, all enrolled patients had a complete lymphadenectomy; further discussion of this topic can be found in the Other Considerations section for Clinical Question 2. The Expert Panel does not believe this affects the strength of the recommendation for these agents, nor does the change in the staging system to the eighth edition AJCC affect any of the adjuvant recommendations.
- Recommendation 2.3
  - For patients with resected stage IIIA/B/C/D BRAF-mutant (V600E/K*) disease, the following therapy options should be offered (in no particular order): nivolumab x 52 weeks OR pembrolizumab x 52 weeks OR dabrafenib plus trametinib x 52 weeks. See

Table 2 for reasonable dosing and scheduling details (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

- Clinical interpretation: The agents described in Recommendation 2.2 are valid treatment options for BRAF V600E/K–mutant melanoma, but the results of the COMBI-AD trial indicate that dabrafenib plus trametinib is also a valid option for those patients and provide preliminary evidence of an OS benefit. In the absence of head-to-head comparisons of the efficacy of these agents in this population, either (anti-PD1 or dabrafenib plus trametinib) of these treatment options can be considered, although severe (grade$ 3) treatment-related toxicity was reportedly higher with dabrafenib and trametinib (41%) as compared with nivolumab (14.4%) or pembrolizumab (14.7%). Additionally, the treatment discontinuation rate was higher in COMBI-AD (26%) than in Checkmate 238 (8%) or Keynote 054 (10%).

- Recommendation 2.4
  - No recommendation can be made for or against dabrafenib plus trametinib in patients with resected stage III/IV melanoma with BRAF mutations other than V600E/K (Type: No recommendation; Evidence quality: Low; Strength of recommendation: Not applicable).
  - Clinical interpretation: In the absence of data on other BRAF mutations, dabrafenib plus trametinib cannot be specifically recommended for these patients.

Referenzen aus Leitlinien

13. Suciu S, Eggermont AMM, Lorigan P, et al: Relapse-free survival as a surrogate for overall survival in the evaluation of stage II-III melanoma adjuvant therapy. J Natl Cancer Inst 110:87-96, 2018

Cancer Council Australia. Melanoma Guidelines Working Party, 2020 [4].

Clinical practice guidelines for the diagnosis and management of melanoma.

Zielsetzung/Fragestellung

The purpose of evidence-based clinical guidelines for the management of any medical condition is to achieve early diagnosis whenever possible, make doctors and patients aware of the most effective treatment options, and minimise the financial burden on the health system by documenting investigations and therapies that are inappropriate.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse erwähnt, aber nicht näher beschrieben; externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Basiert auf Adaptation und Aktualisierung der systematischen Reviews für die deutsche S3-Leitlinie
- Bezüglich der adjuvanten systemischen Therapie: Suche in Cochrane Library (Feb 2017), Embase (Feb 2017), Pubmed (März 2018) , Trip (Feb 2017)

LoE

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study

III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

GoR

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Type of recommendation	Definition
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Sonstige Hinweise

- Leitlinie ist ausschließlich als online Version verfügbar, letztes Update der Abschnitte zur systemsichen, adjuvanten Therapie im August 2018

What is the role of adjuvant systemic therapy in patients with resected stage II and stage III melanoma?

Evidence summary	Level	References
Combination dabrafenib and trametinib treatment for one year in resected IIIA (nodal deposit >1mm diameter), IIIB, IIIC BRAF V600E/K melanoma improves RFS compared to placebo (HR 0.47; P<0.001).	II	[2]
Nivolumab for one year in resected IIIB, IIIC, IV melanoma improves RFS compared to ipilimumab (10mg/kg) (HR 0.65; P<0.001).	II	[3]
Pembrolizumab for one year in resected IIIA (nodal deposit >1mm diameter), IIIB, IIIC melanoma improves RFS compared to placebo (HR 0.57; P<0.001).	II	[17]
Ipilimumab (10mg/kg for 4 doses followed by 3 monthly maintenance treatment for 3 years) in resected IIIA (nodal deposit >1mm diameter), IIIB, IIIC melanoma improves RFS (HR 0.76, P<0.001) and OS (HR 0.72; P=0.001) compared to placebo.	II	[5]
Adjuvant IFN-α in resected stage II, III melanoma improves RFS (HR 0.83; P<0.00001) and overall survival (HR 0.91; P=0.003) compared to observation.	I	[9]

Evidence-based recommendation?	Grade
Outside of a clinical trial adjuvant systemic therapy is not recommended for patients with resected stage II melanoma.	C

Is adjuvant radiotherapy of value following resection of involved lymph nodes?

Evidence summary	Level	References
Adjuvant RT following therapeutic lymph node dissection decreased the risk of locoregional recurrence but did not improve survival compared with surgery alone.	II	[1]
Adjuvant RT following therapeutic lymph node dissection increased late toxicity, especially soft tissue fibrosis in the treated lymph node basin and leg oedema after groin irradiation.	II	[2]

Evidence-based recommendation?	Grade
Adjuvant RT following regional lymph node dissection may be considered following histopathological identification of high risk features if potentially effective systemic therapy is not available.	B

Practice point[?]

Patients at high risk of locoregional recurrence are also at high risk of distant metastases. The decision to recommend adjuvant RT should be made in a multidisciplinary forum where all options for further local and systemic therapy are addressed. In particular, the role of local treatments including adjuvant RT is changing rapidly as effective systemic therapies become available.

Practice point[?]

Adjuvant RT may be considered also for (i) positive margins (ii) after therapeutic dissection where further surgical clearance is not feasible (eg parotid) and (iii) further recurrence after surgery.

How should melanoma in children be managed?

Practice point[?]

All facets of melanoma treatment and follow-up in adults may be integrated into the treatment and follow-up of children. Parents may be assured that survival in children is at least equivalent and probably better than it is in adults with the same stage of disease.

Leitlinienprogramm Onkologie (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe), 2018 [2].

AWMF, DKG, DKH

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms; Langfassung, Version 3.3. Last Updated: 07.2020

Zielsetzung/Fragestellung

Ziel der S3-Leitlinie Melanom ist es, den onkologisch tätigen Ärzten in der Praxis und Klinik eine akzeptierte, evidenzbasierte Entscheidungshilfe für die Auswahl sowie Durchführung von geeigneten Maßnahmen zur Diagnostik und Therapie und Nachsorge des kutanen Melanoms zur Verfügung zu stellen. Die systematische Darstellung von Studienergebnissen hinsichtlich Nutzen und Risiken soll Ärzte wie auch Patienten in der Entscheidungsfindung unterstützen.

Updates:

Oktober 2019 – Version 3.2: Komplette Überarbeitung des Kapitels zur adjuvanten Therapie im Rahmen eines Amendments (siehe Einleitung).

Juli 2020 – Version 3.3: Ausschließlich redaktionelle Korrekturen nach umfangreichem Lektorat.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Das Kapitel 6.4: Adjuvante medikamentöse Therapie wurde neu strukturiert. Dazu wurden neue Schlüsselfragen definiert, die nicht mehr die einzelnen Substanzen expliziert thematisierten, sondern klinische Indikationssituationen (adjuvante Therapie im Stadium II, im Stadium III und im Stadium IV(NED)). Zudem wurde eine Schlüsselfrage zur Lebensqualität in der adjuvanten Therapie aufgenommen. Die Schlüsselfragen wurden bei Präsenztreffen der Mandatsträger im Januar 2018 konsentiert. Basierend auf diesen Schlüsselfragen wurde die Suchstrategie für diese Indikationssituation definiert und die Literatursuche durchgeführt.
- LoE

Level	Therapie/Prävention, Ätiologie/Nebenwirkungen
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“

GoR

Tabelle 2: Schema der Empfehlungsgraduierung

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

6. Diagnostik und Therapie bei lokoregionaler Metastasierung

6.3 Adjuvante Radiotherapie nach Lymphadenektomie

6.3. Adjuvante Radiotherapie nach Lymphadenektomie

6.26.	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad **B**	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, • Lymphogenes Rezidiv	
Level of Evidence **1b**	De-Novo-Recherche: [370-383]	
	Konsensstärke: 76%	

6.27.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad **A**	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.	
Level of Evidence **2b**	De-novo-Recherche: [370-378]	
	Konsensstärke: 100%	

6.28.	Evidenzbasiertes Statement	geprüft 2018
Level of Evidence **1b**	Ein positiver Einfluss einer postoperativen adjuvanten Radiotherapie des regionalen Lymphabflussgebietes auf die Überlebenszeit ist bisher nicht belegt worden.	
	De-novo-Recherche: [370-383]	
	Konsensstärke: 100%	

6.4. Adjuvante medikamentöse Therapie

6.29.	Konsensbasiertes Statement	geprüft 2019
EK	In der adjuvanten Therapie ist der relevante Endpunkt für eine Nutzenbewertung das Gesamtüberleben.	
	Konsensstärke: 85,7 %	

6.4.1. Adjuvante Therapie im Stadium II

6.30.	Evidenzbasierte Empfehlung	geprüft 2019
Empfehlungsgrad **0**	Patienten im Stadium IIA kann eine niedrig dosierte adjuvante Interferontherapie angeboten werden.	
Level of Evidence **1b**	De-novo-Recherche: [387, 388]	
	Konsensstärke: 93,8 %	

6.31.	Evidenzbasierte Empfehlung	geprüft 2019
Empfehlungsgrad **A**	Patienten im Tumorstadium IIB/C soll eine adjuvante Interferontherapie angeboten werden.	
Level of Evidence **1a**	De-novo-Recherche: [389-395]	
	Konsensstärke: 93,8 %	

6.32.	Konsensusbasiertes Statement	geprüft 2019
EK	Das individuelle Therapieschema sollte unter sorgfältiger Abwägung von zu erwartendem Benefit und möglichen Nebenwirkungen und Einschränkungen der Lebensqualität mit betroffenen Patienten diskutiert werden.	
	Konsensstärke:100,0 %	

6.33.	Evidenzbasierte Empfehlung	geprüft 2019
Empfehlungsgrad **0**	Patienten mit hohem Metastasierungsrisiko können ausschließlich nachbeobachtet werden, sofern zuvor die adjuvanten Therapiemöglichkeiten diskutiert wurden.	
Level of Evidence **1a**	De-novo-Recherche: [389-394, 396]	
	Konsensstärke: 89,5 %	

6.4.2. Adjuvante Therapie im Stadium III/IV (NED)

6.34.	Evidenzbasierte Empfehlung	neu 2019
Empfehlungsgrad **A**	Patienten im AJCC 2017 Tumorstadium III A-D soll eine adjuvante Therapie mit einem anti-PD1-Antikörper angeboten werden.	
Level of Evidence **1b**	De-novo-Recherche: [407, 408]	
	Konsensstärke: 100,0 %	

6.35.	Evidenzbasierte Empfehlung	neu 2019
Empfehlungsgrad **A**	Patienten im AJCC 2017 Tumorstadium III A-D mit einer BRAF V600E oder V600K Mutation soll eine adjuvante Therapie mit einem BRAF- und MEK-Inhibitor angeboten werden.	
Level of Evidence **1b**	De-novo-Recherche: [409]	
	Konsensstärke: 100,0 %	

6.36.	Evidenzbasierte Empfehlung	neu 2019
Empfehlungsgrad **A**	Patienten im AJCC 2017 Tumorstadium IV (NED) soll eine adjuvante Therapie mit einem anti-PD1-Antikörper angeboten werden.	
Level of Evidence **1b**	De-novo-Recherche: [408]	
	Konsensstärke: 100,0 %	

6.4.5. Lebensqualität unter einer adjuvanten Therapie

6.38.	Evidenzbasiertes Statement	neu 2019
Level of Evidence **1b**	Daten zur Lebensqualität sind aus den Phase III Studien zur adjuvanten Therapie mit Interferon-alpha publiziert worden. Dabei berichteten die meisten Studien über eine Verschlechterung der Lebensqualität unter Therapie. Nach Beendigung der Therapie erreicht die Lebensqualität i.d.R. wieder den Ausgangwert. Für Ipilimumab zeigte sich trotz vieler Therapieabbrüche aufgrund unerwünschter Ereignisse keine Verschlechterung der Lebensqualität gegenüber Placebo.	
	De-novo-Recherche: [421-432]	
	Konsensstärke: 100,0 %	

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Scottish Intercollegiate Guidelines Network (SIGN), 2017 [6] (siehe auch: 3-year scoping report [5,6].

SIGN

Cutaneous melanoma: a national clinical guideline

Zielsetzung/Fragestellung

This guideline provides advice at all stages of the patient's pathway of care, from primary prevention to early recognition, treatment and follow up. It does not address melanomas of non-cutaneous origin such as melanomas arising from mucosae, ocular melanomas and other rare non-cutaneous sites.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Informale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert. (Die Gültigkeit der Leitlinie wurde auf 3 Jahre festegelegt)

Recherche/Suchzeitraum:

- Systematische Literaturrecherche (Medline, Embase, Cinahl, PsycINFO and the Cochrane Library) im Zeitraum 2004-2016

LoE

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR

RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

7 Adjuvant treatment of stage II and III melanoma

7.1 ADJUVANT RADIOTHERAPY FOR RESECTED STAGE III MELANOMA

A single randomised phase 3 trial comparing adjuvant radiotherapy and observation was carried out in 250 patients who had undergone complete lymphadenectomy and were thought to be at high risk of local recurrence. Risk of lymph node relapse was significantly reduced in the adjuvant radiotherapy group (hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.32 to 0.98, p=0.041) but no differences were noted for relapse-free or overall survival.[140] Adjuvant radiotherapy is known to be associated with a risk of both short-term (dermatitis) and long-term (lymphoedema) toxicity. Results from trials on long-term radiotherapy complications are awaited. A case series suggested a significant increase in morbidity including lymphoedema rate as a complication of adjuvant radiotherapy.[141] 1++ 3

R **Consider adjuvant radiotherapy for patients with completely resected stage IIIB or IIIC melanoma after discussion of the risk of local recurrence and the benefits and risks of radiotherapy including risk of significant adverse effects.**

Recommendations

7.2 IMMUNOTHERAPY

7.2.1 INTERFERON

The observation that a large number of primary melanomas undergo partial regression and a small number of patients experience total regression of the whole melanoma has led to the concept of using either specific or non-specific immune stimulation as therapy for melanoma.

Adjuvant interferon alpha has been used in at least 10 large RCTs involving over 5,000 patients.[142-151] Interferon dosage, frequency and route of administration and total duration of therapy all varied, but no trial reported significant overall survival benefit for interferon-treated patients. Several of the larger studies do report longer disease-free intervals after surgery[145-147] but there is no evidence of a dose or duration of treatment effect. Toxic effects of interferon include extreme lassitude, muscle aches, headache, rigors, nausea, vomiting, and marrow toxicity, the latter being the cause of death in two patients in the first reported high-dose study. 1++

R **Adjuvant interferon should not be used for patients with AJCC stage II and III melanoma other than in a trial setting.**

A number of well-designed trials of adjuvant immunotherapy (including ipilmumab, nivolumab and pembrolizumab) are ongoing.

2019 - How does this potentially change current recommendations?

SIGN recommends nivolumab monotherapy or ipilimumab/nivolumab combination therapy are recommended for patients with unresectable stage IIIC and IV melanoma.

As above, SIGN could consider adding nivolumab for the treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.

7.3 IMMUNOSUPPRESSION

Numerous studies have investigated the relationship between immunosuppression and melanoma incidence. A poor-quality systematic review of population studies found that compared to the general population, there is a 2.4-fold (95% CI, 2.0 to 2.9) increased incidence of melanoma after transplantation.[152] A meta-analysis also found that inflammatory bowel disease was associated with a 37% increased risk of melanomas compared to the general population.[153] In addition, cohort studies have shown that patients with HIV have an increased risk of melanoma (standardized rate ratio of 2.6 (95% CI, 1.9 to 3.6),[154] patients with a history of non-Hodgkin lymphoma (NHL) have a risk of subsequent melanoma that is increased 1.8 to 2.4 times,[155] and patients with chronic lymphocytic leukaemia (CLL) have an increased risk of 2.3 to 3.1 times that of controls.[156] **1⁻ 2⁺⁺ 2⁺**

Although iatrogenic immunosuppression has been associated with increased risk of malignancy there is little data that is specific to melanoma. A population-based cohort study found that patients with rheumatoid arthritis treated with tumour necrosis factor (TNF) inhibitors had an increased risk of melanoma compared with patients with rheumatoid arthritis not treated with TNF inhibitors (HR 1.5, 95% confidence interval 1.0 to 2.2).[157] A case-control study found that the use of TNF-alpha antagonists was independently associated with an increased melanoma risk in patients with inflammatory bowel disease (OR 1.9, 95% CI, 1.1 to 3.3)[158] however, in a second cohort, the adjusted odds ratio was non-significant (OR 1.3, 95% CI, 0.6 to 2.7).[159] **2⁻**

Several studies have investigated the relationship between immunosuppression and melanoma prognosis. A retrospective review of immunosuppressed transplant patients found that those with thick melanoma (>3 mm) had a significantly poorer melanoma cause-specific survival rate.[160] A second retrospective review found that the outcome for post-transplant patients with melanoma was significantly worse for those with tumours of Breslow thickness >2 mm.[161] A further retrospective review found that patients taking immunosuppressants at the time of diagnosis of melanoma had a higher mortality than controls (42% v 23%, p=0.01) suggesting that immunosuppressive therapy may be associated with a more aggressive disease course.[162] There is limited data on the prognosis for patients who were diagnosed with melanoma before having a transplant.[152] **3 2⁺⁺**

A case-series has described the spontaneous regression of advanced melanoma in patients on long-term azothioprine for autoimmune disease on withdrawal of the immunsuppression.[163] **3**

✓ All patients with melanoma and a history of immunosuppression should have an MDT approach to care and minimising the immunosuppressive therapy should be considered where possible.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews Reviews (Issue 2 of 12, February 2022) am 08.02.2022

#	Suchfrage
1	[mh Melanoma]
2	melanom*:ti,ab,kw
3	(skin* OR cutaneous):ti AND (neoplas* OR tum*r* OR sarcoma* OR cancer* OR malignant):ti
4	{OR #1-#3}
5	#4 with Cochrane Library publication date from Feb 2017 to present

Systematic Reviews in PubMed am 08.02.2022

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

#	Suchfrage
1	melanoma/TH[mh]
2	melanom*[tiab]
3	("skin*"[Ti] OR "cutaneous"[Ti]) AND ("tumor"[Ti] OR "tumors"[Ti] OR "tumour*"[Ti] OR "carcinoma*"[Ti] OR "neoplas*"[Ti] OR "sarcoma*"[Ti] OR "cancer*"[Ti] OR "malignant"[Ti])
4	#2 OR #3
5	(#4) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR

#	Suchfrage
	standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2017/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 08.03.2022

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

#	Suchfrage
1	Melanoma[mh]
2	Melanom*[tiab]
3	("skin*"[Ti] OR "cutaneous"[Ti]) AND ("tumor"[Ti] OR "tumors"[Ti] OR "tumour*"[Ti] OR "carcinoma*"[Ti] OR "neoplas*"[Ti] OR "sarcoma*"[Ti] OR "cancer*"[Ti] OR "malignant"[Ti])
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
6	(((#5) AND ("2017/02/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 08.02.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

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

- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

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

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Anhang

Tabelle 1: Patient characteristics in randomized controlled trials included in network meta-analyses (Toor K et al., 2021 [9].)

Trial ID	Intervention	N	Median age, years (range)	Male, n (%)	Race, n (%)		
					Caucasian	Asian	Hispanic
ECOG 1697[1]	IFN alfa-2b (high-dose)	581	52 (10-85)	336 (58)	547 (94)	0	4 (1)
	Observation	569	52 (19-81)	320 (56)	536 (94)	2 (< 1)	4 (1)
Scottish Study[2]	IFN alfa-2b (low-dose)	47	NR	NR	NR	NR	NR
	Observation	49	NR	NR	NR	NR	NR
WHO Melanoma Programme Trial 16[3]	IFN alfa-2b (low-dose)	225	NR	131 (58)	NR	NR	NR
	Observation	219	NR	114 (52)	NR	NR	NR
EORTC 18071[4]	Ipilimumab	475	51 (20-84)[a]	296 (62)	470 (99)	1 (< 1)	NR
	Placebo	476	52 (18-78)[a]	293 (62)	476 (100)	0	NR
EORTC 18952[5]	IFN alfa-2b (high-dose/13 months)	553	49 (17-74)	312 (56)	NR	NR	NR
	IFN alfa-2b (low-dose/15 months)	556	50 (16-75)	308 (55)	NR	NR	NR
	Observation	279	47 (20-75)	152 (54)	NR	NR	NR
EORTC 18991[6]	PEG IFN alfa-2b	627	50 (19-70)	366 (58)	NR	NR	NR
	Observation	629	50 (18-70)	367 (58)	NR	NR	NR
KEYNOTE-054[7,8]	Pembrolizumab	514	54 (19-83)	324 (63)	NR	NR	NR
	Placebo	505	54 (19-83)	304 (60)	NR	NR	NR
S0008[9]	IFN alfa-2b (high-dose)	203	48 (12-73)	141 (69)	195 (96)	NR	NR
	Other chemotherapy	199	46 (10-74)	141 (71)	190 (95)	NR	NR
Garbe et al. (2008; DeCOG)[10]	IFN alfa-2a (low-dose)	146	NR	92 (63)	NR	NR	NR
	IFN alfa-2a + dacarbazine	148	NR	93 (63)	NR	NR	NR
	Observation	147	NR	85 (58)	NR	NR	NR
COMBI-AD[11]	Dabrafenib + trametinib	435	50 (18-89)	244 (56)	NR	NR	NR
	Placebo	432	51 (20-85)	239 (55)	NR	NR	NR
AIM HIGH Study[12]	IFN alfa-2a (low-dose)	338	51 (16-79)[a]	191 (56)	NR	NR	NR
	Observation	336	52 (15-85)[a]	190 (57)	NR	NR	NR
Nordic IFN Trial[13]	IFN alfa-2b (1 year)	285	53 (18-73)	177 (62)	-	-	-

	IFN alfa-2b (2 years)	286	51 (22-77)	183 (64)	-	-	-
	Observation	284	51 (18-76)	167 (59)	-	-	-
Kim et al. (2009)[14]	Cisplatin, vinblastine, dacarbazine, IFN alfa-2b, interleukin-2	71	NR	44 (62)	NR	NR	NR
	IFN alfa-2b (high-dose)	33	NR	17 (52)	NR	NR	NR
	IFN alfa-2b (low-dose)	33	NR	19 (58)	NR	NR	NR
ECOG 1690[15]	IFN alfa-2b (low-dose)	215	NR	147 (68)	NR	NR	NR
	IFN alfa-2b (high-dose)	215	NR	128 (60)	NR	NR	NR
	Observation	212	NR	140 (66)	NR	NR	NR
ECOG 1684[16]	IFN alfa-2b (high-dose)	143	NR	90 (63)	NR	NR	NR
	Observation	137	NR	79 (58)	NR	NR	NR
EORTC 18871[17]	rIFN alfa-2b	240	52 (14-84)	127 (53)	NR	NR	NR
	Observation	244	52 (14-84)	138 (57)	NR	NR	NR
Stadler et al. (2006)[18]	Dacarbazine + natural human IFN alfa	128	53 (25-86)[a]	73 (57)	NR	NR	NR
	Observation	124	54 (23-82)[a]	69 (56)	NR	NR	NR
E1609[19]	Ipilimumab (high-dose)	406	54 (19-80)	NR (63)	NR	NR	NR
	Ipilimumab (low-dose)	367	55 (19-80)	NR (67)	NR	NR	NR
CheckMate 238[20,21]	Nivolumab	452	56 (19-83)	258 (57)	NR	NR	NR
	Ipilimumab	453	54 (18-86)	269 (59)	NR	NR	NR

[a] mean age

Tabelle 2: Cochrane risk of bias assessment of randomized controlled trials included in the feasibility assessment (Toor K et al., 2021 [9]..)

Trial ID	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
ECOG 1697[1]	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Scottish Study[2]	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk
WHO Melanoma Programme Trial 16[3]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
EORTC 18071[4]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
EORTC 18952[5]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
EORTC 18991[6]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
KEYNOTE-054[7,8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
S0008[9]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk
Garbe et al. (2008; DeCOG)[10]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
COMBI-AD[11]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
AIM HIGH Study[12]	Unclear risk	Low risk	Low risk	Unclear risk	High risk	Low risk	Low risk
Nordic IFN Trial[13]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Kim et al. (2009)[14]	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
ECOG 1690[15]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
ECOG 1684[16]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
EORTC 18871[17]	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Stadler et al. (2006)[18]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk
E1609[19]	Unclear risk	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk
CheckMate 238[20,21]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Tabelle 3: Demographics and characteristics of patients at baseline (Christofyllakis K et al., 2021 [1].)

Trial	Substance	Patients enrolled (n)	Gender		Stage					BRAF mutation (n)
			male	female	IIC	IIIA	IIIB	IIIC	IV	
IMMUNED	Nivolumab + Ipilimumab	56	31 (55 %)	25 (45 %)	-	-	-	-	56	27 (48 %)
	Nivolumab	59	31 (53 %)	28 (47 %)	-	-	-	-	59	27 (46 %)
	Placebo	52	33 (63 %)	19 (37 %)	-	-	-	-	52	21 (40 %)
EORC-18071	Ipilimumab	475	296 (62 %)	179 (38 %)	-	98 (21 %)	213 (38 %)	164 (41 %)	-	-
	Placebo	476	293 (62 %)	183 (38 %)	-	98 (21 %)	182 (38 %)	196 (41 %)	-	-
COMBI-AD	Dabrafenib + Trametinib	438	195 (45 %)	243 (55 %)	-	83 (19 %)	169 (39 %)	181 (41 %)	-	438 (100 %)
	Placebo	432	193 (45 %)	239 (55 %)	-	71 (16 %)	187 (43 %)	166 (38 %)	-	438 (100 %)
BRIM8	Vemurafenib	157	84 (54 %)	73 (46 %)	15 (10 %)	36 (23 %)	106 (68 %)	-	-	157 (100 %)
Cohort I	Placebo	157	88 (56 %)	69 (44 %)	12 (8 %)	39 (25 %)	106 (68 %)	-	-	157 (100 %)
BRIM8	Vemurafenib	93	52 (56 %)	41 (44 %)	-	-	-	93 (100 %)	-	93 (100 %)
Cohort II	Placebo	91	59 (65 %)	32 (35 %)	-	-	-	91 (100 %)	-	91 (100 %)
EORTC-1325	Pembrolizumab	514	324 (63 %)	190 (37 %)	-	80 (16 %)	237 (46 %)	197 (38 %)	-	245 (48 %)
	Placebo	505	304 (60 %)	201 (40)	-	80 (16 %)	230 (45 %)	195 (39 %)	-	262 (52 %)

Tabelle 4: Adverse events characteristics (Christofyllakis K et al., 2021 [1].)

Trial	Substance	Evaluated patients (n)	Adverse events	Grade I-II	Grade III-IV	Patients discontinuing treatment	Deaths
IMMUNED	Nivolumab + Ipilimumab	55	55 (100 %)	-	45 (82 %)	34 (62 %)	1 (not drug related)
	Nivolumab	56	54 (96 %)	-	23 (41 %)	7 (13 %)	2 (not drug related)
	Placebo	51	49 (96 %)	-	13 (25 %)	1 (2 %)	0
EORC-18071	Ipilimumab	471	465 (98 %)	205 (44 %)	254 (54 %)	245 (52 %)	6 (1 %) (5 drug-related)
	Placebo	474	432 (91 %)	307 (65 %)	124 (26 %)	20 (4 %)	6 (1 %) (0 drug-related)
COMBI-AD	Dabrafenib + Trametinib	435	422 (97 %)	-	180 (41 %)	114 (26 %)	1 (drug related)
	Placebo	432	380 (88 %)	-	61 (14 %)	12 (3 %)	0
BRIM8	Vemurafenib	247	245 (99 %)	104 (42 %)	141 (59 %)	49 (20 %)	1 (not drug related)
	Placebo	247	219 (89 %)	182 (74 %)	37 (15 %)	5 (2 %)	0
EORTC-1325	Pembrolizumab	509	475 (93 %)	-	161 (32 %)	70 (14 %)	3 (1 treatment related (myositis))
	Placebo	502	453 (90 %)	-	93 (19 %)	11 (2 %)	0

Tabelle 5: List of publications and key trial characteristics, arranged by trial (Lorenzi M et al., 2019 [3].)

Trial ID	Phase	Multi-center	Age (years)	Disease stage	Performance Score	Principal publication	Subsequent publications
BRIM-8*	III	Yes	≥ 18	IIC-IIIC	ECOG 0-1	Maio et al.[14]	Lewis et al.[13]
Caraceni 1998	-	-	18-70	IIIB	Karnofsky 100	Caraceni et al.[24]	-
CheckMate 238*	III	Yes	≥ 15	IIIB-IV	ECOG 0-1	Weber et al.[10]	Weber et al.[25]
COMBI-AD	III	Yes	≥ 18	IIIA-IIIC	ECOG 0-1	Long et al.[26]	Hauschild et al.[27]
EORTC 18071	III	Yes	≥ 18	IIIA-IIIC	ECOG 0-1	Eggermont et al.[9]	Coens et al.[28] Eggermont et al.[29] Eggermont et al.[30]
EORTC 18952	III	Yes	18-70	IIB-IIIC	-	Eggermont et al.[31]	Eggermont et al.[32]
EORTC 18991	III	Yes	18-70	III	ECOG 0-1	Eggermont et al.[33]	Fusi et al.[34] Bottomley et al.[35] Eggermont et al.[36] Herndon et al.[37]
KEYNOTE 054	III	Yes	≥ 18	III	ECOG 0-1	Eggermont et al.[11]	-
Lian 2013	II	No	≥ 18	II-III	ECOG 0-1	Lian et al.[38]	-
Nordic IFN trial*	III	Yes	≥ 18	IIB-III	ECOG 0-1	Hansson et al.[39]	Vihinen et al.[40]
SWOG S0008	II	Yes	≥ 18	IIIA-IIIC	Zubrod 0-1	Flaherty et al.[41]	-
WHO MPT 16	II	Yes	18-70	III	-	Cascinelli et al.[42]	-

*denotes trials that provide stage III sub-group data

Tabelle 6: Cochrane risk of bias assessment of randomized controlled trials (Lorenzi M et al., 2019 [3].)

Trial	Random sequence	Allocation concealment	Blinding of participants	Blinding of outcomes	Attrition	Selective reporting	Other sources
BRIM-8	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Caraceni 1998	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
WHO MPT 16	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
EORTC 18952	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
EORTC 18991	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
EORTC 18071	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SWOG S0008	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Nordic IFN trial	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Lian 2013	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
KEYNOTE 054	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
COMBI-AD	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CheckMate 238	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO