Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-07-01-D-372 Ipilimumab

Stand: August 2018

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

Ipilimumab
in Kombination mit Nivolumab zur Behandlung von fortgeschrittenen Melanomen

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.	• Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Vemurafenib: Beschluss vom 6. März 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Pembrolizumab: Beschluss vom 4. Februar 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Dabrafenib: Beschluss vom 17. März 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Trametinib: Beschluss vom 17. März 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Ipilimumab (neues Anwendungsgebiet): Beschluss vom 7. April 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Cobimetinib: Beschluss vom 2. Juni 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Dabrafenib: Beschluss vom 16. Juni 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nivolumab: Beschluss vom 15. Dezember 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nivolumab (neues Anwendungsgebiet: Melanom; in Kombination mit Ipilimumab): Beschluss vom 15. Dezember 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nivolumab (Melanom, in Kombination mit Ipilimumab, Neubewertung nach Fristablauf):

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ipilimumab in Kombination mit Nivolumab zur Behandlung von fortgeschrittenen Melanomen Kriterien gemäß 5. Kapitel § 6 VerfO	
	Beschluss vom 7. Dezember 2017 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Talimogen laherparepvec: Beschluss vom 15. Dezember 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V
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:	
Ipilimumab	YERVOY ist in Kombination mit Nivolumab zur Behandlung von fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanomen bei Erwachsenen indiziert.
Cobimetinib L01XE38 Cotellic®	Cotellic wird in Kombination mit Vemurafenib angewendet zur Behandlung bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.
Dabrafenib L01XE23 Tafinlar®	Dabrafenib ist angezeigt als Monotherapie oder in Kombination mit Trametinib zur Behandlung von erwachsenen Patienten mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.
Dacarbazin L01AX04 z. B. Detimedac®	Detimedac ist indiziert zur Behandlung des metastasierten, malignen Melanoms.
Ipilimumab L01XC11 YERVOY®	YERVOY ist zur Behandlung von fortgeschittenen (nicht resezierbaren oder metastasierten) Melanomen bei Erwachsenen indiziert.
Lomustin L01AD02 Cecenu®	Cecenu wird in Kombinationstherapie eingesetzt: - Bei bösartigen Tumorerkrankungen der Haut (metastasierte, maligne Melanome)
Nivolumab L01XC17 Opdivo®	OPDIVO ist als Monotherapie oder in Kombination mit Ipilimumab bei Erwachsenen für die Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms indiziert. Im Vergleich zur Nivolumab Monotherapie wurde in der Kombination Nivolumab mit Ipilimumab nur bei Patienten mit niedriger Tumor-PD-L1-Expression ein Anstieg des progressionsfreien Überlebens (PFS) und des Gesamtüberlebens (OS) gezeigt (siehe Abschnitte 4.4 und 5.1).
Pembrolizumab L01XC18 KEYTRUDA®	KEYTRUDA ist als Monotherapie zur Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms bei Erwachsenen angezeigt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Talimogen laherparepvec L01XX51 IMLYGIC®	Imlygic ist indiziert zur Behandlung von Erwachsenen mit nicht resezierbarem, lokal oder entfernt metastasiertem Melanom (Stadium IIIB, IIIC und IVM1a) ohne Knochen- , Hirn-, Lungen- oder andere viszerale Beteiligung
Trametinib L01XE25 Mekinist®	Trametinib ist angezeigt als Monotherapie oder in Kombination mit Dabrafenib zur Behandlung von erwachsenen Patienten mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation. Eine Trametinib-Monotherapie hat keine klinische Aktivität bei Patienten gezeigt, deren Erkrankung auf eine vorhergehende Therapie mit einem BRAF-Inhibitor fortschritt.
Vemurafenib L01XE15 Zelboraf®	Vemurafenib ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit BRAF-V600 Mutation-positivem nicht resezierbarem oder metastasiertem Melanom.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

(S)AE	(Serious) adverse events
AM-RL	Arzneimittel-Richtlinie
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CR	complete response
Dab	Dabrafenib
Dac/ DTIC	Dacarbazine;
DAHTA	DAHTA Datenbank
DCR	disease control rate
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
Int	Intetumumab
Ipi	Ipilimumab
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MM	Malignant Melanoma
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
Niv	Nivolumab
OR	Odds Ratio
ORR	objective response rate
OS	overall survival
PD	progressive disease
Pem	Pembrolizumab
PFS	progression-free survival
PR	Partial response

RR	Relatives Risiko
SD	stable disease
Sel	Selumetinib
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
Vem	Vemurafenib
WHO	World Health Organization

Indikation

Zur Behandlung von fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanomen bei Erwachsenen.

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Melanom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.03.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1202 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Nachträglich wurden 10 Referenzen des G-BA (Geltende Fassungen der Arzneimittel-Richtlinie: Anlage XII) aufgenommen. Insgesamt ergab dies 44 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Ergebnisse

IQWiG-Berichte/G-BA-Beschlüsse

G-BA, 2014 [14].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Vemurafenib, Beschluss vom 6. März 2014 (gültig bis: unbefristet)

Siehe auch IQWiG, 2013 [33].

Anwendungsgebiet

Vemurafenib (Zelboraf®) ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit BRAF-V600 Mutation-positivem nicht resezierbarem oder metastasiertem Melanom.

Vergleichstherapie

Dacarbazin.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis für einen beträchtlichen Zusatznutzen.

G-BA, 2016 [11].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Pembrolizumab, Beschluss vom 4. Februar 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2015 [30] & IQWiG, 2016 [29]

Anwendungsgebiet

KEYTRUDA® ist als Monotherapie zur Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierenden) Melanoms bei Erwachsenen angezeigt.

Vergleichstherapie

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutiertem Tumor: Vemurafenib

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Ipilimumab

Vorbehandelte Patienten: Eine patientenindividuelle Therapie nach Maßgabe des behandelnden Arztes unter Berücksichtigung des Zulassungsstatus und der jeweiligen Vortherapie.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutiertem Tumor: Ein Zusatznutzen ist nicht belegt.

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Anhaltspunkt für einen beträchtlichen Zusatznutzen.

Vorbehandelte Patienten: Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2016 [6].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Dabrafenib (neues Anwendungsgebiet: Melanom in Kombination mit Trametinib), Beschluss vom 17. März 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2015 [22] & IQWiG, 2016 [23]

Anwendungsgebiet

Dabrafenib ist angezeigt in Kombination mit Trametinib zur Behandlung von erwachsenen Patienten mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.

Vergleichstherapie

Vemurafenib

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2016 [13].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Trametinib, Beschluss vom 17. März 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2016 [32] & IQWiG, 2016 [23]

Anwendungsgebiet

Trametinib ist angezeigt in Kombination mit Dabrafenib zur Behandlung von erwachsenen Patienten mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.

Trametinib ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation (siehe Abschnitte 4.4 und 5.1). Eine Trametinib-Monotherapie hat keine klinische Aktivität bei Patienten gezeigt, deren Erkrankung auf eine vorhergehende Therapie mit einem BRAF-Inhibitor fortschritt.

Vergleichstherapie

Trametinib-Monotherapie bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation: Vemurafenib

Trametinib in Kombination mit Dabrafenib bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation: Vemurafenib

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Trametinib-Monotherapie bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation: Ein Zusatznutzen ist nicht belegt.

Trametinib in Kombination mit Dabrafenib bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation: Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2016 [8].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Ipilimumab (neues Anwendungsgebiet: nicht-vorbehandelte Patienten mit fortgeschrittenem Melanom), Beschluss vom 5. Juni 2014 / 7. April 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2014 [18,24].

Anwendungsgebiet

Yervoy® ist zur Behandlung von fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanomen bei Erwachsenen indiziert.

Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet, d. h. auf nicht-vorbehandelte Patienten mit fortgeschrittenem (nicht resezierbarem oder metastasiertem) Melanom.

Vergleichstherapie

Patienten mit BRAF-V600-Mutation-negativem Melanom: Dacarbazin

Patienten mit BRAF-V600-Mutation-positivem Melanom: Vemurafenib

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Patienten mit BRAF-V600-Mutation-negativem Melanom: Ein Zusatznutzen ist nicht belegt.

Patienten mit BRAF-V600-Mutation-positivem Melanom: Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [5].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Cobimetinib, Beschluss vom 2. Juni 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2016 [20] & IQWiG, 2016 [19]

Anwendungsgebiet

Cobimetinib (Cotellic®) wird in Kombination mit Vemurafenib angewendet zur Behandlung bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.

Vergleichstherapie

Vemurafenib

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis auf einen beträchtlichen Zusatznutzen

G-BA, 2016 [7].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Dabrafenib, Beschluss vom 3. April 2014 / 16. Juni 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2013 [21] & IQWiG, 2014 [17]

Anwendungsgebiet

Dabrafenib ist angezeigt zur Monotherapie von erwachsenen Patienten mit BRAF-V600-Mutation-positivem nicht-resezierbarem oder metastasiertem Melanom.

Vergleichstherapie

Vemurafenib

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [10].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Nivolumab, Beschluss vom 7. Januar 2016 / 15. Dezember 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2015 [25] & IQWiG, 2015 [26]

Anwendungsgebiet

OPDIVO® ist als Monotherapie bei Erwachsenen für die Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms indiziert.

Vergleichstherapie

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutierten Tumor: Vemurafenib

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Dacarbazin oder Ipilimumab

Vorbehandelte Patienten: Eine patientenindividuelle Therapie nach Maßgabe des behandelnden Arztes unter Berücksichtigung des Zulassungsstatus und der jeweiligen Vortherapie.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutierten Tumor: Ein Zusatznutzen ist nicht belegt.

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Hinweis auf einen beträchtlichen Zusatznutzen.

Vorbehandelte Patienten: Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [12].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Talimogen laherparepvec, Beschluss vom 15. Dezember 2016 (gültig bis: unbefristet)

Siehe auch IQWiG, 2016 [31].

Anwendungsgebiet

IMLYGIC® ist indiziert zur Behandlung von Erwachsenen mit nicht resezierbarem, lokal oder entfernt metastasiertem Melanom (Stadium IIIB, IIIC und IVM1a) ohne Knochen-, Hirn-, Lungen- oder andere viszerale Beteiligung

Vergleichstherapie

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutierten Tumor: Vemurafenib oder Vemurafenib in Kombination mit Cobimetinib oder Dabrafenib in Kombination mit Trametinib

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Pembrolizumab oder Nivolumab

Vorbehandelte Patienten: Eine patientenindividuelle Therapie nach Maßgabe des behandelnden Arztes unter Berücksichtigung des Zulassungsstatus und der jeweiligen Vortherapie.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutierten Tumor: Ein Zusatznutzen ist nicht belegt.

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Ein Zusatznutzen ist nicht belegt.

Vorbehandelte Patienten: Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [9].

Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Nivolumab (Melanom; in Kombination mit Ipilimumab, Neubewertung nach Fristablauf), Beschluss vom 15. Dezember 2016 / 7. Dezember 2017

Hinweis: Gültig bis: Patientengruppe 1b) 15.06.2018, Patientengruppe 1a), 2) unbefristet

Siehe auch IQWiG, 2016 [27] & IQWiG, 2016 [28]

Anwendungsgebiet

OPDIVO ist als Monotherapie oder in Kombination mit Ipilimumab bei Erwachsenen für die Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms indiziert.

Im Vergleich zur Nivolumab Monotherapie wurde in der Kombination Nivolumab mit Ipilimumab nur bei Patienten mit niedriger Tumor PD-L1-Expression ein Anstieg des progressionsfreien Überlebens (PFS) und des Gesamtüberlebens (OS) gezeigt.

[Hinweis: Der vorliegende Beschluss bezieht sich nur auf die Kombination von Nivolumab mit Ipilimumab]

Vergleichstherapie

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutierten Tumor: Vemurafenib oder Vemurafenib plus Cobimetinib oder Dabrafenib plus Trametinib

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Nivolumab oder Pembrolizumab

Vorbehandelte Patienten: Eine patientenindividuelle Therapie nach Maßgabe des behandelnden Arztes unter Berücksichtigung des Zulassungsstatus und der jeweiligen Vortherapie

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Nicht vorbehandelte Patienten mit einem BRAF-V600-mutierten Tumor: Ein Zusatznutzen ist nicht belegt.

Nicht vorbehandelte Patienten mit einem BRAF-V600-wildtyp Tumor: Ein Zusatznutzen ist nicht belegt.

Vorbehandelte Patienten: Ein Zusatznutzen ist nicht belegt.

Cochrane Reviews

Pasquali S et al., 2018 [40].

Systemic treatments for metastatic cutaneous melanoma

Fragestellung

to assess the beneficial and harmful effects of systemic treatments for metastatic cutaneous melanoma.

Methodik

Population:

People with unresectable lymph node metastasis (AJCC TNM stage IIIC) and distant metastatic (AJCC TNM stage IV) cutaneous melanoma. No restrictions in terms of age, sex, drug dosage, radiologic examination, or treatment duration were applied.

Intervention/Komparator:

All comparisons of systemic therapies for the treatment of metastatic cutaneous melanoma, including:

- o polychemotherapy (experimental arm) versus single-agent chemotherapy (comparator arm);
- o biochemotherapy (experimental arm) versus chemotherapy (comparator arm);
- o immune checkpoint inhibitors (experimental arm) versus any other agent (comparator arm);
- o small-molecule targeted drugs (experimental arm) versus any other agent (comparator arm);
- o chemotherapy plus other agents (e.g. anti-angiogenic drugs) (experimental arm) versus chemotherapy alone (comparator arm); and
- o Other comparisons (e.g. single agent chemotherapy verus other single agent chemotherapy).

Endpunkt:

Primary: Overall survival; Progression-free survival; toxicity

Secondary: Tumour response; Quality of life; Economic evaluation

Recherche/Suchzeitraum:

Up to October 2017: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase and LILACS.

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

We included 122 RCTs (28,561 participants). Of these, 83 RCTs, encompassing 21 different comparisons, were included in metaanalyses. Most interventions were compared with chemotherapy.

Charakteristika der Population:

Included participants were men and women with a mean age of 57.5 years who were recruited from hospital settings. 29 studies included people whose cancer had spread to their brains. Interventions were categorised into five groups: conventional chemotherapy (including single agent and polychemotherapy), biochemotherapy (combining chemotherapy with cytokines such as interleukin-2 and interferon-alpha), immune checkpoint inhibitors (such as anti-CTLA4 and anti-PD1 monoclonal antibodies), small molecule targeted drugs used for melanomas with specific gene changes (such as BRAF inhibitors and MEK inhibitors), and other agents (such as anti-angiogenic drugs).

Qualität der Studien:

Overall, the risk of bias of the included trials can be considered as limited. When considering the 122 trials included in this review and the seven types of bias we assessed, we performed 854 evaluations only seven of which (< 1%) assigned high risk to six trials.

Studienergebnisse:

When compared to single agent chemotherapy, the combination of multiple chemotherapeutic agents (polychemotherapy) did not translate into significantly better survival (OS: 6 studies, 594 participants; high-quality evidence; progression-free survival: 5 studies, 398 participants; high-quality evidence).

Those who received combined treatment are probably burdened by higher toxicity rates (RR 1.97, 95%CI 1.44 to 2.71, 3 studies, 390 participants; moderate-quality evidence). (We defined toxicity as the occurrence of grade 3 (G3) or higher adverse events according to the World Health Organization scale.)

Compared to chemotherapy, biochemotherapy (chemotherapy combined with both interferon-alpha and interleukin-2) improved progression-free survival (HR 0.90, 95% CI 0.83 to 0.99, 6 studies, 964 participants; high-quality evidence), but did not significantly improve overall survival (7 studies, 1317 participants; high-quality evidence).

Biochemotherapy had higher toxicity rates (RR 1.35, 95% CI 1.14 to 1.61, 2 studies, 631 participants; high-quality evidence).

With regard to immune checkpoint inhibitors, anti-CTLA4 monoclonal antibodies plus chemotherapy probably increased the chance of progression-free survival compared to chemotherapy alone (HR 0.76, 95% CI 0.63 to 0.92, 1 study, 502 participants; moderate quality evidence), but may not significantly improve overall survival (2 studies, 1157 participants; low quality evidence).

Compared to chemotherapy alone, anti-CTLA4 monoclonal antibodies is likely to be associated with higher toxicity rates (RR 1.69, 95% CI 1.19 to 2.42, 2 studies, 1142 participants; moderate-quality evidence).

Compared to chemotherapy, anti-PD1 monoclonal antibodies (immune checkpoint inhibitors) improved overall survival (HR 0.42, 95% CI 0.37 to 0.48, 1 study, 418 participants; high-quality evidence) and probably improved progression-free survival (HR 0.49, 95% CI 0.39 to 0.61, 2 studies, 957 participants; moderate-quality evidence).

Anti-PD1 monoclonal antibodies may also result in less toxicity than chemotherapy (RR 0.55, 95% CI 0.31 to 0.97, 3 studies, 1360 participants; low-quality evidence).

Anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival (HR 0.63, 95% CI 0.60 to 0.66, 1 study, 764 participants; high-quality evidence) and progression-free survival (HR 0.54, 95%CI 0.50 to 0.60, 2 studies, 1465 participants; high-quality evidence).

Anti-PD1 monoclonal antibodies may result in better toxicity outcomes than anti-CTLA4 monoclonal antibodies (RR 0.70, 95% CI 0.54 to 0.91, 2 studies, 1465 participants; low-quality evidence).

Compared to anti-CTLA4 monoclonal antibodies alone, the combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies was associated with better progression-free survival (HR 0.40, 95% CI 0.35 to 0.46, 2 studies, 738 participants; high-quality evidence).

There may be no significant difference in toxicity outcomes (2 studies, 764 participants; low-quality evidence) (no data for overall survival were available).

The class of small-molecule targeted drugs, BRAF inhibitors (which are active exclusively against BRAF-mutated melanoma), performed better than chemotherapy in terms of overall survival (HR 0.40, 95%CI 0.28 to 0.57, 2 studies, 925 participants; high-quality evidence) and progression-free survival (HR 0.27, 95% CI 0.21 to 0.34, 2 studies, 925 participants; high-quality evidence), and there may be no significant difference in toxicity (2 studies, 408 participants; low-quality evidence).

Compared to chemotherapy, MEK inhibitors (which are active exclusively against BRAF-mutated melanoma) may not significantly improve overall survival (3 studies, 496 participants; low-quality evidence), but they probably lead to better progression-free survival (HR 0.58, 95%CI 0.42 to 0.80, 3 studies, 496 participants; moderate-quality evidence).

However, MEK inhibitors probably have higher toxicity rates (RR 1.61, 95% CI 1.08 to 2.41, 1 study, 91 participants; moderate-quality evidence).

Compared to BRAF inhibitors, the combination of BRAF plus MEK inhibitors was associated with better overall survival (HR 0.70, 95% CI 0.59 to 0.82, 4 studies, 1784 participants; high-quality evidence). BRAF plus MEK inhibitors was also probably better in terms of progression-free survival (HR 0.56, 95% CI 0.44 to 0.71, 4 studies, 1784 participants; moderate-quality evidence), and there appears likely to be no significant difference in toxicity (4 studies, 1774 participants; moderate-quality evidence).

Compared to chemotherapy, the combination of chemotherapy plus anti-angiogenic drugs was probably associated with better overall survival (HR 0.60, 95% CI 0.45 to 0.81; moderate-quality evidence) and progression-free survival (HR 0.69, 95% CI 0.52 to 0.92; moderate-quality evidence). There may be no difference in terms of toxicity (low-quality evidence). All results for this comparison were based on 324 participants from 2 studies.

Network meta-analysis focused on chemotherapy as the common comparator and currently approved treatments for which high- to moderate-quality evidence of efficacy (as represented by treatment effect on progression-free survival) was available (based on the above results) for: biochemotherapy (with both interferon-alpha and interleukin-2); anti-CTLA4 monoclonal antibodies; anti-PD1 monoclonal antibodies; anti-CTLA4 plus anti-PD1 monoclonal antibodies; BRAF inhibitors; MEK inhibitors, and BRAF plus MEK inhibitors. Analysis (which included 19 RCTs and 7632 participants) generated 21 indirect comparisons.

The best evidence (moderate-quality evidence) for progression-free survival was found for the following indirect comparisons:

- o both combinations of immune checkpoint inhibitors (HR 0.30, 95% CI 0.17 to 0.51) and small-molecule targeted drugs (HR 0.17, 95% CI 0.11 to 0.26) probably improved progression-free survival compared to chemotherapy;
- o both BRAF inhibitors (HR 0.40, 95% CI 0.23 to 0.68) and combinations of small-molecule targeted drugs (HR 0.22, 95% CI 0.12 to 0.39) were probably associated with better progression-free survival compared to anti-CTLA4 monoclonal antibodies;
- o biochemotherapy (HR 2.81, 95% CI 1.76 to 4.51) probably lead to worse progression-free survival compared to BRAF inhibitors; • the combination of small-molecule targeted drugs probably improved progression-free survival (HR 0.38, 95% CI 0.21 to 0.68) compared to anti-PD1 monoclonal antibodies;
- o both biochemotherapy (HR 5.05, 95% CI 3.01 to 8.45) and MEK inhibitors (HR 3.16, 95% CI 1.77 to 5.65) were probably associated with worse progression-free survival compared to the combination of small-molecule targeted drugs; and
- o biochemotherapy was probably associated with worse progression-free survival (HR 2.81, 95% CI 1.54 to 5.11) compared to the combination of immune checkpoint inhibitors.

The best evidence (moderate-quality evidence) for toxicity was found for the following indirect comparisons:

- o combination of immune checkpoint inhibitors (RR3.49, 95%CI 2.12 to 5.77) probably increased toxicity compared to chemotherapy;
- o combination of immune checkpoint inhibitors probably increased toxicity (RR 2.50, 95% CI 1.20 to 5.20) compared to BRAF inhibitors;
- o the combination of immune checkpoint inhibitors probably increased toxicity (RR 3.83, 95% CI 2.59 to 5.68) compared to anti-PD1 monoclonal antibodies; and
- o biochemotherapy was probably associated with lower toxicity (RR 0.41, 95% CI 0.24 to 0.71) compared to the combination of immune checkpoint inhibitors.

Network meta-analysis-based ranking suggested that the combination of BRAF plus MEK inhibitors is the most effective strategy in terms of progression-free survival, whereas anti-PD1 monoclonal antibodies are associated with the lowest toxicity.

Anmerkung/Fazit der Autoren

We found high-quality evidence that many treatments offer better efficacy than chemotherapy, especially recently implemented treatments, such as small-molecule targeted drugs, which are used to treat melanoma with specific gene mutations. Compared with chemotherapy, biochemotherapy (in this case, chemotherapy combined with both interferon-alpha and interleukin-2) and BRAF inhibitors improved progression-free survival; BRAF inhibitors (for BRAF-mutated melanoma) and anti-PD1 monoclonal antibodies improved overall survival. However, there was no difference between polychemotherapy and monochemotherapy in terms of achieving progression-free survival and overall survival. Biochemotherapy did not significantly improve overall survival and has higher toxicity rates compared with chemotherapy.

There was some evidence that combined treatments worked better than single treatments: anti-PD1 monoclonal antibodies, alone or with anti-CTLA4, improved progression-free survival compared with anti-CTLA4monoclonal antibodies alone. Anti-PD1monoclonal antibodies

performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival, and a combination of BRAF plus MEK inhibitors was associated with better overall survival for BRAF-mutated melanoma, compared to BRAF inhibitors alone.

The combination of BRAF plus MEK inhibitors (which can only be administered to people with BRAF-mutated melanoma) appeared to be the most effective treatment (based on results for progression-free survival), whereas anti-PD1 monoclonal antibodies appeared to be the least toxic, and most acceptable, treatment.

Evidence quality was reduced due to imprecision, between-study heterogeneity, and substandard reporting of trials. Future research should ensure that those diminishing influences are addressed. Clinical areas of future investigation should include the longer-term effect of new therapeutic agents (i.e. immune checkpoint inhibitors and targeted therapies) on overall survival, as well as the combination of drugs used in melanoma treatment; research should also investigate the potential influence of biomarkers.

Systematische Reviews

Devji T et al., 2017 [4].

Systemic Therapy for Previously Untreated Advanced BRAF-Mutated Melanoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials

Fragestellung

to estimate the relative efficacy and safety of systemic therapies for advanced, treatment-naive, BRAF-mutated melanoma.

Methodik

Population:

treatment-naive adult patients with unresectable lymph node metastasis or distant metastatic melanoma (based on proven efficacy of immunotherapy in melanoma regardless of BRAF mutation status, immunotherapy studies in BRAF mixed or BRAF wild-type population were included).

Intervention:

either targeted (BRAF or MEK) or an immune checkpoint (CTLA-4 or PD-1) inhibitor therapy

Komparator:

k.A.

Endpunkt:

OS, PFS, objective response rate (ORR) and serious adverse events (SAE)

Recherche/Suchzeitraum:

MEDLINE, EMBASE, and Cochrane Central Registry of Controlled Trials until April 29, 2016

Qualitätsbewertung der Studien:

Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

15 RCTs, 6662 patients

Qualität der Studien:

overall risk of bias was low

Studienergebnisse:

OS (13 trials, 5361 patients):

- BRAF/MEK and PD-1 associated with improved OS benefit compared with all other treatments except CTLA-4/GM-CSF
- no significant difference in OS between BRAF/MEK and PD-1 (HR, 1,02; 95% CrI: 0,72-1,45)

A Overall survival

BRAF								
0.69 (0.59-0.82)	*BRAF/MEK*							
1.22 (0.94-1.58)	1.76 (1.29-2.40)	CTLA-4						
0.99 (0.75-1.32)	1.43 (1.03-2.00)	0.81 (0.64-1.05)	CTLA-4/CHEMO					
0.90 (0.50-1.64)	1.31 (0.70-2.43)	0.74 (0.44-1.26)	0.91 (0.51-1.64)	CTLA-4/GM-CSF				
1.94 (1.29-2.92)	2.81 (1.80-4.37)	1.59 (1.08-2.34)	1.96 (1.31-2.92)	2.15 (1.12-4.13)	*MEK*			
1.47 (0.96-2.26)	2.12 (1.33-3.36)	1.20 (0.80-1.80)	1.47 (0.97-2.26)	1.62 (0.83-3.15)	0.75 (0.45-1.27)	*MEK*/CHEMO		
0.71 (0.52-0.96)	1.02 (0.72-1.45)	0.58 (0.47-0.71)	0.71 (0.53-0.96)	0.78 (0.44-1.38)	0.36 (0.24-0.55)	0.48 (0.31-0.75)	PD-1	
1.44 (1.17-1.77)	2.08 (1.59-2.71)	1.18 (1.01-1.38)	1.45 (1.19-1.76)	1.59 (0.92-2.76)	0.74 (0.52-1.06)	0.98 (0.68-1.42)	2.04 (1.62-2.57)	CHEMO

PFS (14 trials, 6738 patients):

advantage of BRAF/MEK compared with all other treatment strategies

B Progression-free survival

BRAF									
0.58 (0.51-0.66)	*BRAF/MEK*								
2.13 (1.52-2.97)	3.65 (2.56-5.21)	CTLA-4							
2.05 (1.58-2.66)	3.52 (2.63-4.71)	0.96 (0.68-1.36)	CTLA-4/CHEMO						
2.19 (1.30-3.69)	3.76 (2.19-6.44)	1.03 (0.69-1.54)	1.07 (0.63-1.82)	CTLA-4/GM-CSF					
2.89 (1.99-4.17)	4.96 (3.34-7.32)	1.36 (0.88-2.09)	1.41 (0.96-2.07)	1.32 (0.73-2.39)	*MEK*				
1.84 (1.27-2.66)	3.15 (2.13-4.68)	0.86 (0.56-1.33)	0.90 (0.61-1.31)	0.84 (0.46-1.52)	0.64 (0.40-1.01)	*MEK*/CHEMO			
1.16 (0.86-1.57)	1.99 (1.44-2.76)	0.55 (0.48-0.63)	0.57 (0.41-0.77)	0.53 (0.35-0.82)	0.40 (0.27-0.61)	0.63 (0.42-0.96)	PD-1		
0.87 (0.61-1.24)	1.49 (1.03-2.18)	0.41 (0.34-0.49)	0.42 (0.29-0.61)	0.40 (0.26-0.62)	0.30 (0.19-0.47)	0.98 (0.30-0.75)	0.75 (0.62-0.91)	PD-1/CTLA-4	
2.70 (2.27-3.20)	4.63 (3.73-5.74)	1.27 (0.95-1.69)	1.32 (1.08-1.60)	1.23 (0.75-2.03)	0.93 (0.67-1.30)	1.47 (1.06-2.04)	2.32 (1.81-2.98)	3.11 (2.26-4.25)	CHEMO

ORR (13 trials, 5580 patients):

- BRAF/MEK was associated with a higher ORR compared compared with BRAF alone (OR (95 % CrI) = 2,00 (1,64; 2,45))
- BRAF/MEK & BRAF advantage compared with all other treatments (BRAF/MEK vs PD-1/CTLA-4 OR (95 % CrI) = 0,26 (0,14; 0,48))

C Objective response rate

BRAF								
2.00 (1.64-2.45)	BRAF/MEK							
0.08 (0.05-0.14)	0.04 (0.02-0.07)	CTLA-4						
0.11 (0.06-0.21)	0.05 (0.03-0.11)	1.35 (0.70-2.65)	CTLA-4/CHEMO					
0.04 (0.01-0.13)	0.02 (0.01-0.07)	0.50 (0.15-1.58)	0.37 (0.11-1.24)	MEK				
0.16 (0.07-0.35)	0.08 (0.03-0.18)	1.95 (0.90-4.36)	1.45 (0.60-3.49)	3.89 (1.08-15.01)	MEK/CHEMO			
0.28 (0.16-0.49)	0.14 (0.08-0.25)	3.54 (2.59-4.86)	2.62 (1.35-5.08)	7.03 (2.24-23.68)	1.82 (0.81-3.97)	PD-1		
0.52 (0.28-0.94)	0.26 (0.14-0.48)	6.45 (4.67-8.94)	4.77 (2.37-9.57)	12.82 (3.99-43.88)	3.30 (1.44-7.50)	1.82 (1.34-2.47)	PD-1/CTLA-4	
0.07 (0.05-0.10)	0.03 (0.02-0.05)	0.87 (0.59-1.28)	0.64 (0.37-1.09)	1.72 (0.58-5.47)	0.44 (0.22-0.88)	0.24 (0.17-0.36)	0.13 (0.09-0.21)	CHEMO

SAE (8 trials, 4395 patients):

- range: 38,4 % for chemotherapy to 68,7% for CTLA-4/PD-1
- no significant difference between chemotherapy and PD-1 (OR (95 % CrI) = 1,00 (0,74; 1,34))
- among immunotherapy: CTLA-4/PD-1 higher risk of SAE compared with CTLA-4 (OR (95 % CrI) =1,63 (1,19;2,26)) and PD-1 (OR (95 % CrI) =2,99 (2,18; 4,12))
- BRAF/MEK associated with lower risk of SAE than BRAF (OR (95 % CrI) =0,84 (0,66; 1,06))

Anmerkung/Fazit der Autoren

Compared with other treatments, BRAF/MEK and PD-1 inhibition significantly improved OS. The favorable safety profile of PD-1 inhibitors supports using this treatment option as first line therapy in circumstances where rapid response is not a priority.

Kommentare zum Review

sparse networks for all outcomes -> imprecise estimates

most direct comparisons based on a single trial

¾ of all treatment comparisons from indirect evidence alone

publication bias could not be assessed

Chen P et al., 2017 [3].

Therapeutic efficacy and safety of combined BRAF and MEK inhibition in patients with malignant melanoma: a meta-analysis

Siehe auch Kim S et al. 2017 [36]

Fragestellung

The objective of this study was to conduct a meta-analysis of randomized controlled trials to compare the efficacy and adverse events risk between monotherapy and combination therapy.

Methodik

Population:

patients with melanoma or metastatic melanoma

Intervention:

combined use of BRAF and MEK inhibitors

Komparator:

single-agent BRAF inhibitor

Endpunkt:

overall response rate (ORR), PFS, and OS, as well as adverse events

Recherche/Suchzeitraum:

The PubMed, EMBASE, and Cochrane Library electronic databases were searched for articles published from January 2000 to January 2017

Qualitätsbewertung der Studien:

A modified Jadad scale was used to assess the quality of the included randomized studies. The scores of high-quality studies ranged from 4 to 8, whereas that of low-quality studies from 0 to 3. For non-randomized studies, the Newcastle-Ottawa Quality Assessment Scale was used. Each study was graded as either of low quality (0–5) or high quality (6–9).

Ergebnisse

Anzahl eingeschlossener Studien:

8 Studien, (davon 6 RCT), 2664 Patienten

Qualität der Studien:

Mean score was 4.25 (range, 3–6), which indicates that the overall quality of the study was fair.

Studienergebnisse:

Wirksamkeit:

- combination therapy significantly improved the ORR in comparison to monotherapy (RR: 1.34 [95% CI: 1.24–1.45], P<0.00001, I2=13%, 4 trials)
- PFS in combination therapy was significantly longer than that in monotherapy (HR: 0.58 [95% CI: 0.52–0.64], P<0.00001, I2=20%, 6 trials)
- combination therapy was associated with a significant enhancement of OS compared to monotherapy (HR: 0.70 [95% CI: 0.62–0.80], P<0.00001; I2=0%, 6 trials)

Unerwünschte Ereignisse:

Subgroup	Control		Analysis number	All-grade RR	95% CI	P-value
	Combined therapy	Monotherapy				
Pyrexia						
Combined *BRAF* and MEK inhibition vs *BRAF* alone	922	852	11–14, 16	2.00	1.40–2.84	0.0001
Dabrafenib+trametinib vs dabrafenib	318	264	11, 16	2.22	1.76–2.81	<0.00001
Vemurafenib+cobimetinib vs vemurafenib	254	239	12	1.17	0.85–1.61	0.32
Dabrafenib+trametinib vs vemurafenib	350	349	14	2.51	2.00–3.15	<0.00001
Nausea						
Combined *BRAF* and MEK inhibition vs *BRAF* alone	922	852	11–14, 16	1.41	1.03–1.94	0.03
Dabrafenib+trametinib vs dabrafenib	318	264	11, 16	1.64	1.03–2.62	0.04
Vemurafenib+cobimetinib vs vemurafenib	254	239	12	1.63	1.24–2.15	0.0004
Dabrafenib+trametinib vs vemurafenib	350	349	14	1.03	0.84–1.26	0.77
Diarrhea						
Combined *BRAF* and MEK inhibition vs *BRAF* alone	922	852	11–14, 16	1.50	1.08–2.06	0.01
Dabrafenib+trametinib vs dabrafenib	527	475	11, 16	1.44	0.76–2.71	0.26
Vemurafenib+cobimetinib vs vemurafenib	254	239	12	2.02	1.61–2.54	<0.0001
Dabrafenib+trametinib vs vemurafenib	350	349	14	1.23	1.01–1.50	0.04
Vomiting						
Combined *BRAF* and MEK inhibition vs *BRAF* alone	922	852	11–14, 16	1.87	1.52–2.31	<0.0001
Dabrafenib+trametinib vs dabrafenib	318	264	11, 16	1.94	1.28–2.94	0.002
Vemurafenib+cobimetinib vs vemurafenib	254	239	12	1.75	1.16–2.65	0.008
Dabrafenib+trametinib vs vemurafenib	350	349	14	1.90	1.41–2.56	<0.0001
Arthralgia						
Combined *BRAF* and MEK inhibition vs *BRAF* alone	922	852	11–14, 16	0.71	0.50–1.02	0.06
Dabrafenib+trametinib vs dabrafenib	527	475	11, 16	0.85	0.57–1.26	0.17
Vemurafenib+cobimetinib vs vemurafenib	254	239	12	0.81	0.64–1.03	0.08
Dabrafenib+trametinib vs vemurafenib	350	349	14	0.47	0.38–0.58	<0.0001

Abbreviations: RR, relative risk; MEK, mitogen-activated extracellular signal-regulated kinase.

Anmerkung/Fazit der Autoren

In summary, this study shows that combined therapy of BRAF and MEK inhibitors may moderately improve the overall response, PFS, and OS, although it may increase the incidence of some adverse events. In addition, prompt and effective management of these adverse events might allow for the safer use of combination therapy. We believe that our results could provide a reference point for physicians in clinical practice and ensure the safety and efficacy of treatment regimen for melanoma patients.

Kommentare zum Review

only eight studies met our inclusion criteria, and hence the small number of trials and low quality of most of the work could make the conclusion less convincing.

publication bias could not be completely excluded.

most researchers applied their personal experience in diagnosing the toxicities in the clinical trials, there were different judgements based on the same signs.

the treatment regimens and doses of drugs are different among the studies included in the meta-analysis, which led to significant heterogeneity of the data.

Abdel-Rahman O et al., 2016 [1].

Doublet BRAF/MEK inhibition versus single-agent BRAF inhibition in the management of BRAF-mutant advanced melanoma, biological rationale and meta-analysis of published data

Fragestellung

comparative systematic review and meta-analysis of the efficacy and toxicity of doublet BRAF/MEK inhibition versus single-agent BRAF inhibitor in the management of BRAF-mutant advanced melanoma.

Methodik

Population:

adult patients with BRAF-mutant advanced malignant melanoma.

Intervention:

Doublet BRAF/MEK inhibition

Komparator:

Single-agent BRAF inhibition

Endpunkt:

PFS, OS, ORR, and toxicities

Recherche/Suchzeitraum:

01/1966-03/2015

Qualitätsbewertung der Studien:

Quality of the included studies was assessed by using Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

4/ 1775

Qualität der Studien:

Qualitätsbewertung der Einzelstudien:

- Robert et al. 2015: Trametinib/dabrafenib combination vs. Vemurafenib, Jadad Score: 3 (open-label)
- Long et al. 2014: Trametinib/dabrafenib combination vs. dabrafenib + placebo, Jadad Score 5
- Flaherty et al 2012: Trametinib/dabrafenib combination vs. dabrafenib mono, Jadad Score: 3 (open label)
- Larkin et al 2014: Cobimetinib/vemurafenib combination vs. vemurafenib + placebo, Jadad Score: 4 (blinding method not described)

Studienergebnisse:

Efficacy outcomes: doublet regimens versus BRAF-inhibitor monotherapy

- OR for ORR was 1.35 [95 % CI (1.16, 1.58); P = 0.0002]
- HR for PFS was 0.56 [95 % CI (0.49, 0.64); P<0.00001]
- HR for OS was 0.70 [95 % CI (0.58, 0.84); P = 0.0001]
- combination strategy is associated with a statistically significant enhancement in ORR, PFS and OS

- However, it has to be noted that OS meta-analysis derives from just two trials (as OS was reported in only two studies).

Toxicities doublet regimens versus BRAF-inhibitor monotherapy:

- The RR of all grade diarrhea was 1.30 [95 % CI (1.30, 1.49); P = 0.0002]; while for high grade diarrhea it was 5.50 [95 % CI (1.92, 15.74); P = 0.001]
- The RR of all grade hypertension was 1.22 [95 % CI (0.99, 1.52); P = 0.07]; while for high grade hypertension it was 0.78 [95 % CI (0.33, 1.82); P = 0.56]
- The RR of all grade decreased ejection fraction was 4.63 [95 % CI (2.56, 8.37); P =<0.00001]
- doublet regimens are associated with a significantly higher RR for all grade diarrhea, decreased ejection fraction, acneiform dermatitis and pyrexia as well as higher RR for high grade diarrhea. Paradoxically, BRAF-inhibitor monotherapy is associated with a higher RR for cutaneous SCC compared to doublet regimens.
- The RR of all grade hypertension is, however, on the margin of significance and may need further assessment.

Anmerkung/Fazit der Autoren

Our meta-analysis has demonstrated that combination of MEK/BRAF inhibitors is associated with higher ORR, PFS and OS. However, this comes at the expense of a higher risk of selected toxicities.

Yun S et al., 2016 [44].

Targeting immune checkpoints in unresectable metastatic cutaneous melanoma: a systematic review and meta-analysis of anti-CTLA-4 and anti-PD-1 agents trials

Fragestellung

to determine the efficacy and safety of immune checkpoint inhibitors in comparison with conventional regimens.

Methodik

Population:

patients with unresectable metastatic cutaneous melanoma

Intervention:

immune check point inhibitors (ipilimumab, tremelimumab, nivolumab, pembrolizumab [previously known as lambrolizumab])

Komparator:

chemotherapy or vaccination (dacarbazine, carboplatin, temozolomide, paclitaxel, or gp100)

Endpunkt:

6-month PFS, ORR, 1- year OS rate, grade 3/4 immune- related adverse events rate

Recherche/Suchzeitraum:

Relevant studies were identified by searching PubMed, EMBASE, and Cochrane database of systematic review up to Sep 2015.

Qualitätsbewertung der Studien:

bias risk assessment using the Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

6 RCTs, 3196 patients

Qualität der Studien:

Four trials were double-blinded and two were open-label studies. Random sequence generation and allocation concealment were performed adequately in all studies. The adequacy of blinding was judged by whether treatment response was evaluated by a third person who did not know the treatment group of the patients. Four studies performed blinded assessments, but blinding was unclear in two studies.

Studienergebnisse:

Immune check point inhibitors were associated with

- higher 6- month PFS rate of 28.5% versus 17.7% (RR: 0.84, 95% CI: 0.76–0.93, P = 0.0004, I2 = 85%,),
- 1- year OS rate of 51.2% versus 38.8% (RR: 0.72, 95% CI: 0.59–0.88, P = 0.001, I2 = 84%,),
- higher ORR of 29.6% versus 17.7% (RR: 0.85, 95% CI: 0.76–0.95, P = 0.005, I2 = 89%)
- Grade 3/4 immune- related adverse events were more frequently associated with immune check point inhibitors at 13.7% versus 2.4% (RR: 6.74, 95% CI: 4.65–9.75, P < 0.0001, I2 = 0%)
- heterogeneity largely attributable to the experimental agent used (anti- CTLA- 4 vs. anti-PD- 1)
- Both anti- CTLA- 4 and anti- PD- 1 inhibitor treatments were associated with higher PFS rates when each treatment was compared to control, however, with a significant subgroup difference favoring nivolumab or pembrolizumab over ipilimumab or tremelimumab treatments (RR: 0.92 vs. 0.74, P < 0.00001)

Subgroup analyses

- BRAF mutation status did not have a statistically significant prognostic impact on ORR

Anmerkung/Fazit der Autoren

In a meta-analysis of randomized controlled trials with unresectable cutaneous metastatic melanoma patients, agents targeting immune checkpoints were associated with better PFS, OS, and ORR compared to conventional treatments. Subgroup analyses showed that survival benefit was significantly higher with anti-PD-1 treatment regardless of previous response to ipilimumab treatment, suggesting that nivolumab or pembrolizumab is a better choice as the first-line treatment. Our meta-analysis also indicates that there is a need for future study to assess the prognostic values of PD-L1 expression level and optimal sequential treatments for better clinical outcome.

Guan X et al., 2016 [15].

The Efficacy and Safety of Programmed Cell Death 1 and Programmed Cell Death 1 Ligand Inhibitors for Advanced Melanoma: A Meta-Analysis of Clinical Trials Following the PRISMA Guidelines

Siehe auch: Lin Z et al., 2016 [38].

Fragestellung

to investigate the efficacy and safety of programmed cell death 1 (PD-1) and programmed cell death 1 ligand (PD-L1) inhibitors using a meta-analysis of present trials for advanced melanoma.

Methodik

Population:

Patients with melanoma

Intervention/Komparator:

PD-1 antibody or an anti-PD-L1 antibody

Endpunkt:

ORR, PFS, AEs

Recherche/Suchzeitraum:

A systematic literature search of studies published until July 2015 was performed in EMBASE, Medline, Cochrane Controlled Trials Register Databases, and the Chinese Biomedical Literature Database

Qualitätsbewertung der Studien:

Cochrane methodology

Ergebnisse

Anzahl eingeschlossener Studien:

12 clinical trials provided sufficient data that satisfied the inclusion criteria for this meta-analysis.

Qualität der Studien:

Durch 2 unabhängige Reviewer durchgeführt, jedoch wurden die Ergebnisse nicht genannt.

Studienergebnisse:

The ORR of PD-1 and PD-L1 inhibitors was 30% (95% CI: 25–35%). No significant difference in the ORR was observed after the comparisons of low-dose, median-dose, and high-dose cohorts.

In addition, the rate of Grade 3–4 AEs was 9% (95% CI: 6–12%).

According to the 3 randomized controlled trials that compared PD-1 inhibitors with chemotherapy, the difference between these 2 groups was found to be statistically significant with respect to the ORR, PFS and the incidence of Grade 3–4 AEs; that is, the relative risk (RR) of the ORR was 3.42 (95% CI: 2.49–4.69, P<0.001), the hazard ratio (HR)

of the PFS was 0.50 (95% CI: 0.44–0.58, P<0.001), and the RR of Grade 3–4 AEs was 0.45 (95% CI: 0.31–0.65, P<0.001).

Anmerkung/Fazit der Autoren

In conclusion, according to this meta-analysis of limited concurrent studies, PD-1 and PD-L1 inhibitors appear to be associated with improved response rates, superior response durability and tolerable toxicity in patients with advanced melanoma. We may inevitably encounter some limitations because the concurrent studies included in the meta-analysis were mostly phase I trials, and only 3 phase II and III RCTs were included. As a hot issue in the area of cancer treatment, the initiation of a greater number of successive clinical trials associated with immune checkpoint blockade along with a further exploration into the mechanism of tumor immunity would not fail to surprise us.

Kommentare zum Review

Keine Stratifizierung hinsichtlich BRAF-Mutation

Hao C et al., 2017 [16].

Efficacy and safety of anti-PD-1 and anti-PD-1 combined with anti-CTLA-4 immunotherapy to advanced melanoma: A systematic review and meta-analysis of randomized controlled trials

Fragestellung

Anti-PD-1monoclonalantibodies, nivolumab and pembrolizumab, and anti-CTLA-4antibody ipilimumab are being in clinic trials to treat melanoma. Here, we performed a meta-analysis to evaluate the efficacy and toxicity of them against advanced melanoma.

Methodik

Population:

adult patients with advanced cutaneous melanoma

Intervention:

nivolumab or pembrolizumab

Komparator:

chemotherapy or ipilimumab

Endpunkt:

ORR, PFS, OS, AEs

Recherche/Suchzeitraum:

from 1990 to February 2017

Qualitätsbewertung der Studien:

Cochrane methodology

Ergebnisse

Anzahl eingeschlossener Studien:

6 Studies with 3284 patients: In all included 6 randomized control trials, 4 were randomized phase 3 trials and 2 were randomized phase 2 trials.

Qualität der Studien:

The methodological quality of included trials.

Trials	A	B	C	D	E	F
CheckMate066	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
CheckMate 037	Low risk	Unclear	High risk	Low risk	Low risk	Unclear
CheckMate 067	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
CheckMate 069	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
KeyNote006	Unclear	Unclear	High risk	Low risk	Low risk	Unclear
KeyNote002	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear

A = random sequences generation, B = allocation concealment, C = blinding of participants and personnel, D = incomplete outcome data, E = selective outcome reporting, F = other source of bias.

Studienergebnisse:

For nivolumab/pembrolizumab versus chemotherapy, nivolumab versus ipilimumab, and nivolumab-plus-ipilimumab versus ipilimumab, the pooled risk ratios (RR) of the ORR were 3.43 (95% CI: 2.57–4.58), 2.51 (95% CI: 2.03–3.09), and 3.28 (95% CI: 2.58–4.17), respectively.

The pooled HR of PFS were 0.42 (95% CI: 0.36–0.49), 0.58 (95% CI: 0.50–0.66), and 0.41 (95% CI: 0.30–0.52), respectively. The pooled RR of 1-yearOSwas 1.37 (95%CI: 1.08–1.74) and 1.54 (95%CI: 0.90–2.63) for nivolumab versus ipilimumab and nivolumab-plus-ipilimumab versus ipilimumab. These results suggested that anti-PD-1 monotherapy and nivolumab plus-ipilimumab therapy had ORR and PFS benefit compared with the control group.

Anti-PD-1 treatment increased 1-year OS for patients compared with ipililumab treatment. But there is no significantly difference on 1-year OS between the nivolumab-plus ipilimumab treatment and the ipilimumab treatment group.

The toxicity analysis showed that there is less risk of adverse events in the anti-PD-1 treatment group compared with the chemotherapy and ipilimumab group.

Combining nivolumab with ipilimumab increased the risk for high-grade adverse events compared with ipilimumab alone but the adverse events were generally manageable.

Anmerkung/Fazit der Autoren

Our meta-analysis suggests that anti-PD-1 monotherapy and nivolumab-plus-ipilimumab combination therapy would be a promising approach for the treatment of advanced melanoma, regardless of the patients of untreated or after anti-CTLA-4 treatment, with significant improvement in ORR and PFS and fewer adverse events relative to chemotherapy or ipilimumab treatments. Anti-PD-1 monotherapy could improve 1-year OS than ipilimumab. The nivolumab-plus-ipilimumab treatment could significantly improve ORR and PFS and increase adverse events, which could be managed, but did not increase 1-year OS significantly compared with ipilimumab monotherapy treatment. Because our analysis is based on a small number of included trials for each subgroup, the inherent limitations of included studies prevent us from reaching definitive conclusions. Future large volume, well-designed RCTs with extensive follow-up are awaited to confirm and update the findings of this analysis.

Kommentare zum Review

Our results were based on unadjusted analysis, more accurate outcomes would result from adjustments for other confounders such as gender, age, BRAF mutation status, PD-L1 status, prior systemic therapy, etc.

The small number of included trials for each subgroup make the outcomes more prone to be influenced by a potential publication bias

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Karlsson AK et al., 2017 [35].

Checkpoint inhibitors for malignant melanoma: a systematic review and meta-analysis

Fragestellung

to establish whether these three drugs – ipilimumab, nivolumab, and pembrolizumab – offer greater efficacy and tolerability compared to control interventions (placebo, immunotherapy, or chemotherapy) in patients with stage III or IV unresectable cutaneous melanoma.

Methodik

Population:

Patients with unresectable cutaneous melanoma

Intervention:

ipilimumab, nivolumab, and pembrolizumab

Komparator:

control interventions (placebo, immunotherapy, or chemotherapy)

Endpunkt:

survival (overall or progression free), tumor response, or adverse events

Recherche/Suchzeitraum:

An electronic search was carried out on four databases:

- Embase Classic and Embase: 1947–March 26, 2016
- Medline and Medline In-Process and Other Non-Indexed Citations: 1946–March 27, 2016
- Web of Science Core Collection: 1970–March 27, 2016
- Cochrane library: all years–March 27, 2016

Qualitätsbewertung der Studien:

Using the 2010 CONSORT (Consolidated Standards of Reporting Trials) checklist/ risk-of-bias assessment

Ergebnisse

Anzahl eingeschlossener Studien:

7 studies and data from 3,628 patients

Qualität der Studien:

The mean score across the seven studies for the 2010 CONSORT checklist was 64.4%, with only one study scoring <60%. The three parameters of the CONSORT checklist that were consistently done poorly, however, were providing a hypothesis or objective, describing the randomization procedure, and identifying any weaknesses or limitations in the study. There was a positive correlation (Pearson's r=0.57) between the CONSORT checklist score and the HR for the primary efficacy outcome, wherein the lower quality studies reported more significant HRs (ie, closer to 0).

Studienergebnisse:

The hazard ratio for progression or death was 0.54 (95% confidence interval [CI]: 0.44–0.67), and the odds ratio for best overall response rate was 4.48 (95% CI: 2.77–7.24), both in favor of checkpoint inhibitors.

However, control treatments were associated with an insignificantly lower rate of discontinuation of treatment due to adverse effects or treatment-related adverse events.

Anmerkung/Fazit der Autoren

This meta-analysis has found that checkpoint inhibitors provide a statistically significant advantage over control interventions for PFS, OS, and BORR in patients with unresectable stage III or IV melanoma, without significantly worsening tolerability. The combination of ipilimumab and nivolumab was the most effective, but not surprisingly was less tolerable than monotherapy. Reliable and predictive biomarkers, along with clear guidelines for the optimal use of checkpoint inhibitors, holds the potential of improving the prognosis of patients with advanced melanoma, and moving immunotherapy toward becoming the fourth generation of cancer treatment, along with surgery, chemotherapy, and radiotherapy.

Jin C et al., 2016 [34].

The efficacy and safety of nivolumab in the treatment of advanced melanoma: a meta-analysis of clinical trials

Fragestellung

to assess the efficacy and safety of nivolumab in patients with advanced melanoma.

Methodik

Population:

Patients with adavanced melanoma

Intervention:

Nivolumab

Komparator:

Siehe Ergebnisteil

Endpunkt:

PFS, OS, ORR, CR, PR

Recherche/Suchzeitraum:

Embase, PubMed (MEDLINE), and Cochrane Library from January 2008 to August 2015

Qualitätsbewertung der Studien:

Cochrane criteria

Ergebnisse

Anzahl eingeschlossener Studien:

four trials with 1,910 patients

Table 1 The patients' characteristics of four clinical trials included

Reference (year)	Group	Patients (N)	Median age (years)	Sex (F; n)	Metastasis stage M1c (n)	LDH > ULN (n)	History of brain metastases (n)
Postow et al[25] (2015)	BRAF wild-type						
	Nivolumab + ipilimumab	72	66	24	34	15	4
	Ipilimumab	37	69	14	16	7	0
	All						
	Nivolumab + ipilimumab	95	64	32	44	24	4
	Ipilimumab	47	67	15	21	11	0
Larkin et al[24] (2015)	Nivolumab	316	59	114	184	112	8
	Nivolumab + ipilimumab	314	59	108	181	114	11
	Ipilimumab	315	61	113	183	115	15
Robert et al[26] (2015)	Nivolumab	210	64	89	128	79	7
	Dacarbazine	208	66	83	127	74	8
Weber et al[27] (2015)	Nivolumab	272	59	96	202	139	53
	Dacarbazine ± paclitaxel	133	62	48	102	46	18

Abbreviations: F, female; LDH, lactate dehydrogenase; ULN, upper limits of normal.

Qualität der Studien:

Table 2 The quality assessment of four randomized controlled trials included

Reference	Patients (N)	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias*
Postow et al[25]	142	Yes	Yes	Yes	Yes	Yes	Yes
Larkin et al[24]	945	Yes	Yes	Yes	Yes	Yes	Yes
Robert et al[26]	418	Yes	Yes	Yes	Yes	Yes	Yes
Weber et al[27]	405	Yes	Yes	Yes	Yes	Yes	Yes

Note: *Other bias refers to selective bias and measurement bias.

Studienergebnisse:

No aggregated HR for OS was available

The pooled hazard ratio of PFS was 0.53 (95% CI, 0.43–0.66; P,0.001).

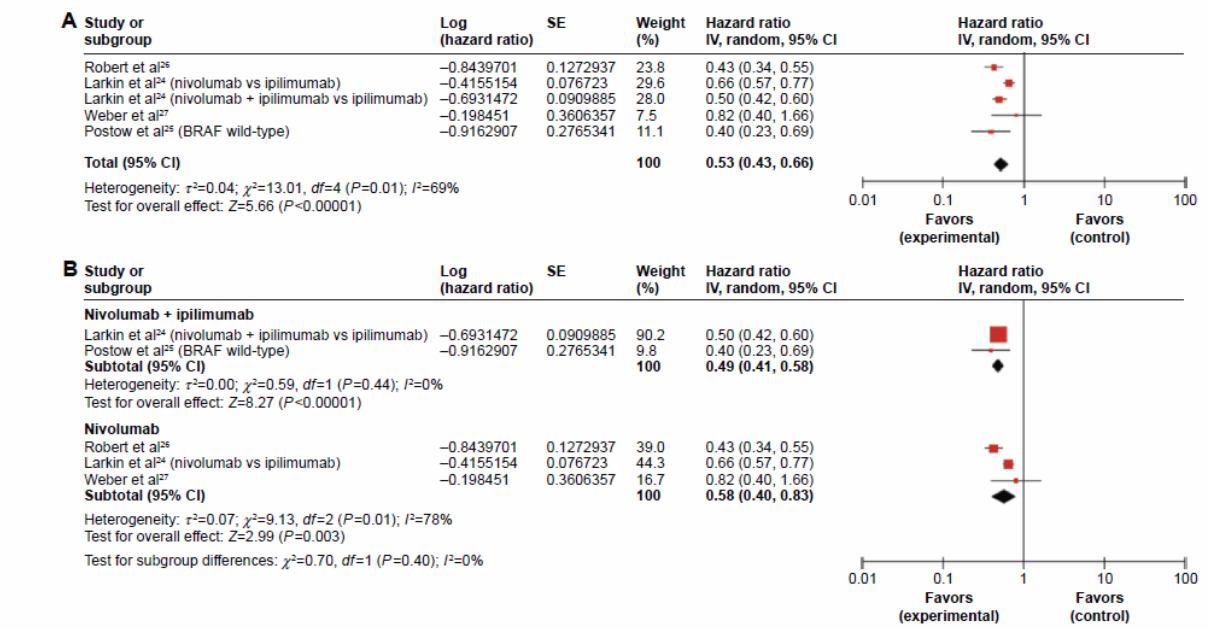

Figure 2 Forest plots for the aggregate progression-free survival of patients with advanced melanoma.
Notes: (A) All groups. (B) Subgroup (nivolumab combined group and nivolumab single group).
Abbreviations: SE, standard error; CI, confidence interval; IV, inverse variance.

The pooled risk ratio for the objective response rate, complete response, and partial response was 2.98% (95% CI, 2.38%–3.73%; P,0.001), 3.71% (95% CI, 2.67%–5.14%; P,0.001), and 2.51% (95% CI, 2.12%–2.99%; P,0.001), respectively.

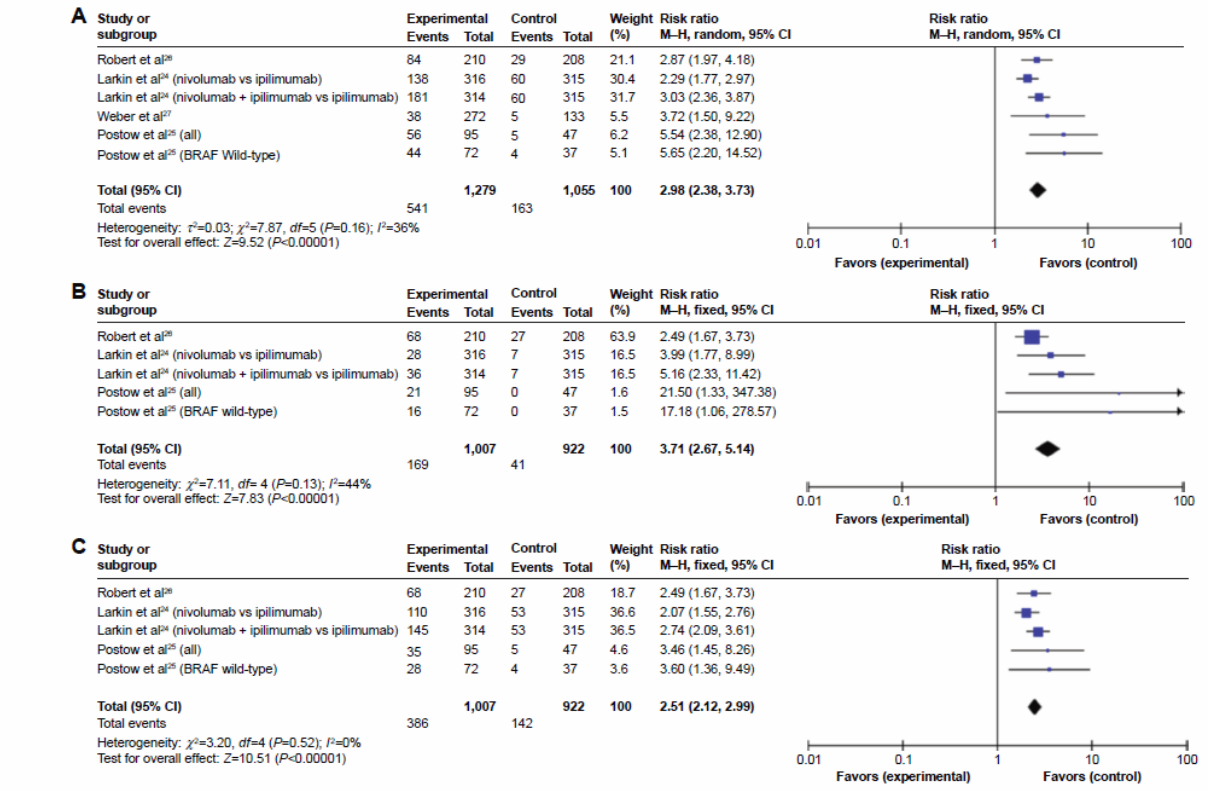

Figure 3 Forest plots of risk ratio for response from four randomized controlled trials.
Notes: (A) Objective response rate. (B) Complete response. (C) Partial response.
Abbreviations: SE, standard error; CI, confidence interval; M–H, Mantel–Haenszel.

Nivolumab plus ipilimumab therapy significantly increased the risk of grade 3/4 rash and fatigue

Table 3 The toxic effects of nivolumab in advanced melanoma

Adverse events	Nivolumab + ipilimumab vs ipilimumab		Nivolumab vs dacarbazine	
	Pooled RR and 95% CI	*P*-value	Pooled RR and 95% CI	*P*-value
Grade 3 and 4				
Diarrhea	1.38 (0.85–2.26)	0.19	0.70 (0.09–5.41)	0.73
Rash	2.70 (1.11–6.57)	0.03	NA*	NA*
Pruritus	4.27 (0.75–24.35)	0.10	2.99 (0.12–73.71)	0.50
Fatigue	4.51 (1.44–14.15)	0.01	0.23 (0.05–1.01)	0.05
Vomiting	5.41 (1.03–28.34)	0.05	0.45 (0.08–2.46)	0.36
Nausea	2.30 (0.65–8.15)	0.20	None^	None^
All grades				
Diarrhea	1.32 (1.10–1.59)	0.003	0.68 (0.31–1.50)	0.35
Rash	1.28 (1.05–1.56)	0.01	NA*	NA*
Pruritus	0.99 (0.81–1.21)	0.93	4.96 (1.47–16.72)	0.01
Fatigue	2.30 (0.33–15.83)	0.40	5.69 (0.05–636.7)	0.47
Vomiting	1.91 (1.25–2.92)	0.003	0.27 (0.17–0.43)	0.000

Notes: NA*: not provided; none^: there were no patients with nausea.
Abbreviations: RR, risk ratio; CI, confidence interval.

Anmerkung/Fazit der Autoren

In conclusion, nivolumab provides a statistically significant and clinically relevant extension of life in patients with advanced melanoma. Toxicity analyses suggest that nivolumab side effects are mostly mild to moderate. Further randomized, blinded, placebo-controlled trials are required to compare the efficacy and safety of nivolumab with other treatments used for advanced melanoma.

Kommentare zum Review

Keine Stratifizierung nach BRAF

Amdahl J et al., 2016 [2].

Network Meta-analysis of Progression-Free Survival and Overall Survival in First-Line Treatment of BRAF Mutation-Positive Metastatic Melanoma.

Fragestellung

to estimate hazard ratios (HRs) for progression-free survival (PFS)and overall survival (OS) of dabrafenib plus trametinib versus other first-line treatments of BRAF mutation-positive metastatic melanoma including dabrafenib, trametinib, vemurafenib, ipilimumab, and dacarbazine (DTIC).

Methodik

Population:

Patients with BRAF mutation-positive advanced or metastatic melanoma.

Intervention/ Komparator:

First-line treatments: dabrafenib plus trametinib, dabrafenib, vemurafenib, trametinib, ipilimumab, and DTIC

Endpunkt:

PFS, OS

Recherche/Suchzeitraum:

two systematic literature reviews: The first review was undertaken to evaluate efficacy, safety, and tolerability of dabrafenib and trametinib monotherapy versus other first-line treatments for unresectable advanced or metastatic melanoma. The second review was undertaken to evaluate the efficacy and safety of the dabrafenib plus trametinib therapy compared to other first-line or second-line treatments for patients with unresectable or metastatic melanoma. For both reviews, Embase, MEDLINE, Cochrane Central Trials Register, and key conferences were searched.

Qualitätsbewertung der Studien:

k.A.

Ergebnisse

Anzahl eingeschlossener Studien:

ombiningtheresultsof thesetworeviews, and focusing on trials of previously untreated patients receiving any one of the comparators yielded seven studies.

Charakteristika der Population:

COMBI-v was the largest trial; BRF113220 was the smallest. Mean age ranged from 49 years (BRF113220, dabrafenib plus trametinib 1 mg) to 58 years (BRF113220, dabrafenib plus trametinib 2 mg). The percent male ranged from 49% (METRIC, DTIC) to 63% (BRF113220, dabrafenib plus trametinib 2 mg). The percent with Eastern Cooperative Oncology Group performance status [0 ranged from 25% (COMBI-d, dabrafenib plus trametinib) to 37% (BRF113220, dabrafenib). The percent with stage M1C at diagnosis ranged from 55% (CA184-024, DTIC) to 70% (BRF113220, dabrafenib plus trametinib 2 mg). The percent with elevated lactate dehydrogenase ranged from 30% (BREAK-3, DTIC) to 58% (BRIM-3, DTIC).

Studienergebnisse:

The HRs for PFS for the research arm versus the control arm were statistically significant for all trials.

In multivariate network-meta analyses (HRs for PFS and OS estimated simultaneously to account for the correlation of treatment effects on PFS and OS), HRs (95% credible interval) for PFS and OS favored dabrafenib plus trametinib

- PFS: 0.23 (0.18–0.29) versus DTIC, 0.32 (0.24–0.42) versus ipilimumab plus DTIC, 0.52 (0.32–0.83) versus trametinib, 0.57 (0.48–0.69) versus vemurafenib, and 0.59 (0.50–0.71) versus dabrafenib;
- OS: [0.41 (0.29–0.56) versus DTIC, 0.52 (0.38–0.71) versus ipilimumab plus DTIC, 0.68 (0.47–0.95) versus trametinib, 0.69 (0.57–0.84) versus vemurafenib, and 0.72 (0.60–0.85) versus dabrafenib].

The beneficial effects on OS of dabrafenib plus trametinib versus ipilimumab plus DTIC and versus trametinib were attenuated when HRs were estimated using univariate network meta-analysis (HRs for PFS and OS estimated separately).

Anmerkung/Fazit der Autoren

In conclusion, this network meta-analysis demonstrates improved PFS and OS with dabrafenib plus trametinib versus dabrafenib, trametinib, vemurafenib, ipilimumab, and DTIC

as first-line therapy for patients with BRAF mutation-positive metastatic melanoma. Future research should be conducted which includes other novel treatments, if feasible, and based on network meta-analysis of survival distributions rather than HRs to account for non-proportionality of hazards.

Kommentare zum Review

this analysis did not consider new immunotherapies such as nivolumab and pembrolizumab, or the combination of vemurafenib plus the MEK inhibitor, cobimetinib

Differences in patients, study design, and duration of follow-up may have affected treatment effects thus violating the similarity assumption and confounding the comparisons.

Quinn C et al., 2016 [41].

Indirect Treatment Comparison of Talimogene Laherparepvec Compared with Ipilimumab and Vemurafenib for the Treatment of Patients with Metastatic Melanoma

Fragestellung

to examine the relative treatment effect of talimogene laherparepvec compared with ipilimumab and vemurafenib

Methodik

Population:

Patients with metastatic melanoma

Intervention:

Talimogene laherparepvec

Komparator:

Ipilimumab or vemurafenib

Endpunkt:

OS

Recherche/Suchzeitraum:

systematic review conducted in September 2015 of English-language studies, published since January 1990

Qualitätsbewertung der Studien:

Studies with a low risk of bias were identified using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria

Ergebnisse

Anzahl eingeschlossener Studien:

Four trials were included in the final indirect treatment comparison: two of ipilimumab, one of vemurafenib, and one of talimogene laherparepvec.

Table 2 Summary of randomized controlled Phase 3 trials included in the indirect treatment comparison, and patient characteristics used for adjustment of survival

Trial (reference)	OPTiM 005/05 [6]	OPTiM 005/05 [6]	MDX0101-20 [23]	CA184-024 [24, 25][a]	BRIM-3 [26]
Comparator (dose)	Talimogene laherparepvec	Talimogene laherparepvec	Ipilimumab (3 mg/kg)	Ipilimumab (10 mg/kg)	Vemurafenib (960 mg orally twice daily)
Patients	Previously untreated and previously treated	Previously untreated and previously treated	Previously treated	Previously untreated	Previously untreated
Disease stage	Unresectable, stage IIIB/C or IV	Unresectable, stage IIIB/C or IV M1a	Unresectable, stage III or IV	Unresectable, stage III or IV	Unresectable, stage IIIC or IV, positive for the *BRAF* V600E mutation
Female (%)	41	44	41	39	41
ECOG 0 (%)	71	74	53	71	68
Normal LDH (%)	90	94	61	63	58
No visceral disease (%)	55	100	11	17	16
No brain metastases (%)	99	100	89	99	100

ECOG Eastern Cooperative Oncology Group performance status, *LDH* Lactate dehydrogenase, *NICE* National Institute for Health and Care Excellence

[a] In the Bristol-Myers Squibb Pharmaceuticals Ltd. NICE submission [25], a derived first-line, 3 mg/kg overall survival for ipilimumab was accepted by NICE; these derived data are included in this analysis

Studienergebnisse:

Note: a valid network of evidence could not be established because of a lack of comparative data or studies with sufficient common comparators. A conventional adjusted indirect treatment comparison via network meta-analysis was, therefore, not feasible. Instead, a meta-analysis of absolute efficacy was undertaken, adjusting overall survival (OS) data for differences in prognostic factors between studies using a published algorithm.

- Median OS for ipilimumab and vemurafenib increased significantly when adjustment was applied, demonstrating that variation in disease and patient characteristics was biasing OS estimates; adjusting for this made the survival data more comparable. For both ipilimumab and vemurafenib, the adjustments improved Kaplan–Meier OS curves; the observed talimogene laherparepvec OS curve remained above the adjusted OS curves for ipilimumab and vemurafenib, showing that long-term survival could differ from the observed medians.

Unadjusted OS analyses:

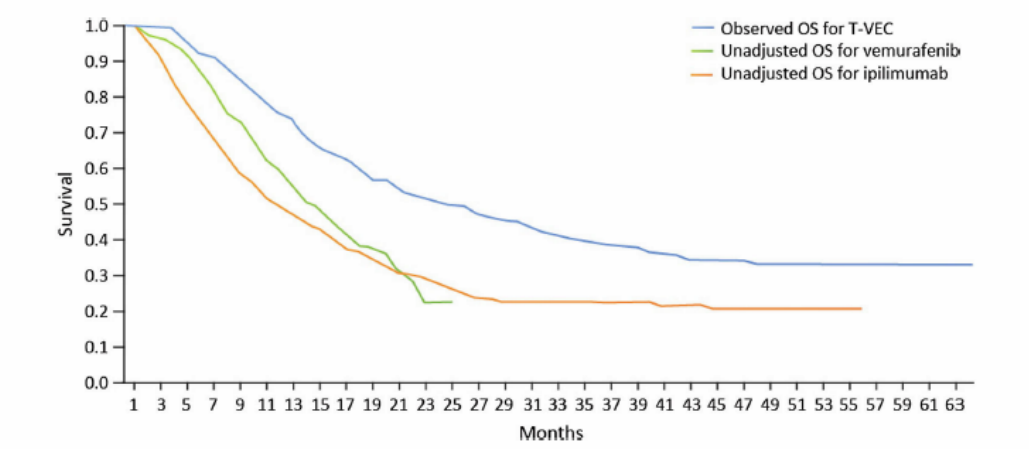

Fig. 1 Unadjusted Kaplan–Meier OS curves for ipilimumab and vemurafenib vs. observed OS curve for talimogene laherparepvec, all patients. *OS* overall survival, *T-VEC* talimogene laherparepvec

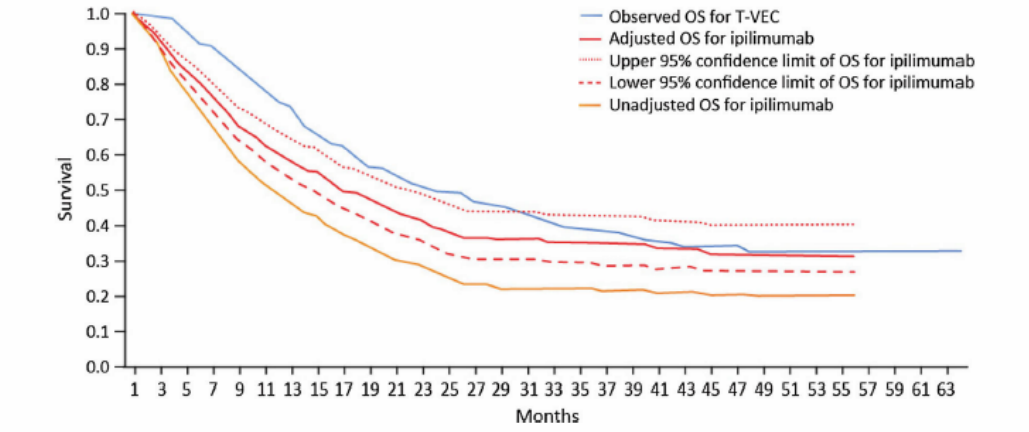

Fig. 2 Unadjusted and adjusted Kaplan–Meier OS curves for ipilimumab vs. observed OS curve for talimogene laherparepvec, all patients. *OS* overall survival, *T-VEC* talimogene laherparepvec

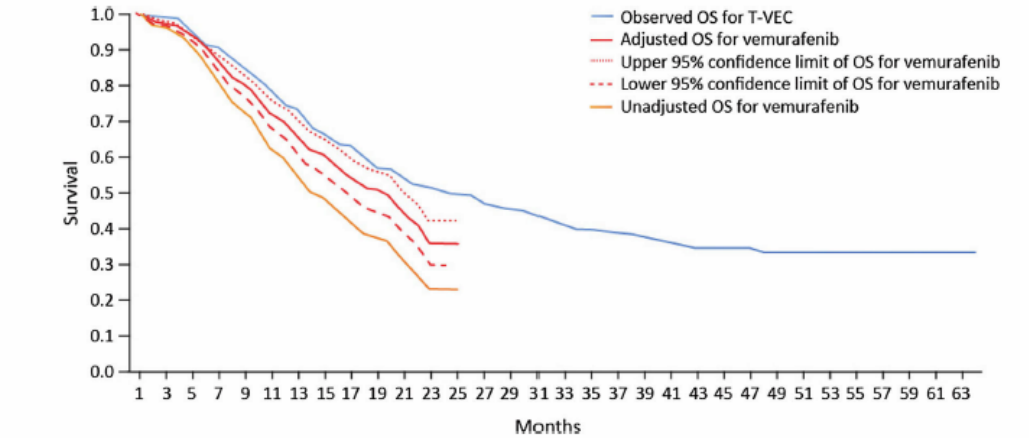

Fig. 3 Unadjusted and adjusted Kaplan–Meier OS curves for vemurafenib vs. observed OS curve for talimogene laherparepvec, all patients. *OS* overall survival, *T-VEC* talimogene laherparepvec

Adjusted OS analyses:

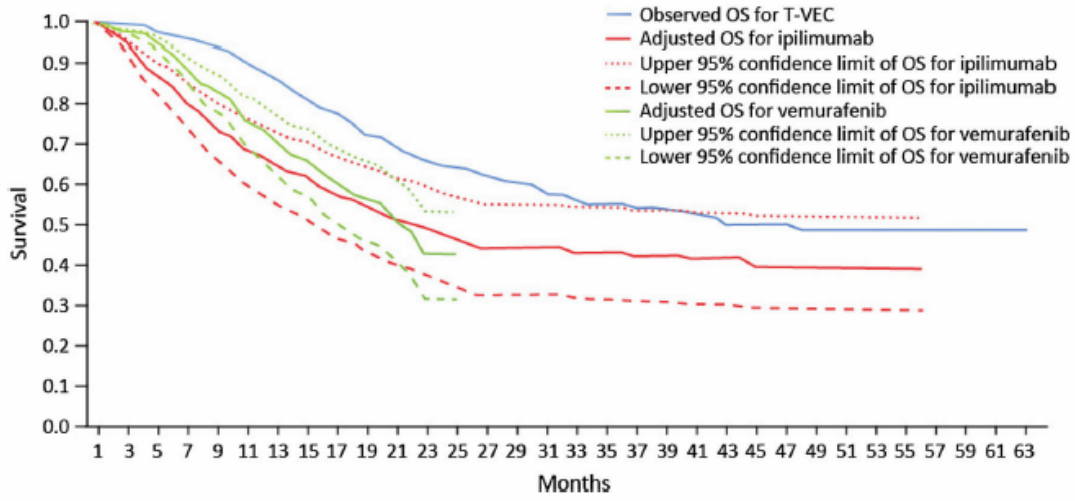

Fig. 4 Adjusted Kaplan–Meier OS curves for ipilimumab and vemurafenib vs observed OS curve for talimogene laherparepvec, patients with no bone, brain, lung, or other visceral metastases (stage IIIB–IV M1a disease). *OS* overall survival, *T-VEC* talimogene laherparepvec

Anmerkung/Fazit der Autoren

Even with limited data, talimogene laherparepvec, ipilimumab, and vemurafenib could be compared following adjustments, thereby providing a more reliable understanding of the relative effect of treatment on survival in a more comparable patient population. The results of this analysis suggest that overall survival with talimogene laherparepvec is at least as good as with

ipilimumab and vemurafenib and improvement was more pronounced in patients with no bone, brain, lung or other visceral metastases.

Kommentare zum Review

no network of RCTs for metastatic melanoma for which both direct and indirect comparisons exist

the algorithm used to adjust for differences in survival, specifically the original and modified Korn algorithms, has been used previously to adjust for heterogeneity, but has not been widely used in melanoma and might reflect specific clinical trials rather than patients with advanced melanoma generally

the impact of subsequent therapies on the results of OS in talimogene laherparepvec, ipilimumab, and vemurafenib was not specifically adjusted for

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Xie T et al., 2018 [43].

A Network Meta-Analysis of Short and Long-Term Efficacy of Targeted Therapy With Single or Double-Drug Regimens in the Treatment of Stage III/IV Malignant Melanoma Based on 16 Randomized Controlled Trials

Fragestellung

to compare the short and long-term efficacy of targeted therapy with single or double-drug regimens.

Methodik

Population:

Patients with stage III/IV MM

Intervention/ Komparator:

targeted therapy with single or double-drug regimens

Endpunkt:

complete response (CR), partial response (PR), overall response rate (ORR), stable disease (SD), progressive disease (PD), disease control rate (DCR), progression-free survival (PFS), or overall survival (OS)

Recherche/Suchzeitraum:

PubMed and Cochrane Library from inception to June 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

sixteen RCTs including 15 single-drug or double-drug regimens involving targeted therapy those of which are as followed: Dac, Ipi, Vem, Dab, Niv, Int, Pem, Dab+Tra, Niv+Ipi, Vem+Cob, Sel+Dac, End+Dac, Ipi+Dac, Int+Dac, and Sor+Dac

Studienergebnisse:

PAIRWISE META-ANALYSIS OF THE SHORT AND LONG-TERM EFFICACY OF FIFTEEN REGIMENS

In terms of the short-term efficacy compared with Dac, the ORR of single-drug regimens (Vem, Dab and Niv) was higher, the PR and DCR of Dab and Niv were higher but the PD was relatively lower. In comparison with Ipi, the CR and PR of Niv and Pem were higher. While compared to Dac, the DCR of double-drug regimens Sel+Dac, End+Dac) was higher. Besides, the ORR, CR, PR, and DCR of single-drug regimens (Vem) were relatively lower and the SD and PD were higher than those of double-drug regimens (Dab+Tra and Vem+Cob). The ORR, PR, and DCR of single-drug regimen (Dab) were lower but the PD was higher than those of double-drug regimen (Dab+Tra). The ORR, PR, and DCR of single drug regimen (Niv) were lower but the PD was higher than those of the double-drug regimen (Niv+Ipi). Compared with Niv and Niv+Ipi, the SD and PD of Ipi were relatively higher but the DCR was relatively lower. The SD and PD of Int were relatively lower than those of Int+Dac (Tables I and II).

TABLE I. Pairwise Meta-Analysis Results of ORR, CR, and PR in Malignant Melanoma Patients

Included study	Comparison	Efficacy event		Pairwise meta-analysis
		Treatment1	Treatment2	OR (95%CI)
ORR				
2 studies	A vs. C	35/327	188/328	0.09 (0.06–0.13)
1 study	A vs. D	4/63	93/187	0.07 (0.02–0.20)
1 study	A vs. E	29/208	84/210	0.24 (0.15–0.39)
1 study	A vs. F	3/32	2/33	1.60 (0.25–10.29)
1 study	A vs. K	12/46	18/45	0.53 (0.22–1.29)
1 study	A vs. L	2/54	5/53	0.37 (0.07–1.99)
1 study	A vs. M	26/252	38/250	0.64 (0.38–1.09)
1 study	A vs. N	3/32	1/32	3.21 (0.32–32.60)
1 study	A vs. O	6/50	12/51	0.44 (0.15–1.29)
1 study	B vs. E	60/315	138/316	0.30 (0.21–0.43)
1 study	B vs. G	33/278	94/279	0.27 (0.17–0.41)
3 studies	B vs. I	65/362	237/409	0.16 (0.11–0.22)
1 study	B vs. M	2/37	5/35	0.34 (0.06–1.90)
1 study	C vs. H	180/350	226/351	0.59 (0.43–0.79)
1 study	C vs. J	111/248	167/247	0.39 (0.27–0.56)
2 studies	D vs. H	141/266	185/265	0.49 (0.34–0.70)
1 study	E vs. I	138/316	181/314	0.57 (0.42–0.78)
1 study	F vs. N	3/33	1/32	2.00 (0.17–23.21)
CR				
1 study	A vs. D	1/63	6/187	0.49 (0.06–4.12)
1 study	A vs. E	2/208	16/210	0.12 (0.03–0.52)
1 study	A vs. F	1/32	1/33	1.03 (0.06-17.24)
1 study	A vs. K	1/46	1/45	0.98 (0.06–16.12)
1 study	A vs. L	1/54	1/53	0.98 (0.06–16.10)
1 study	A vs. M	2/252	4/250	0.49 (0.09–2.71)
1 study	A vs. N	1/32	1/32	1.00 (0.06–16.71)
1 study	A vs. O	1/50	1/51	1.02 (0.06–16.77)
1 study	B vs. E	7/315	28/316	0.23 (0.10–0.54)
1 study	B vs. G	4/278	14/279	0.28 (0.09–0.85)
3 studies	B vs. I	7/362	57/409	0.16 (0.07–0.34)
1 study	B vs. M	0/37	2/35	0.18 (0.01–3.86)
1 study	C vs. H	27/350	47/351	0.54 (0.33–0.89)
1 study	C vs. J	11/248	25/247	0.41 (0.20–0.86)
2 studies	D vs. H	30/266	38/265	0.76 (0.45–1.28)
1 study	E vs. I	28/316	36/314	0.75 (0.45–1.26)
1 study	F vs. N	1/33	1/32	0.97 (0.06–16.18)
PR				
1 study	A vs. D	3/63	87/187	0.06 (0.02–0.19)
1 study	A vs. E	27/208	68/210	0.31 (0.19–0.51)
1 study	A vs. F	3/32	2/33	1.60 (0.25–10.29)
1 study	A vs. K	11/46	17/45	0.52 (0.22–1.28)
1 study	A vs. L	2/54	5/53	0.37 (0.07–1.99)
1 study	A vs. M	24/252	34/250	0.67 (0.38–1.16)
1 study	A vs. N	3/32	1/32	3.21 (0.32-32.60)
1 study	A vs. O	6/50	12/51	0.44 (0.15–1.29)
1 study	B vs. E	53/315	110/316	0.38 (0.26–0.55)
1 study	B vs. G	29/278	80/279	0.29 (0.18–0.46)
3 studies	B vs. I	58/362	180/409	0.23 (0.16–0.33)
1 study	B vs. M	2/37	3/35	0.61 (0.10–3.89)
1 study	C vs. H	153/350	179/351	0.75 (0.55–1.00)
1 study	C vs. J	100/248	142/247	0.50 (0.35–0.71)
2 studies	D vs. H	111/266	147/265	0.57 (0.40–0.81)
1 study	E vs. I	110/316	145/314	0.62 (0.45–0.86)
1 study	F vs. N	2/33	1/32	2.00 (0.17–23.21)

ORR, overall response rate; CR, complete response; PR, partial response; OR, odds ratio; CI, confidence intervals; A, Dacarbazine; B, Ipilimumab; C, Vemurafenib; D, Dabrafenib; E, Nivolumab; F, Intetumumab; G, Pembrolizumab; H, Dabrafenib + Trametinib; I, Nivolumab + Ipilimumab; J, Vemurafenib + Cobimetinib; K, Selumetinib + Dacarbazine; L, Endostar + Dacarbazine; M, Ipilimumab + Dacarbazine; N, Intetumumab + Dacarbazine; O, Sorafenib + Dacarbazine.

TABLE II. Pairwise Meta-Analysis Results of SD, PD, and DCR in Malignant Melanoma Patients

		Efficacy events		Pairwise meta-analysis
Included study	Comparison	Treatment 1	Treatment 2	OR (95%CI)
SD				
1 study	A vs. D	30/63	78/187	1.27 (0.72–2.25)
1 study	A vs. E	46/208	35/210	1.42 (0.87–2.31)
1 study	A vs. F	10/32	8/33	1.42 (0.48–4.23)
1 study	A vs. K	10/46	13/45	0.68 (0.26–1.77)
1 study	A vs. L	16/54	25/53	0.47 (0.21–1.04)
1 study	A vs. M	50/252	45/250	1.13 (0.72–1.76)
1 study	A vs. N	10/32	16/32	0.45 (0.16–1.26)
1 study	A vs. O	22/50	24/51	0.88 (0.40–1.94)
1 study	B vs. E	69/315	34/316	2.33 (1.49–3.63)
3 studies	B vs. I	83/362	53/409	2.04 (1.39–2.99)
1 study	B vs. M	6/37	8/35	0.65 (0.20–2.12)
1 study	C vs. H	106/350	92/351	1.22 (0.88–1.70)
1 study	C vs. J	105/248	49/247	2.97 (1.99–4.43)
2 studies	D vs. H	88/266	63/265	1.58 (1.08–2.32)
1 study	E vs. I	34/316	41/314	0.80 (0.49–1.30)
1 study	F vs. N	8/33	16/32	0.32 (0.11–0.92)
PD				
1 study	A vs. D	23/63	10/187	10.18 (4.49–23.06)
1 study	A vs. E	101/208	69/210	1.93 (1.30–2.87)
1 study	A vs. F	16/32	23/33	0.43 (0.16–1.20)
1 study	A vs. K	24/46	14/45	2.42 (1.03–5.69)
1 study	A vs. L	36/54	26/53	2.08 (0.95–4.54)
1 study	A vs. M	131/252	111/250	1.36 (0.95–1.93)
1 study	A vs. N	16/32	13/32	1.46 (0.54–3.93)
1 study	A vs. O	21/50	15/51	1.74 (0.76–3.96)
1 study	B vs. E	154/315	119/316	1.58 (1.15–1.27)
3 studies	B vs. I	176/362	86/409	3.49 (2.54–4.79)
1 study	B vs. M	28/37	20/35	2.33 (0.85–6.38)
1 study	C vs. H	38/350	22/351	1.82 (1.05–3.15)
1 study	C vs. J	25/248	19/247	1.35 (0.72–2.51)
2 studies	D vs. H	22/266	3/265	1.64 (0.81–3.34)
1 study	E vs. I	119/316	71/314	2.07 (1.46–2.93)
1 study	F vs. N	23/33	13/32	3.36 (1.21–9.36)
DCR				
1 study	A vs. D	34/63	171/187	0.11 (0.05–0.22)
1 study	A vs. E	75/208	119/210	0.43 (0.29–0.64)
1 study	A vs. F	13/32	10/33	1.57 (0.57–4.38)
1 study	A vs. K	22/46	31/45	0.41 (0.18–0.97)
1 study	A vs. L	18/54	30/53	0.38 (0.17–0.84)
1 study	A vs. M	76/252	83/250	0.87 (0.60–1.27)
1 study	A vs. N	13/32	17/32	0.60 (0.22–1.62)
1 study	A vs. O	28/50	36/51	0.53 (0.23–1.21)
1 study	B vs. E	129/315	172/316	0.58 (0.42–0.80)
3 studies	B vs. I	148/362	290/409	0.28 (0.21–0.38)
1 study	B vs. M	8/37	13/35	0.47 (0.16–1.32)
1 study	C vs. H	286/350	318/351	0.46 (0.30–0.73)
1 study	C vs. J	216/248	216/247	0.97 (0.57–1.64)
2 studies	D vs. H	229/266	248/265	0.44 (0.24–0.80)
1 study	E vs. I	172/316	222/314	0.49 (0.36–0.69)
1 study	F vs. N	10/33	17/32	0.38 (0.14–1.06)

SD, stable disease; PD, progressive disease; DCR, disease control rate; OR, odds ratio; CI, confidence intervals; A, Dacarbazine; B, Ipilimumab; C, Vemurafenib; D, Dabrafenib; E, Nivolumab; F, Intetumumab; H, Dabrafenib + Trametinib; I, Nivolumab + Ipilimumab; J, Vemurafenib + Cobimetinib; K, Selumetinib + Dacarbazine; L, Endostar + Dacarbazine; M, Ipilimumab + Dacarbazine; N, Intetumumab + Dacarbazine; O, Sorafenib + Dacarbazine.

In terms of the long-term efficacy compared with Dac, the single drug regimens (Vem and Niv) had longer PFS and higher 12 month- OS rate. The PFS of Niv and Pem were also longer than that of Ipi. Compared with Dac, the PFS, and OS of double-drug regimens (Sel+Dac and End+Dac) were longer, while the PFS of Sor+Dac was longer, the OS of Sor+Dac was relatively shorter, and the 6 month-PFS rate of Sor+Dac was relatively higher (Table III).

TABLE III. Pairwise Meta-Analysis Results of PFS, OS, 6 month-PFS rate, and 12 Month-OS Rate in Malignant Melanoma Patients

		Pairwise meta-analysis
Included study	Comparison	WMD/OR (95%CI)
PFS (months)		
2 studies	A vs. C	−4.79 (−5.87 to −3.72)
1 study	A vs. E	−2.90 (−3.29 to −2.51)
1 study	A vs. K	−3.40 (−4.07 to −2.73)
1 study	A vs. L	−3.00 (−3.39 to −2.61)
1 study	A vs. O	−2.35 (−2.67 to −2.03)
1 study	B vs. E	−4.00 (−4.15 to −3.85)
1 study	B vs. G	−2.70 (−2.78 to −2.62)
1 study	B vs. I	−8.60 (−8.89 to −8.31)
1 study	E vs. I	−4.60 (−4.93 to −4.27)
OS(months)		
1 study	A vs. C	−3.30 (−3.55 to −3.05)
1 study	A vs. K	−2.60 (−2.84 to −2.36)
1 study	A vs. L	−4.00 (−4.34 to −3.66)
1 study	A vs. M	−2.10 (−2.28 to −1.92)
1 study	A vs. O	1.43 (0.30–2.56)
6 month-PFS rate		
1 study	A vs. F	0.80 (0.19–3.29)
1 study	A vs. K	0.42 (0.17–1.05)
1 study	A vs. N	0.77 (0.19–3.18)
1 study	A vs. O	0.36 (0.15–0.87)
1 study	F vs. N	0.96 (0.25–3.71)
12 month-OS rate		
1 study	A vs. C	0.62 (0.45–0.85)
1 study	A vs. E	0.27 (0.18–0.41)
1 study	A vs. F	0.30 (0.11–0.83)
1 study	A vs. L	0.30 (0.13–0.69)
1 study	A vs. M	0.63 (0.44–0.90)
1 study	A vs. N	0.59 (0.22–1.63)
1 study	C vs. H	0.72 (0.53–1.00)
1 study	D vs. H	0.75 (0.49–1.14)
1 study	F vs. N	1.98 (0.74–5.35)

PFS, profession-free survival; OS, overall survival; WMD, weighted mean difference; OR, odd ratios; CI, confidence intervals; A, Dacarbazine; B, Ipilimumab; C, Vemurafenib; D, Dabrafenib; E, Nivolumab; F, Intetumumab; G, Pembrolizumab; H, Dabrafenib + Trametinib; I, Nivolumab + Ipilimumab; K, Selumetinib + Dacarbazine; L, Endostar + Dacarbazine; M, Ipilimumab + Dacarbazine; N, Intetumumab + Dacarbazine; O, Sorafenib + Dacarbazine. PFS (month) and OS (month) are stated as WMD values, while 6 month-PFS rate, and 12 month-OS rate are stated as OR values.

NETWORK META-ANALYSIS OF THE SHORT AND LONG-TERM EFFICACY OF FIFTEEN REGIMENS

The NMA indicated that when compared with Dac, the ORR of single-drug regimens (Vem, Dab, and Niv) was higher, while the ORR of double-drug regimens (Dab+Tra, Niv+Ipi and Vem+Cob) was relatively higher (see Fig. 2).

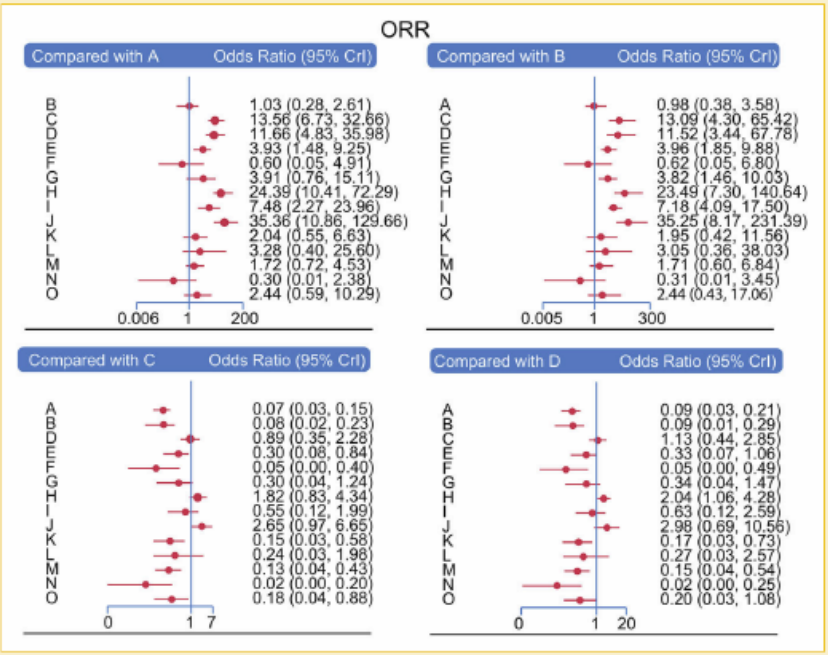


Fig. 2. Forest plots of relative relationship of the ORR of 15 targeted therapy regimens in the treatment of stage III/IV MM. ORR, overall response rate; MM, malignant melanoma; A, Dacarbazine; B, Ipilimumab; C, Vemurafenib; D, Dabrafenib; E, Nivolumab; F, Intetumumab; G, Pembrolizumab; H, Dabrafenib + Trametinib; I, Nivolumab + Ipilimumab; J, Vemurafenib + Cobimetinib; K, Selumetinib + Dacarbazine; L, Endostar + Dacarbazine; M, Ipilimumab + Dacarbazine; N, Intetumumab + Dacarbazine; O, Sorafenib + Dacarbazine).

Meanwhile, the DCR of single-drug regimens (Vem and Dab) and that of double-drug regimen (Dab+Tra) were relatively higher in comparison to Dac (Supplementary Table SIII and Fig. 3).

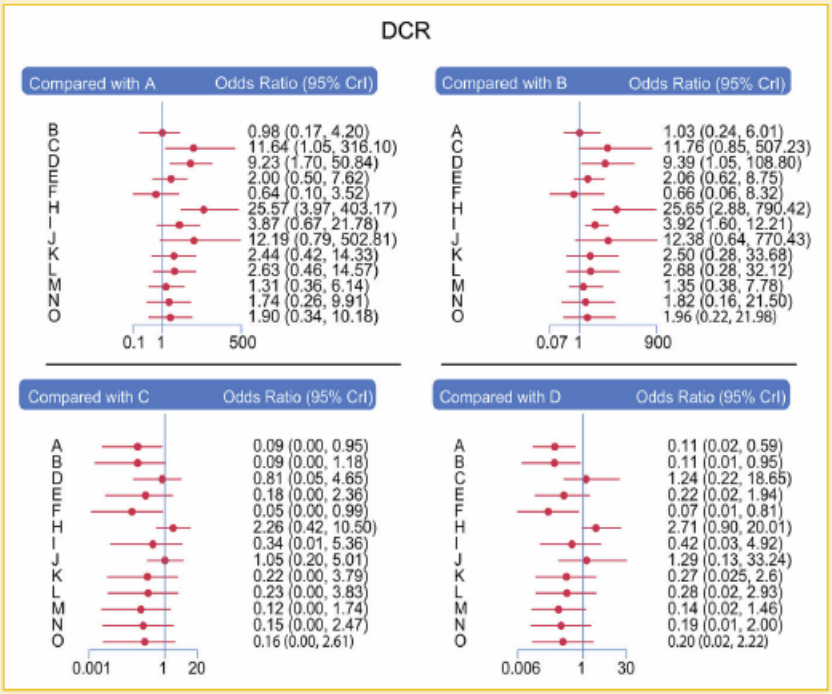


Fig. 3. Forest plots of relative relationship of DCR of 15 targeted therapy regimens in the treatment of stage III/IV MM. DCR, disease control rate; MM, malignant melanoma; A, Dacarbazine; B, Ipilimumab; C, Vemurafenib; D, Dabrafenib; E, Nivolumab; F, Intetumumab; H, Dabrafenib + Trametinib; I, Nivolumab + Ipilimumab; J, Vemurafenib + Cobimetinib; K, Selumetinib + Dacarbazine; L, Endostar + Dacarbazine; M, Ipilimumab + Dacarbazine; N, Intetumumab + Dacarbazine; O, Sorafenib + Dacarbazine).

In terms of the long-term efficacy, among these 15 targeted therapy regimens, there were no significant differences in the PFS, OS, 6 month-PFS rate, and 12 month-OS rate

As it pertains to the short-term efficacy, the ORR and PR of Ipi were lower than those of Pem (see Fig. 2).

Compared with Ipi, the ORR, and PR of single-drug regimens (Vem, Dab, and Niv) were higher.

The PD in the case of Dab was relatively lower while the DCR of Dab was higher.

In comparison to single-drug regimens of Vem and Dab, the ORR of Sel+Dac, Ipi+Dac, and Int+Dacarbazin was relatively lower (see Fig. 2), as well as the PR of Sel+Dac, Ipi+Dac, Int+Dac, and Sor+Dac was relatively lower.

CUMULATIVE PROBABILITY OF THE EFFICACY OF FIFTEEN REGIMENS

As shown in Table IV, the SUCRA values of the efficacy among the 15 targeted therapy regimens demonstrated that the cumulative probability of ORR, PR, PD, DCR, PFS, and OS in stage III/IV MM patients treated by targeted single-drug regimen (Vem) ranked the highest (ORR: 82.47%; PR: 83.87%; PD: 81.71%; DCR: 83.14%; PFS: 76.44%; OS: 76.33%).

The cumulative probability of CR, SD, and 12 month-OS rate of Niv also ranked the highest (CR: 70.07%; SD: 72.86%; 12 month-OS rate: 76.56%) among the 15 targeted therapy regimens.

Among the targeted double-drug regimens, the cumulative probability of PD and DCR of Dab+Tra ranked the highest (PD: 93.93%; DCR: 96.14%), those involving CR and PFS of Niv+Ipi ranked the highest (CR: 77.67%; PFS: 89.67%), those involving ORR, PR, and SD of Vem+Cob ranked the highest (ORR: 97.27%; PR: 97.07%; SD: 93.00%), and those involving OS and 12 month-OS rate of End+Dac also ranked the highest (OS: 84.83%; 12 month-OS rate: 72.44%).

Anmerkung/Fazit der Autoren

In conclusion, this NMA provided significant evidence that targeted therapy with single-drug regimens (Vem and Dab) might be the best choice in the treatment of stage III/IV MM, while Dab+Tra and Vem+Cob also have better short-term efficacy among different double-drug targeted therapy regimens. On the contrary, it must be pointed out that there are still some differences between the sample size of interventions and the number of the direct or indirect paired comparison among the various interventions, which can result in the restriction of universal conclusion. Nevertheless, for the clinical use and treatment of stage III/IV MM, these results could have certain guiding significance.

Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2016 [37].

Deutsche Krebsgesellschaft

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms; Langfassung, Version 2.0

Leitlinienorganisation/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.

Methodik

Grundlage der Leitlinie

Grundlage der Empfehlungen ist die Aufarbeitung der verfügbaren Evidenz nach den Kriterien der evidenzbasierten Medizin, die Adaptierung vorhandener evidenzbasierter internationaler Leitlinien, sowie bei Fehlen einer Evidenzgrundlage auf Basis guter klinischer Praxis. Alle Empfehlungen wurden durch interdisziplinäre Repräsentanten bewertet und abgestimmt.

Die Empfehlungen wurden auf Basis von Schlüsselfragen erarbeitet, die zu Beginn im Kick-off-Meeting durch die Mandatsträger konsentiert wurden.

Nach Feststehen der Quell-Leitlinien wurde eine tabellarische Übersicht mit den Kernaussagen sowie der zugrundeliegenden Evidenz der Leitlinien in Bezug auf die vor initialer Konferenz (1. Konsensuskonferenz) der Leitliniengruppe vorbereiteten Schlüsselfragen erstellt. Bei übereinstimmender Beantwortung der Schlüsselfragen mit ausreichend hoher Evidenz wurde eine Leitlinienadaptation geplant. Bei fehlender Übereinstimmung wurde eine De-novo-Recherche, bei fehlender Evidenz eine Beantwortung durch Konsens geplant.

De-novo Recherche erfolgte zentral […] im September-Oktober 2015 unter Benutzung von 3 Datenbänken: - Medline über Pubmed, - Cochrane Library (alle Datenbanken),- Embase über Ovid

Die Bewertung der Literatur erfolgte im September-Oktober 2015 unter Verwendung etablierter Instrumente. Evidenzsynthese und Formulierung der Empfehlungen im Anschluss im Konsensverfahren.

LoE/GoR:

Evidenzbasierte Empfehlungen: Angabe von Evidenzlevel (Qualitätsstufe der Evidenz) sowie Empfehlungsgrad (Einbeziehung der klinischen Bewertung) und Konsensstärke. Grundlage: Adaptation der Quell-Leitlinien oder De-novo-Recherche

Konsensbasierte Empfehlungen: Ein kleinerer Anteil der Empfehlungen wurde nicht evidenzbasiert durch Konsens beantwortet: Angabe von EK (Expertenkonsens) und Konsensstärke, kein Evidenzlevel, kein ausgewiesener Empfehlungsgrad (A/B/0).

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“

Tabelle 1: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann/kann verzichtet werden

Sonstige methodische Hinweise

Die Gültigkeitsdauer der Leitlinie beträgt maximal 5 Jahre. Unabhängige Finanzierung und Angaben von Interessenskonflikten.

Lokoregionale Metastasen:

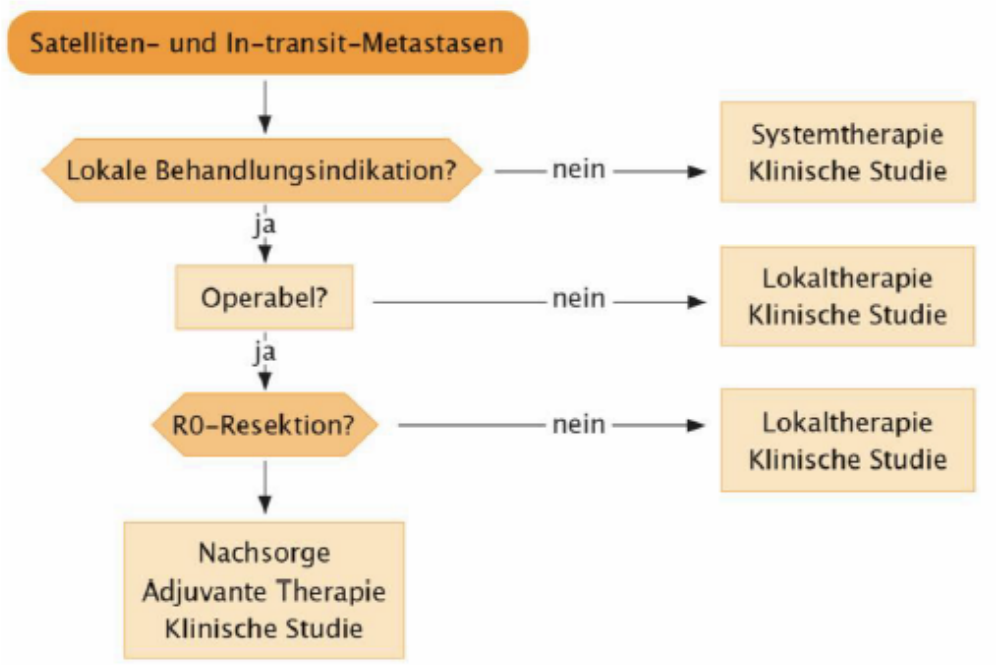


Abbildung 4: Algorithmus bei lokoregionalen Metastasen

Operative Therapie bei lokoregionalen Metastasen

3.85.	Konsensbasierte Empfehlung	2013
EK	Die chirurgische Therapie lokoregionaler Metastasen soll durchgeführt werden, wenn – bei fehlendem Hinweis auf eine Fernmetastasierung – dadurch perspektivisch eine makroskopische und mikroskopische vollständige Entfernung (R0-Resektion) der Metastasen möglich ist.	
	Konsensstärke: 96 %	

Radiotherapie bei lokoregionalen Metastasen

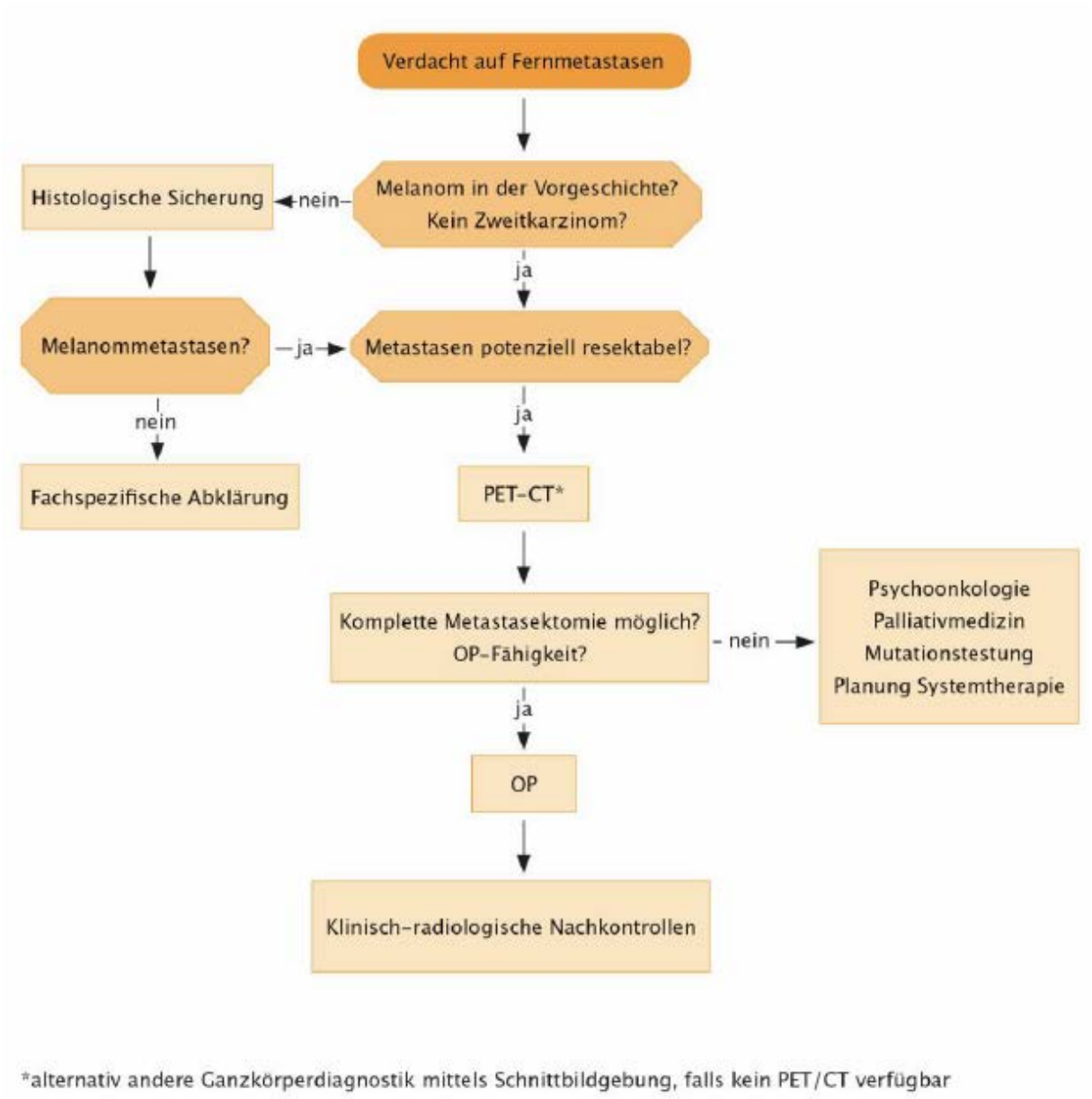
3.86.	Evidenzbasierte Empfehlung	2013
Empfehlungsgrad 0	Die lokale Radiotherapie kann bei Satelliten- und In-transit-Metastasen mit dem Ziel der lokalen Tumorkontrolle eingesetzt werden.	
Level of Evidence 4	De-novo-Recherche: [421-425]	
	Konsensstärke: 100 %	

Medikamentöse Verfahren bei lokoregionalen Metastasen

3.87.	Konsensbasierte Empfehlung	2016
EK	Patienten mit nicht-operablen Satelliten- und In-transit-Metastasen sollten wenn möglich im Rahmen klinischer Studien behandelt werden.	
	Konsensstärke: 100%	

3.88.	Evidenzbasierte Empfehlung	2016
Empfehlungsgrad 0	Bei Patienten mit nicht-operablen Satelliten- und In-transit-Metastasen können verschiedene lokale Verfahren angewandt werden, wobei die höchsten Ansprechraten für die intratumorale Injektion von Interleukin 2 und die intratumorale Elektrochemotherapie mit Bleomycin oder Cisplatin beschrieben sind. Talimogene Laherparepvec (T-VEC) kann als weitere Therapieoption bei lokoregionalen Metastasen eingesetzt werden.	
Level of Evidence 1b (T-VEC) 2a (Sonstige)	De-novo-Recherche: [429-440] De-novo-Recherche 2015: [441]	
	Konsensstärke: 100,0%	

Algorithmus initiales Stadium IV



*alternativ andere Ganzkörperdiagnostik mittels Schnittbildgebung, falls kein PET/CT verfügbar

Operative Therapie von Fernmetastasen

3.106.	Evidenzbasierte Empfehlung	2013
Empfehlungsgrad **B**	Jeder Patient mit Metastasen eines malignen Melanoms bedarf einer interdisziplinären Entscheidung zur Indikation für eine operative Therapie. Die Resektion von Fernmetastasen sollte in Betracht gezogen werden, wenn sie technisch als R0-Resektion machbar ist und • kein inakzeptables funktionelles Defizit erwarten lässt • positive prädiktive Faktoren für das lokale Vorgehen vorliegen (geringe Metastasenzahl, lange Dauer des metastasenfreien Intervalls) • andere Therapieverfahren ausgeschöpft oder weniger erfolgversprechend sind	
Level of Evidence **2b**	De-novo-Recherche: [478-480]	
	Konsensstärke: 100 %	

Medikamentöse Therapie im Stadium IV

Therapie mit Signaltransduktionsinhibitoren (BRAF- und MEK-Inhibitor)

3.108.	Evidenzbasierte Empfehlung	2016
Empfehlungsgrad **A**	Bei BRAF-V600-Mutation soll eine Therapie mit einem BRAF-Inhibitor in Kombination mit einem MEK-Inhibitor oder Checkpoint-Inhibitor- Therapie (PD-1 Monotherapie oder PD-1+CTLA-4 Antikörpertherapie) durchgeführt werden. Aktuell liegen keine Daten zur besten sequentiellen Therapie von BRAF/MEK-Inhibitoren und Checkpoint-Inhibitoren vor.	
Level of Evidence **1b**	De-novo-Recherche: [495-497]	
	Konsensstärke: 95,2%	

Immuntherapie im Stadium IV

3.110.	Evidenzbasierte Empfehlung	2016
Empfehlungsgrad **A**	Bei Melanompatienten mit nicht resezierbaren Metastasen soll die Option einer Immuntherapie mit Checkpoint-Inhibitoren geprüft werden. Dabei sind PD1-Antikörper oder deren Kombination mit Ipilimumab einer Monotherapie mit Ipilimumab hinsichtlich des progressionsfreien Überlebens überlegen*.	
Level of Evidence **1b**	De-novo-Recherche: [502-506]	
	Konsensstärke: 92,3%	

Monochemotherapie

3.111.	Evidenzbasierte Empfehlung	2016
Empfehlungsgrad 0	Falls überlegene Therapieschemata (BRAF/MEK-Inhibitoren oder PD-1-Antikörper) nicht in Frage kommen, kann eine Monochemotherapie mit Dacarbazin als eine etablierte Systemtherapie Melanompatienten mit nicht resezierbaren Metastasen angeboten werden.	
Level of Evidence 1b	De-novo-Recherche: [499, 500, 503, 505, 512, 515, 516, 518-533]	
	Konsensstärke: 95,7%	

Polychemotherapie

3.112.	Evidenzbasiertes Statement	2016
Empfehlungsgrad 0	Falls überlegene Therapieschemata (BRAF/MEK-Inhibitoren oder PD-1-Antikörper) nicht in Frage kommen, kann eine Polychemotherapie als eine etablierte Systemtherapie Melanompatienten mit nicht resezierbaren Metastasen angeboten werden. Unter Polychemotherapie sind höhere Ansprechraten als bei der Monochemotherapie zu erwarten, das mediane Gesamtüberleben wird jedoch nicht signifikant verlängert.	
Level of Evidence 1b	De-novo-Recherche: [534]	
	Konsensstärke: 95,5%	

Lebensqualität im fernmetastasierten Stadium

3.114.	Evidenzbasiertes Statement	2016
Level of Evidence 1b	Daten zur Lebensqualität sind aus den Phase III Zulassungsstudien zur Monotherapie mit BRAF-Inhibitoren (Vemurafenib / Dabrafenib) sowie den Kombinationsstudien aus BRAF/MEK-Inhibitoren (Dabrafenib+Trametinib, Vemurafenib+Cobimetinib) publiziert worden. Dabei zeigte sich eine Verbesserung der Lebensqualität der Kombinationstherapien gegenüber der Monotherapie mit BRAF-Inhibitoren.	
	De-novo-Recherche: [407, 518, 530, 547-563]	
	Konsensstärke: 91,7%	

Radiotherapie von Fernmetastasen

3.115.	Evidenzbasiertes Statement	2013
Level of Evidence 1b	Konventionelle Fraktionierungsschemata zeigen im Vergleich zu höheren Einzeldosen (> 3 Gy) die gleiche Effektivität bezüglich der lokalen Tumorkontrolle.	
	De-novo-Recherche: [564]	
	Konsensstärke: 100 %	

SIGN, 2017 [42].

Scottish Intercollegiate Guidelines Network (SIGN)

Cutaneous melanoma: A national clinical guideline

Leitlinienorganisation/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.

Methodik

Grundlage der Leitlinie

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland.

SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. (Teilnehmer der LL-Gruppe transparent dargestellt)

A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2004–2016.

Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

Relevant Key question: In patients with advanced melanoma (unresectable stage IIIC or stage IV) which is the most clinically and cost effective systemic therapy?

Consultation and peer review of the guideline

This guideline was issued in 2017 and will be considered for review in three years.

CoI available

LoE/GoR

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
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.
GOOD-PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group.

Management of advanced (unresectable stage IIIC or IV) melanoma

✓ All patients with advanced melanoma should be tested for mutations in BRAF and have their management discussed at a specialist MDT in order to determine the optimal management strategy taking into account patient fitness, co-morbidity, disease burden and overall aim of treatment.

All patients with advanced melanoma should be offered the opportunity to participate in clinical trials.

Surgery

✓ Metastasectomy should be considered in patients with stage IV disease

Metastasectomy may be an option for patients with distant skin, node and visceral metastases. In subcutaneous metastases prevention of ulceration of superficial lesions is best prevented by resection when the lesions are at a size where skin closure is possible. Surgery of single or localised metastases has been shown to be associated with improved survival.190 The proportion of patients suitable for metastasectomy ranges from 10% to 25%.[191-193] Five-year survival of 14-33% was described in one retrospective review for those with distant subcutaneous and lung metastases respectively. This study showed prognostic significance for Breslow thickness, number of metastases and prior disease-free interval.[191]

Systemic Therapy

BRAF AND MEK INHIBITORS:

R | **Trametinib in combination with dabrafenib is recommended for patients with unresectable stage IIIC or stage IV melanoma with a *BRAF* V600 mutation.**

BRAF AND MEK INHIBITORS

Development of BRAF inhibitors (vemurafenib and dabrafenib) as single agents or in combination with a MEK inhibitor (cobimetanib and trametinib) represents a major advance for patients with advanced melanoma.

Two open label RCTs demonstrated that BRAF inhibitors (vemurafenib and dabrafanib) improved response and progression-free survival (PFS) compared to chemotherapy alone in patients with unresectable stage IIIC or stage IV *BRAF* mutation-positive melanoma with a response rate of 48% and 50% versus 5% and 6%; PFS 5.3 and 5.1 months versus 1.6 and 2.7 months respectively.[194,195] Response is further improved with the combination of a BRAF inhibitor (vemurafenib or dabrafenib) and a MEK inhibitor (cobimentinib or trametinib), with an improved response rate and PFS compared to a BRAF inhibitors alone (response rate 64–68% versus 45–51% for BRAF inhibitors alone and PFS 9.3 to 11.4 months versus 6.2 to 8.8 months).[196-198] 1⁻ 1⁺

The toxicity profile for BRAF inhibitors compared to combination BRAF and MEK inhibitors is diverse: grade 3-4 toxicity rates range from 28–63% for BRAF inhibitor alone and 35–65% for combination therapy.[194-198]

Vemurafenib and dabrafenib are accepted for use by the SMC as monotherapy for the treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma as first-line therapy (*see section 12.4*). Trametinib in combination with dabrafenib is approved for use in the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation.

IMMUNOTHERAPIES

R | **Ipilimumab, pembrolizumab and nivolumab monotherapy or ipilimumab/nivolumab combination therapy are recommended for patients with unresectable stage IIIC and IV melanoma.**

Development of novel immunotherapies (ipilimumab, pembrolizumab and nivolumab) as single agents or in combination represents a major advance for patients with advanced melanoma.

Several RCTs have demonstrated that novel immunotherapies are effective in improving outcomes in patients with unresectable stage IIIC or stage IV melanoma.

A trial comparing ipilimumab to glycoprotein100 (gp100) for second-line therapy found that ipilimumab was associated with improved overall survival (OS) of 10.1 months versus 6.4 months (HR 0.66; p=0.003).[199]

Compared to chemotherapy for first-line treatment, nivolumab had a PFS of 5.1 versus 2.2 months, HR 0.43, 95% CI 0.34 to 0.56; one-year OS was 72.9% versus 42.1%, HR 0.42, p<0.001.[200] 1+

Ipilimumab has also been compared to nivolumab and pembrolizumab in RCTs.

Pembrolizumab (two-weekly or three-weekly) was associated with an improved six-month PFS of 47.3% (two-weekly) or 46.4% (three-weekly) compared to 26.5% for ipilimumab, HR 0.58; p,0.001; one-year OS was 74.1%, 68.4% or 58.2% respectively HR 0.63; p=0.0005 for two-weekly pembrolizumab, HR 0.69; p=0.0036 for three-weekly pembrolizumab; the response rate was 33.7% versus 32.9% versus 11.9% (p<0.001 for both comparisons).[201] 1+

The combination of nivolumab and ipilimumab improved outcomes compared to ipilimumab or nivolumab alone (PFS 11.5 months (combination) versus 2.9 months (ipilimumab) versus 6.9 months (nivolumab), HR 0.42; p<0.001). This study also confirmed that the outcomes for nivolumab were significantly improved compared to ipilimumab; PFS 6.9 months versus 2.9 months, HR 0.57 (p<0.00001).[191]

All of the novel immunotherapy agents are associated with a significant risk of autoimmune toxicity including colitis. Grade 3–4 toxicity rates are generally lower with single agent nivolumab (11.7%) and pembrolizumab (10.1–13.3%), higher with ipilimumab (10–19.9%) and highest with the combination of nivolumab and ipilimumab (55%).[199-203] 1+

While there is evidence of efficacy for novel immunotherapies, optimal choice, sequence and combination of therapies are still to be determined. Ipilimumab, pembrolizumab and nivolumab monotherapy and ipilimumab/nivolumab combination therapy have been considered and accepted for use by the SMC (with restrictions) (*see section 12.4*).

Radiotherapy

R **Single-dose radiotherapy of a least 8 Gy may be an effective treatment for bone metastases.**

BONE METASTASES

Studies looking at the treatment of bone metastases usually include only a small percentage of patients with melanoma. Recommendations have been extrapolated from the data available from studies of bone metastases from various tumour types. When using single fractions to palliate pain from bone metastases, an 8 Gy fraction is effective and provides superior pain relief to lower doses.[218] There does not appear to be an advantage to using 20 Gy in four fractions over an 8 Gy single fraction.[219] Some patients may benefit from higher dose, fractionated regimens, although this has not been fully established.[220] 2+ 2++ 4

NICE, 2015 [39].

National Institute for Health and Care Excellence

Melanoma: assessment and management

Leitlinienorganisation/Fragestellung

this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact.

Methodik

Grundlage der Leitlinie

Critical Appraisal and Evidence Grading

“Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.”

Review Protokoll

Formulierung von Schlüsselfragen

Systematische Literaturrecherche in The Cochrane Library, Medline and Premedline 1946 onwards, Excerpta Medica (Embase) 1974 onwards, Web of Science

Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informell) - eigene Checklisten - Anwendung von GRADE - GoR spiegelt sich in den Formulierungen wider ""“To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.“

Formulierung der Empfehlungen durch Guideline Development Group (GDG) auf der Basis systematischer klinischer und ggf. ökonomischer Evidenzaufbereitung

Empfehlungen sind mit Literatur verknüpft

Recherche/Suchzeitraum:

bis Oktober 2014

Stage III melanoma

Surgical management

<table>
<tr><td>Recommendations</td><td>Consider completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro-metastases and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.
<table>
<tr><th>Possible advantages of completion lymphadenectomy</th><th>Possible disadvantages of completion lymphadenectomy</th></tr>
<tr><td>Removing the rest of the lymph nodes before cancer develops in them reduces the chance of the cancer returning in the same part of the body.</td><td>Lymphoedema (long-term swelling) may develop, and is most likely if the operation is in the groin and least likely in the head and neck.</td></tr>
<tr><td>The operation is less complicated and safer than waiting until cancer develops in the remaining lymph nodes and then removing them.</td><td>In 4 out of 5 people, cancer will not develop in the remaining lymph nodes, so there is a chance that the operation will have been done unnecessarily.</td></tr>
<tr><td>People who have had the operation may be able to take part in clinical trials of new treatments to prevent future melanoma. These trials often cannot accept people who have not had this operation.</td><td>There is no evidence that people who have this operation live longer than people who do not have it.</td></tr>
<tr><td></td><td>Having any operation can cause complications.</td></tr>
</table>
Offer therapeutic lymph node dissection to people with palpable stage IIIB-IIIC melanoma or nodal disease detected by imaging.</td></tr>
</table>

Quality of the evidence:

The quality of the evidence for each outcome was considered to be very low as assessed using GRADE.

A specific recommendation for patients with micro-metastases in the sentinel lymph node biopsy was included as the GDG recognised that SLNB is the most sensitive staging procedure for melanoma and is likely to remain important in clinical practice for some time. It was therefore important to make a recommendation about proceeding to completion lymphadenectomy in terms of balancing possible benefit and the morbidity associated with the procedure. Although the quality of the evidence for completion lymphadenectomy after a positive SLNB was very low the GDG agreed that the patient should be made aware of the positive and negative consequences of the surgery and that the decision whether or not to proceed should be made by them.

In-transit metastases:

Recommendations	Refer the care of all people with newly diagnosed or progressive in-transit metastases to the specialist skin cancer multidisciplinary team (SSMDT). If palliative treatment for in-transit metastases is needed, offer palliative surgery as a first option if surgery is feasible. If palliative surgery is not feasible for people with in-transit metastases, consider the following options: • systemic therapy (for more information see recommendations in section 7.3) • isolated limb infusion • isolated limb perfusion • radiotherapy • electrochemotherapy in line with NICE's interventional procedure guidance on electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma • CO_2 laser • a topical agent such as imiquimod® (see section 5.2).

Quality of the evidence:

The quality of the evidence was assessed as being very low for all reported outcomes using GRADE.

For those patients for whom surgery or systemic treatment was not suitable the GDG were unable to recommend one treatment option above any other because, despite the very low quality evidence available, all treatment options showed some evidence of a positive clinical effect and not to recommend any treatment was not considered to be appropriate. The GDG agreed therefore that there was no evidence to exclude any of 23 the treatment options, other than those for which there was no evidence at all (amputation and cryotherapy).

As a result of the low quality evidence, all of the recommendations were made on the basis of clinical judgement and expertise.

Stage IV melanoma

Localised treatments for metastatic stage IV melanoma

Recommendations	Refer the care of people who appear to have oligometastatic melanoma to the specialist skin cancer multidisciplinary team (SSMDT) for recommendations about staging and management. Consider surgery or other ablative treatments (including stereotactic radiotherapy or radioembolisation) to prevent and control symptoms of oligometastatic stage IV melanoma in consultation with site-specific MDTs (such as an MDT for the brain or for bones).

Quality of the evidence:

The quality of the evidence was assessed using GRADE methodology and appropriate NICE Checklists. Using these methods it was determined that the quality of the evidence for all reported outcomes was very low. All the studies included in the evidence review were retrospective cohort studies and all have a high degree of patient selection bias.

The role of systemic anticancer therapy

Recommendations	Dabrafenib For adults, see NICE's technology appraisal guidance on dabrafenib[f] for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Dacarbazine Consider dacarbazine[g] for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable. Do not routinely offer further cytotoxic chemotherapy for stage IV metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial. Ipilimumab For adults, see NICE's technology appraisal guidance on ipilimumab[h] for previously treated advanced (unresectable or metastatic) melanoma and ipilimumab[h] for previously untreated advanced (unresectable or metastatic) melanoma. Vemurafenib For adults, 'Vemurafenib[i] is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidance on vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.]

Quality of the evidence:

The evidence for overall survival was assessed to be of high quality, while the evidence for all other outcomes was either low quality or was not available.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 26.03.2018

#	Suchfrage
1	MeSH descriptor: [Melanoma] explode all trees
2	melanom*:ti,ab,kw (Word variations have been searched)
3	(skin* or cutaneous):ti (Word variations have been searched)
4	(neoplasm* or tumor* or tumour* or sarcoma* or cancer*):ti (Word variations have been searched)
5	#3 and #4
6	#1 or #2 or #5
7	#6 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 26.03.2018

#	Suchfrage
1	"melanoma/therapy"[MeSH Terms]
2	melanom*[Title/Abstract]
3	(skin*[Title]) OR cutaneous[Title]
4	(((((neoplasm*[Title]) OR sarcoma*[Title]) OR tumor[Title]) OR tumors[Title]) OR tumour*[Title]) OR cancer*[Title]
5	(#3) AND #4
6	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
7	((#2 OR #5)) AND #6
8	(#1 OR #7)
9	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
10	((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))
11	(#9 OR #10)
12	(#8) AND #11
13	(#12) AND ("2013/03/01"[PDAT] : "3000"[PDAT])

Leitlinien in Medline (PubMed) am 26.03.2018

#	Suchfrage
1	melanoma[MeSH Terms]
2	melanom*[Title/Abstract]
3	(skin*[Title]) OR cutaneous[Title]
4	(((((neoplasm*[Title]) OR sarcoma*[Title]) OR tumor[Title]) OR tumors[Title]) OR tumour*[Title]) OR cancer*[Title]
5	(#3) AND #4
6	(#1 OR #2 OR #5)
7	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
8	(#6) AND #7
9	(#8) AND ("2013/03/01"[PDAT] : "3000"[PDAT])

Referenzen

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2. **Amdahl J, Chen L, Delea TE.** Network Meta-analysis of Progression-Free Survival and Overall Survival in First-Line Treatment of BRAF Mutation-Positive Metastatic Melanoma. Oncol Ther 2016;4(2):239-256.
3. **Chen P, Chen F, Zhou B.** Therapeutic efficacy and safety of combined BRAF and MEK inhibition in patients with malignant melanoma: a meta-analysis. Onco Targets Ther 2017;10:5391-5403.
4. **Devji T, Levine O, Neupane B, Beyene J, Xie F.** Systemic Therapy for Previously Untreated Advanced BRAF-Mutated Melanoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials. JAMA Oncol 2017;3(3):366-373.
5. **Gemeinsamer Bundesausschuss (G-BA).** Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Cobimetinib, Beschluss vom 2. Juni 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 11.07.2018]. URL: https://www.g-ba.de/downloads/91-1385-205/2016-06-02_Geltende-Fassung_Cobimetinib_D-196.pdf.
6. **Gemeinsamer Bundesausschuss (G-BA).** Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Dabrafenib (neues Anwendungsgebiet: Melanom in Kombination mit Trametinib), Beschluss vom 17. März 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 11.07.2018]. URL: https://www.g-ba.de/downloads/91-1385-191/2016-03-17_Geltende-Fassung_Dabrafenib_nAWG_D-182.pdf.
7. **Gemeinsamer Bundesausschuss (G-BA).** Geltende Fassung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Dabrafenib, Beschluss vom 3. April 2014 / 16. Juni 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 11.07.2018]. URL: https://www.g-ba.de/downloads/91-1385-80/2016-06-16_Geltende-Fassung_Dabrafenib_D-076.pdf.
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