



**Kriterien zur Bestimmung der zweckmäßigen
Vergleichstherapie**

und

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

und

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

Vorgang: 2026-B-122-z Nivolumab/Relatlimab

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

Nivolumab/Relatlimab

[Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit nicht resezierbarem oder metastasiertem Melanom]

Kriterien gemäß 5. Kapitel § 6 Verfo

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.

Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.

Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.

Nicht angezeigt.

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:

- Vemurafenib (BRAF-V600-Mutation): Beschluss vom 6. März 2014
- Pembrolizumab: Beschluss vom 4. Februar 2016
- Dabrafenib (BRAF-V600-Mutation): Beschluss vom 3. April 2014 (Aufhebung Befristung 16.06.2016)
- Ipilimumab: Beschluss vom 5. Juni 2014 (Aufhebung Befristung 07.04.2016)
- Nivolumab: Beschluss vom 7. Januar 2016 (Aufhebung Befristung 15.12.2016)
- Dabrafenib (Kombination mit Trametinib, BRAF-V600-Mutation): Beschluss vom 17. März 2016
- Trametinib (BRAF-V600-Mutation): Beschluss vom 17. März 2016
- Trametinib (Kombination mit Dabrafenib, BRAF-V600-Mutation): Beschluss vom 17. März 2016
- Cobimetinib (Kombination mit Vemurafenib, BRAF-V600-Mutation): Beschluss vom 2. Juni 2016
- Nivolumab (Kombination mit Ipilimumab): Beschluss vom 15. Dezember 2016
- Talimogen laherparepvec: Beschluss vom 15. Dezember 2016
- Nivolumab (Kombination mit Ipilimumab): Beschluss vom 7. Dezember 2017

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

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Kriterien gemäß 5. Kapitel § 6 Verfo

- Ipilimumab (≥ 12 bis < 18 Jahre): Beschluss vom 2. August 2018
- Nivolumab (Kombination mit Ipilimumab): Beschluss vom 20. Dezember 2018
- Ipilimumab (Kombination mit Nivolumab): Beschluss vom 20. Dezember 2018
- Binimetinib (Kombination mit Encorafenib, BRAF-V600 Mutation): Beschluss vom 22. März 2019
- Encorafenib (Kombination mit Binimetinib, BRAF-V600 Mutation): Beschluss vom 22. März 2019
- Pembrolizumab (≥ 12 bis < 18 Jahre): Beschluss vom 19. Januar 2023
- Nivolumab (Monotherapie oder Kombination mit Ipilimumab, ≥ 12 bis < 18 Jahre): Beschluss vom 21. Dezember 2023

Beschlüsse über Anwendungsbegleitende Datenerhebung gemäß § 35a Absatz 3b:

- Lifileucel: Beschluss vom 16. Oktober 2025

Beschlüsse über Richtlinie Methoden Krankenhausbehandlung gemäß § 137c SGB V:

- Positronenemissionstomographie (PET); PET/Computertomographie (CT): Beschluss vom 20. November 2020 (Einstellen der Methodenbewertung)

Beschlüsse über Richtlinie Methoden vertragsärztliche Versorgung gemäß § 135 SGB V:

- Positronenemissionstomographie (PET); PET/Computertomographie (CT): Beschluss vom 20. November 2020 (Einstellen der Methodenbewertung)

Die Vergleichstherapie soll nach dem allgemein anerkannten

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

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Kriterien gemäß 5. Kapitel § 6 Verfo

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:	
Nivolumab/ Relatlimab Opdualag L01FY02	<u>Anwendungsgebiet laut Zulassung:</u> Erstlinienbehandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms mit Tumorzell-PD-L1-Expression < 1 % bei Erwachsenen und Jugendlichen im Alter ab 12 Jahren.
Zytostatika:	
Dacarbazin L01AX04 z. B. Detimedac	Detimedac ist indiziert zur Behandlung des metastasierten, malignen Melanoms.
Lomustin L01AD02 Cecenu	Cecenu wird in Kombinationstherapie eingesetzt: – Bei bösartigen Tumorerkrankungen der Haut (metastasierte, maligne Melanome)
Proteinkinase-Inhibitoren (BRAF/MEK)	
Dabrafenib L01EC02 Tafinlar	Dabrafenib ist angezeigt als Monotherapie oder in Kombination mit Trametinib zur Behandlung von Erwachsenen und Jugendlichen im Alter von 12 Jahren und älter mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.
Encorafenib L01EC03 Braftovi	Encorafenib in Kombination mit Binimetinib zur Behandlung des nicht-resezierbaren oder metastasierten Melanoms mit einer BRAF-V600-Mutation.

Vemurafenib L01EC01 Zelboraf	Vemurafenib ist angezeigt als Monotherapie zur Behandlung von erwachsenen Patienten mit BRAF-V600 Mutation-positivem nicht resezierbarem oder metastasiertem Melanom.
Binimetinib L01EE03 Mektovi	Binimetinib in Kombination mit Encorafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit nicht-resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.
Cobimetinib L01EE02 Cotellic	Cotellic wird in Kombination mit Vemurafenib angewendet zur Behandlung bei erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation.
Trametinib L01EE01 Mekinist	Trametinib ist angezeigt als Monotherapie oder in Kombination mit Dabrafenib zur Behandlung von Erwachsenen und Jugendlichen im Alter von 12 Jahren und älter 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.
Immuncheckpoint-Inhibitoren	
Ipilimumab L01FX04 Yervoy	Yervoy ist als Monotherapie zur Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms bei Erwachsenen und Jugendlichen ab einem Alter von 12 Jahren indiziert. Yervoy ist in Kombination mit Nivolumab 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 (progression-free survival, PFS) und des Gesamtüberlebens (overall survival, OS) gezeigt.
Nivolumab L01FF01 Opdivo	Opdivo ist als Monotherapie bei Erwachsenen und Jugendlichen ab 12 Jahren zur adjuvanten Behandlung des Melanoms im Stadium IIB oder IIC oder des Melanoms mit Lymphknotenbeteiligung oder Metastasierung nach vollständiger Resektion indiziert. 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.
Nivolumab/ Relatlimab L01FY02 Opdualag	Opdualag ist für die Erstlinienbehandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms mit Tumorzell-PD-L1-Expression < 1 % bei Erwachsenen und Jugendlichen im Alter ab 12 Jahren indiziert.
Pembrolizumab L01FF02 Keytruda	Keytruda ist als Monotherapie zur Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierenden) Melanoms bei Kindern und Jugendlichen ab 12 Jahren und Erwachsenen angezeigt. Keytruda ist als Monotherapie zur adjuvanten Behandlung des Melanoms in den Tumorstadien IIB, IIC oder III nach vollständiger Resektion bei Kindern und Jugendlichen ab 12 Jahren und Erwachsenen angezeigt.
Onkolytische Immuntherapien	
Talimogen laherparepvec L01XL02 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.
Bispezifische Fusionsproteine	
Tebentafusp L01XX75 Kimmtrak	Kimmtrak wird angewendet als Monotherapie bei der Behandlung von HLA(humanes Leukozyten-Antigen)-A*02:01-positiven erwachsenen Patienten mit inoperablem oder metastasiertem uvealem Melanom.

Quellen: AMIce-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

**Vorgang: 2026-B-122-z (Beratung nach § 35a SGB V)
Nivolumab/Relatlimab**

Auftrag von: Abt. AM
Bearbeitet von: Abt. FB Med
Datum: 2. Juni 2026

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Abkürzungsverzeichnis

ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BRAF	V-raf murine sarcoma viral oncogene homolog B gene or serine/threonine-protein kinase B-RAF
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
ICI	Immune checkpoint inhibitor
IL-2	Interleukin-2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MEK	Mitogen-activated protein kinase
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TIL	Tumor-infiltrating lymphocyte
TRIP	Turn Research into Practice Database
T-VEC	Talimogene laherparepvec
WHO	World Health

1 Indikation

Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit nicht resezierbarem oder metastasiertem Melanom.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Melanom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (*Cochrane Database of Systematic Reviews*), *PubMed*. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (<https://www.google.com/>) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 04.03.2026 abgeschlossen. Am 29.05.2026 erfolgte eine Überprüfung der iterativen Handsuche. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2345 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Peinemann F et al., 2025 [3].

Dual checkpoint inhibitor therapy versus dual targeted therapy of untreated metastatic BRAF-mutant melanoma: a systematic review of randomised controlled trials

Fragestellung

to assess the effects of dual immune checkpoint inhibitor (ICI) therapy versus dual targeted cancer therapy in adult patients with untreated metastatic BRAF-mutant melanoma.

Methodik

Population:

- Adults with untreated, metastatic BRAF V600 mutated melanoma

Intervention:

- First-line dual immune checkpoint inhibitor therapy
 - Nivolumab (PD-1 inhibitor) PLUS Ipilimumab (CTLA-4 inhibitor).

Komparator:

- First-line dual targeted therapy of cancer
 - Encorafenib PLUS binimetinib.
 - Vemurafenib PLUS cobimetinib.
 - Dabrafenib PLUS trametinib

Endpunkte:

- Overall survival, Treatment-related adverse events grade III or higher, Progression-free survival, Brain metastases-free survival, Survival after brain metastases were detected after randomisation

Recherche/Suchzeitraum:

- We performed an unrestricted electronic literature database search in MEDLINE (via PubMed, US National Library of Medicine) on 12 November 2025. We conducted an additional electronic literature database search in the Cochrane Central Register of Controlled Trials (CENTRAL) (via The Cochrane Library, Wiley) on 12 November 2025. We searched reference lists of recent publications, Google, and we used PubMed tools including similar articles and clinical queries. The search on 12 November 2025 is an update of a previous search which was conducted on 5 May 2025.

Qualitätsbewertung der Studien:

- Cochrane's tool for assessing risk of bias

We adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to define the certainty of a body of the identified evidence as described in the Cochrane Handbook for Systematic Reviews of Interventions.²² We established the

initial level of certainty based on study design, considered lowering the level of certainty based on risk of bias, inconsistency, indirectness, imprecision and publication bias, and we rated the certainty in an estimate of effect across those considerations as high, moderate, low or very low.

Ergebnisse

Anzahl eingeschlossener Studien:

- N=2 (DREAMseq & SECOMBIT)

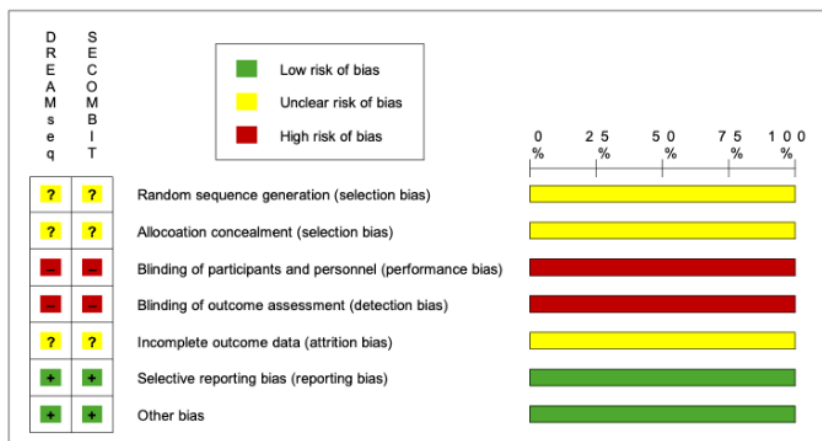
Charakteristika der Population/Studien:

Table S6. Characteristics of participants (ICI versus TT)

	DREAMseq	SECOMBIT
Age, median years (range)	61 (25 to 85) versus 61 (30 to 84)	55 (18 to 81) versus 55 (19 to 77)
Male sex	60.9% (81 of 133) versus 65.2% (86 of 132)	47.9% (34 of 71) versus 60.9% (42 of 69)
ECOG PS "0"	67.8% (90 of 133) versus 67.4% (89 of 132)	87.3% (62 of 71) versus 82.6% (57 of 69)
Metastatic site staging	Clinical staging III unresectable: 6.9% (9 of 130) versus 13.1% (17 of 130) M1a: 12.3% (16 of 130) versus 10.7% (14 of 130) M1b: 18.5% (24 of 130) versus 17.7% (23 of 130) M1c: 62.3% (81 of 130) versus 58.5% (76 of 130)	M0, M1a, M1b: 39.4% (28 of 71) versus 42% (29 of 69) M1c: 59.1% (42 of 71) versus 58% (40 of 69) Not reported: 1.5% (1 of 71) versus 0% (0 of 69)
Number of metastatic sites	Not reported	<3: 57.7% (41 of 71) versus 62.3% (43 of 69) >=3: 40.8% (29 of 71) versus 36.2% (25 of 69) Not eval: 1.4% (1 of 71) versus 1.5% (1 of 69)
History of brain metastases	1 (0.8%) versus 3 (2.3%)	Not reported
Brain metastases at baseline	Not reported	1.4% (1 of 71) versus 0% (0 of 69)
Brain metastases detected during the trial	Not reported	15% (11 of 70) versus 33% (23 of 69)
Type of BRAF mutation	V600E: 81.8% (108 of 132) versus 67.9% (89 of 131) V600K: 12.1% (16 of 132) versus 25.2% (33 of 131) Other: 6.1% (8 of 132) versus 6.9% (9 of 131)	Not reported

Abbreviations. AJCC: American Joint Committee on Cancer; AJCC clinical staging III: any tumor staging, any metastatic nodes staging except N0, metastatic site staging M0; AJCC metastatic site staging M1b: lung metastases; metastatic site staging M1c: all other visceral metastases; ECOG PS: Eastern Cooperative Oncology Group performance status (0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; <https://ecog-acrin.org/resources/ecog-performance-status/>); ICI: immune checkpoint inhibitors; Not eval: not evaluated; PD: progressive disease; TT: targeted therapy

Qualität der Studien:



Grading the certainty of evidence: We established an initial level of high certainty due to the randomised study design. There was an unclear risk of bias concerning selection bias and a high risk of bias concerning performance bias and detection bias in both studies. Thus, we downgraded by one level. There was no unexplained heterogeneity or inconsistency of results, and there was no indirectness of evidence. The studies included an appropriate number of participants and reported wide CIs for the main outcomes. Thus, there was not an imprecision of results. There are two positive studies, and it appears that studies showing no effect or harm have not been published. The studies

reported a specific intervention on a specific disease, and there is no for-profit interest in the intervention. Thus, there was no clear indication of a publication bias. The final level of certainty rating was: Moderate ⊕⊕⊕○.

Studienergebnisse:

	DREAMseq	SECOMBIT	Pooled estimate
OS	HR 0.61 (95% CI 0.41 to 0.91)*	HR 0.75 (95% CI 0.46 to 1.22)†	HR 0.66 (95% CI 0.49 to 0.90), I ² =0%
TRAEs	(75 of 126) versus (68 of 130)* RR 1.14 (95% CI 0.91 to 1.42)	74% (51 of 69) versus (41 of 69)‡ RR 1.24 (95% CI 0.98 to 1.58)	RR 1.18 (95% CI 1.01 to 1.39), I ² =0%
PFS	HR 0.73 (95% CI 0.54 to 1.00)*	HR 0.62 (95% CI 0.40 to 0.95)†	HR 0.69 (95% CI 0.54 to 0.89), I ² =0%

*OS and PFS extracted from Kaplan-Meier curves, TRAE data extracted from section *Safety* and [table 4](#) of the article by Atkins *et al.*²³
†OS and PFS data extracted from Kaplan-Meier curves of the article by Ascierto 2024.²⁸
‡TRAE data extracted from [table 2](#) of the article by Ascierto *et al.*²⁶
.DREAMseq, Doublet, Randomized Evaluation in Advanced Melanoma Sequencing; ICI, immune checkpoint inhibitor(s); OS, overall survival; PFS, progression-free survival; RR, risk ratio; SECOMBIT, Sequential Combo Immuno and Target Therapy; TRAE, treatment-related adverse event; TT, targeted therapy of cancer.

Table S8. Outcomes with respect to brain metastases (ICI versus TT)

	DREAMseq	SECOMBIT	Pooled estimate
Brain metastases-free survival (BMFS)	Not reported	HR 0.56 (95% CI 0.29 to 1.07) ^(a)	Data from one study only
Survival after brain metastases	Not reported	HR 0.66 (95% CI 0.31 to 1.41) ^(a)	Data from one study only

Abbreviations. CI: confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitors; TT: targeted therapy

Anmerkung/Fazit der Autoren

The evidence base is compatible with a favourable effect of first-line nivolumab plus ipilimumab for adults with untreated metastatic BRAF-mutant melanoma on survival and an unfavourable effect on toxicity when compared with first-line TT. Future RCTs could provide more data on therapy failure and quality of life.

Kommentare zum Review

Limitations of the evidence contained in this paper We focused on the new treatment recommendations of the European consensus-based interdisciplinary guideline for melanoma. Previous recommendations were regarded as outdated. This was especially true for single-drug treatments. Therefore, the evidence depended on new studies. These studies had to implement the current conception of a treatment that could promise a survival benefit. Therefore, we expected a small number of studies for inclusion from the outset. This turned out to be true, and we identified only two relevant RCTs.

Jarab AS et al., 2024 [1].

New emerging treatment options for metastatic melanoma: a systematic review and meta-analysis of skin cancer therapies

Fragestellung

This study aims to systematically review systemic treatment options for advanced melanoma, focusing on efficacy and safety in the first-line setting.

Methodik

Population:

- treatment-naive adult patients diagnosed with metastatic melanoma

Intervention/Komparator:

- Interventions including mono- or combined therapy options of ipilimumab, dacarbazine, vemurafenib, cobimetinib, dabrafenib, and trametinib

Endpunkte:

- Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and serious adverse events (SAEs).

Recherche/Suchzeitraum:

- databases such as MEDLINE, EMBASE, and Cochrane, spanning from their inception to 2023.

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk-of-bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=11

Charakteristika der Population/Studien:

- The review encompassed 2816 participants across diverse studies investigating metastatic melanoma treatments. Gender distribution varied, with majority included male (89%). Participant ages ranged from 49.0 to 55.0 years. Underlying conditions included unresectable/metastatic melanoma with BRAFV600 mutations and treatment-naive metastatic melanoma. Studies utilized varied designs (phases I-III, multicenter), assessing BRAF inhibitors (vemurafenib, dabrafenib), alone or with MEK inhibitors (trametinib, cobimetinib), and immunotherapy (ipilimumab). Follow-up spanned 5 years to 28.0 months. Median overall survival ranged from 6.8 to 443.0 days.

Superior clinical outcomes with combined therapy vs. vemurafenib monotherapy:

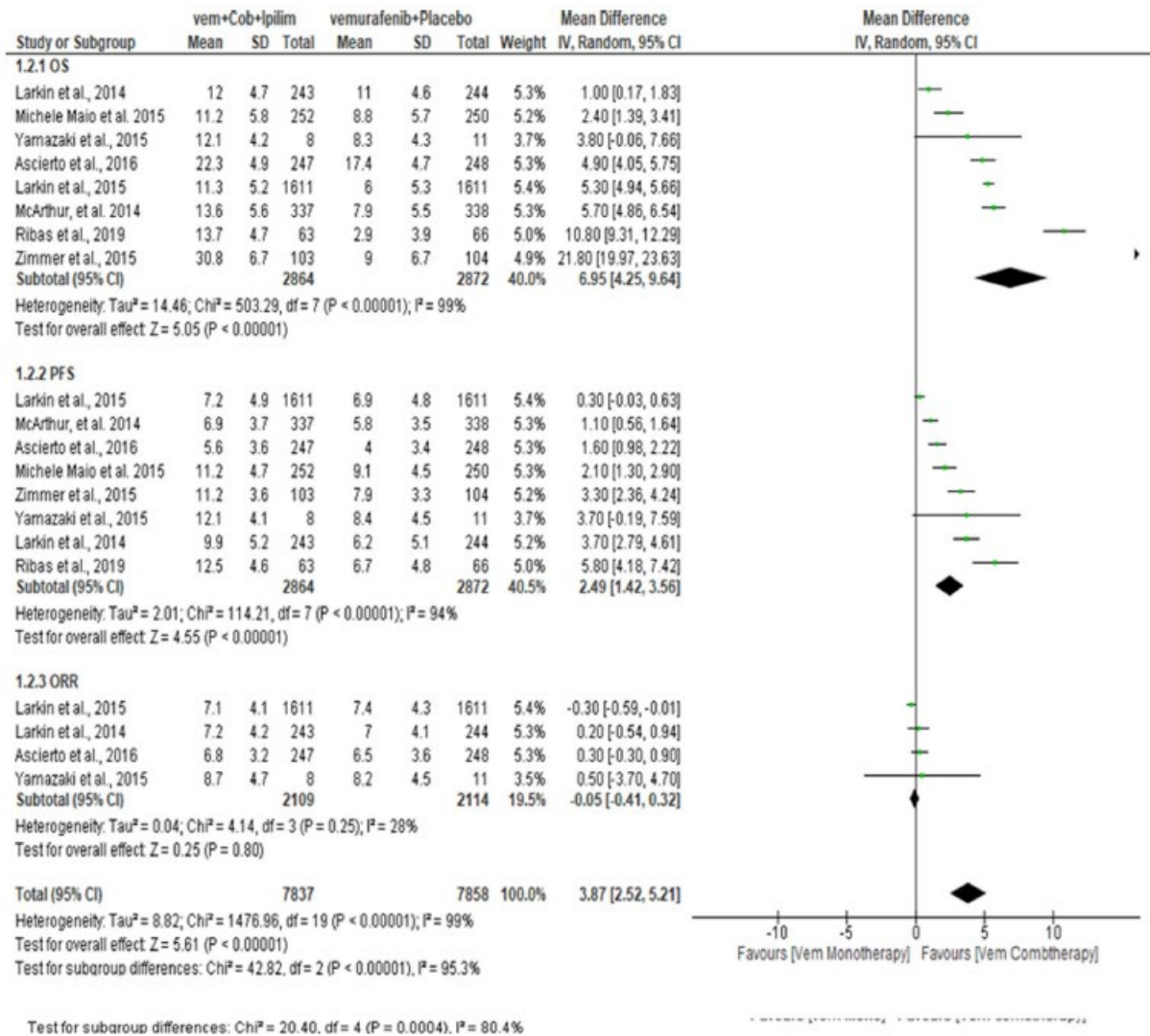


Fig. 6 Forest plot showing Superior Clinical Outcomes with Combined Therapy vs. Vemurafenib Monotherapy

Enhanced clinical outcomes with dabrafenib + trametinib combined therapy vs. dabrafenib monotherapy

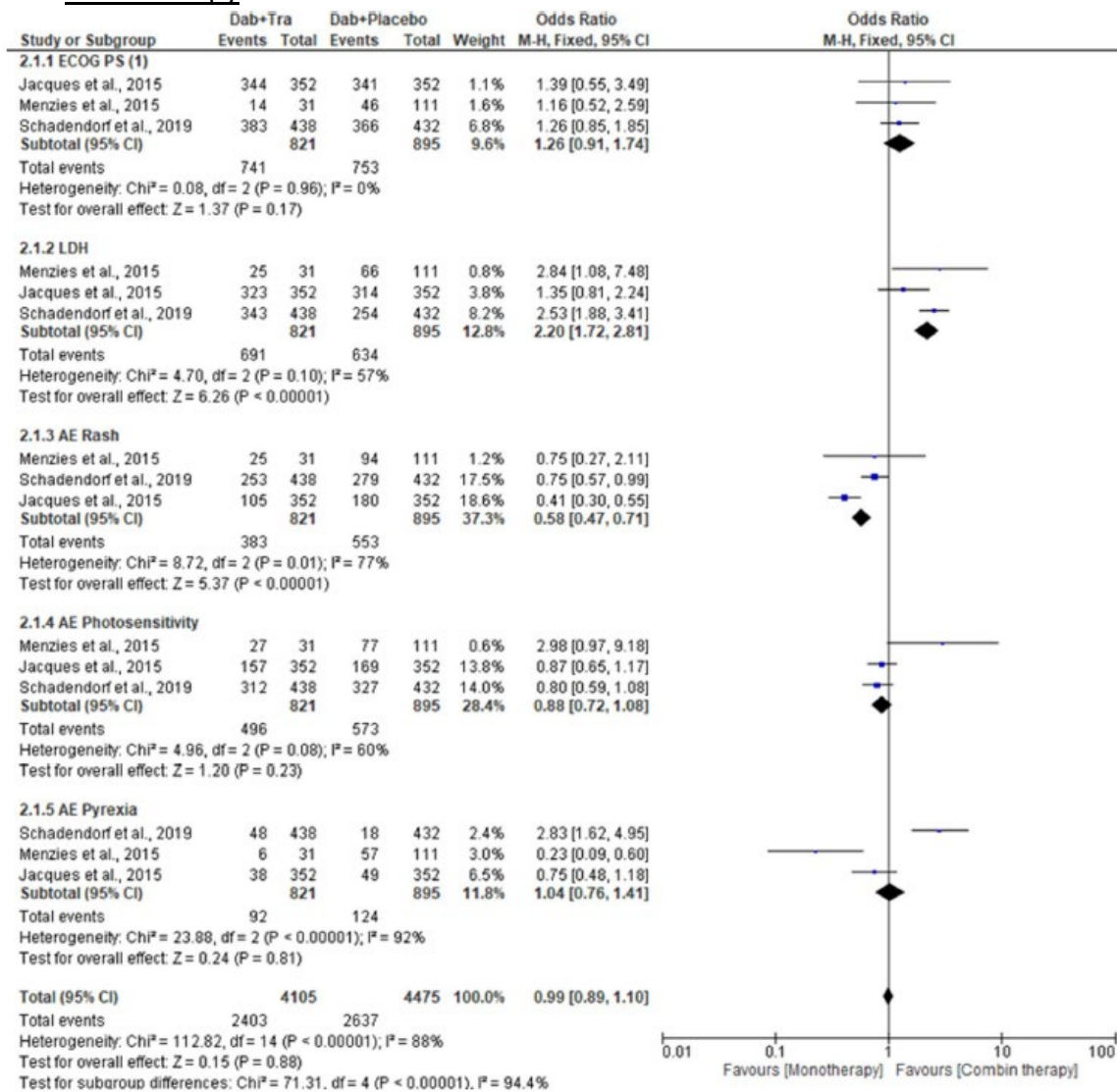


Fig. 7 Forest plot showing Enhanced Clinical Outcomes with Dabrafenib + Trametinib Combined Therapy vs. Dabrafenib Monotherapy

Improved clinical outcomes with dabrafenib + trametinib combined therapy vs. dabrafenib monotherapy

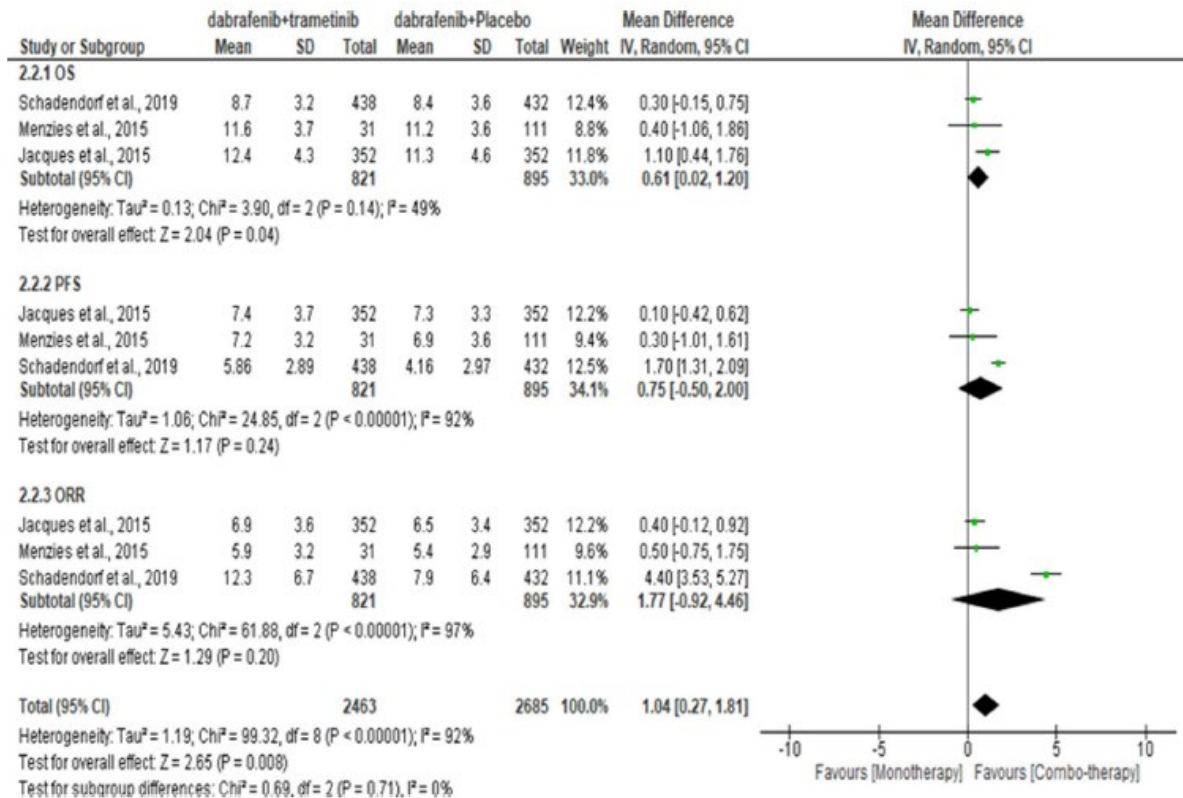


Fig. 8 Forest plot showing Improved Clinical Outcomes with Dabrafenib + Trametinib Combined Therapy vs. Dabrafenib Monotherapy

Anmerkung/Fazit der Autoren

In conclusion, the meta-analysis provides valuable insights into advanced melanoma treatments, favoring combined therapy over monotherapy, particularly with vemurafenib, cobimetinib, and ipilimumab. Dermatological toxicities linked to vemurafenib underscore the importance of effective management strategies. Additionally, dabrafenib and trametinib combination therapy showed promise in improving recurrence-free survival. Future research should address meta-analysis limitations and evaluate long-term treatment implications for optimizing advanced melanoma management.

3.3 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020

Deutsche Krebsgesellschaft

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms; Langfassung, Version 3.3
Im Jahr 2019 wurde das Kapitel zur adjuvanten Therapie zuletzt aktualisiert. Aufgrund der aktuellen, rasch voranschreitenden Neuentwicklungen, insbesondere im Bereich der adjuvanten und der Systemtherapie, ist eine Aktualisierung dringend erforderlich. Die geplante Fertigstellung der S3-LL ist der 31.12.2026.

Seth R et al., 2023 [5, 6].

American Society of Clinical Oncology (ASCO)

Systemic Therapy for Melanoma: ASCO Guideline Update.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren: trifft zu (modified Delphi technique);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität: trifft teilweise zu (Gültigkeit der LL und zeitliche Planung der Überprüfung nicht identifiziert.)

Recherche/Suchzeitraum:

- The recommendations were developed by using several resources:
 - A group systematic review published by Pasquali et al (the Cochrane review) that included trials of systemic therapy for metastatic cutaneous melanoma published in 2016 or earlier.
 - A systematic review conducted by ASCO staff for the 2020 guideline of randomized clinical trials (RCTs) of adjuvant and neoadjuvant systemic therapies for cutaneous melanoma, systemic therapy for metastatic melanoma published after 2016, and systemic therapy for noncutaneous melanoma. The methods of that review are fully described in the original 2020 guideline publication.
 - An updated systematic review conducted by ASCO staff of RCTs published since the 2020 guideline, described here.
- PubMed was searched on March 6, 2023, for studies published on June 1, 2019, or later to that date, and articles were selected for inclusion on the basis of the following criteria:
 - Population: Patients with any form of melanoma
 - Interventions and comparisons: Trials of systemic therapy versus other systemic therapy or observation or placebo.
 - Fully published reports of RCTs with at least 50 patients per arm. The restriction of 50 patients per arm was not present in the original 2020 guideline criteria.

LoE/GoR

Table 1. Definitions for Quality of Evidence Grades¹⁰

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- **GRADE (Grading of Recommendations Assessment, Development and Evaluation)**

Strength of Recommendations

Guideline recommendations fall along a continuum depicted below; the strength of recommendations fall into two categories: strong and conditional.¹⁴

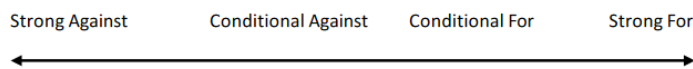


Table 2. Definitions for Strength of Recommendation

Strength of Recommendation	Definition
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention.
Conditional/Weak ^a	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

^a The label 'Weak' was previously used to label these recommendations. This term has now been replaced by 'Conditional.' Both labels have the same definition in the context of ASCO strength of the recommendation.

Recommendations

Clinical Question 3:

What systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with unresectable/ metastatic cutaneous melanoma? Are there subpopulations of patients (eg, clinical features, biomarker status, presence of brain metastases) who benefit more or less from those options?

- **Recommendation 3.1** For patients with BRAF wild-type, unresectable and/or metastatic cutaneous melanoma, the following treatment options should be offered (in no particular order): nivolumab plus ipilimumab followed by nivolumab OR nivolumab plus relatlimab OR nivolumab OR pembrolizumab. See Table 2 for recommended dosing and scheduling details. See the Clinical Interpretation section on shared decision making with patients between these options (*Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong*).

Literature review and analysis.

Summary of the 2020 guideline. The meta-analyses of the Cochrane review provided key evidence for trials published before 2017. Anti-PD-1 therapy was associated with statistically significant improvements in OS (HR, 0.63; 95% CI, 0.60 to 0.66; one trial) and progression-free survival (PFS; HR, 0.54; 95% CI, 0.50 to 0.60; two trials) compared with anti-CTLA-4 therapy, as well as statistically significantly reduced grade 3 and 4 toxicities (relative risk [RR], 0.70; 95% CI, 0.54 to 0.91; two trials). These results were driven by the CheckMate 067/14,87 trial of nivolumab plus ipilimumab versus nivolumab alone versus ipilimumab alone, and the KEYNOTE-006/16 trial of pembrolizumab versus ipilimumab. The combination of anti-PD-1 therapy plus anti-CTLA-4 therapy was associated with statistically significant improvements in PFS (HR, 0.40; 95% CI, 0.35 to 0.46; two trials) and significantly increased grade 3 and 4 toxicities (RR, 1.57; 95% CI, 0.85 to

2.92; two trials) compared with anti-CTLA-4 therapy alone. In addition, two other randomized trials that were potentially relevant to recommendations were identified in the 2020 guideline: CheckMate 51179 studied an alternate dosing schedule of nivolumab and ipilimumab, and Ascierto et al¹⁷⁷ studied higher-dose single-agent ipilimumab.

Updates for the 2023 guideline. Two new randomized trials^{15,33} in patients with BRAF wild-type melanoma and considered relevant to recommendations were published with full details in the Data Supplement (Tables 1-5). The RELATIVITY-047 trial¹⁵ compared the combination of relatlimab and nivolumab with nivolumab alone in previously untreated patients with unresectable or metastatic stage III-IV melanoma. The median PFS was 10.12 months with the combination versus 4.63 months with single-agent nivolumab. The PFS HR was 0.75 (95% CI, 0.62 to 0.92). The estimated 12-month PFS rate was 47.7% versus 36.0%. OS is not yet reported. Grade 3 or 4 TRAEs were more frequent with the combination (18.9%) than single-agent (9.7%) therapy. The IMSpire170 trial³³ compared the combination of cobimetinib and atezolizumab with single-agent pembrolizumab in patients with BRAF wild-type unresectable or metastatic melanoma. No significant differences in PFS or OS were found.

An exploratory network meta-analysis was conducted, fully described in the Data Supplement 2, to investigate whether the available evidence was sufficient to prioritize between the different options for patients with BRAF-mutant unresectable and/or metastatic melanoma. This analysis suggests the following:

- In general, two drug combinations (nivolumab plus ipilimumab, relatlimab plus nivolumab) have better estimated PFS than single drugs alone (pembrolizumab, nivolumab)
- Nivolumab plus ipilimumab has the highest estimated serious adverse event frequency, and nivolumab alone has the lowest.

However, given the limitations of this analysis described in the Data Supplement 2, none of these points can be considered as high certainty evidence on which to base recommendations and are therefore areas for future research.

Clinical interpretation. In the 2020 guideline, single agent nivolumab and single-agent pembrolizumab were recommended as reasonable treatment options on the basis of data from two trials, CheckMate 067¹⁴ and KEYNOTE-006¹⁶ trials. Both trials reported significant OS benefit for anti-PD-1 therapy over ipilimumab. In addition, although the 067 trial was not powered for a comparison between the combination versus nivolumab monotherapy, the trial found increased PFS for the combination of ipilimumab and nivolumab compared with nivolumab alone, but the OS difference was not statistically significant, and the combination also had significantly increased toxicity. Therefore, the combination of ipilimumab and nivolumab was considered a reasonable treatment option in patients willing to accept the likely increased toxicity of the combination. Similarly, the reported PFS benefit for nivolumab plus relatlimab in RELATIVITY-047,¹⁵ published in 2022, provides sufficient evidence to recommend combination as an additional reasonable option for therapy. In the 2020 guideline, the alternate dosages studied in CheckMate 51179 (for the combination of nivolumab and ipilimumab) and Ascierto 201777 (for single-agent ipilimumab) were not recommended. IMSpire170³³ found no benefits for atezolizumab plus cobimetinib compared with pembrolizumab.

Therefore, there are four reasonable therapy options for patients with BRAF wild-type unresectable or metastatic melanoma: nivolumab plus ipilimumab, nivolumab plus relatlimab, single-agent nivolumab, and single-agent pembrolizumab. In deciding between these options, several factors can be considered. First, combination therapy is associated with a greater PFS benefit than single-agent nivolumab, but with increased toxicity. Although there is no direct trial comparison, the exploratory meta-analysis and the similarity in results across many trials in benefits and harms between these anti-PD-1 agents suggest that this is likely the case with single-agent pembrolizumab as well. For patients with brain metastases, the joint ASCO, Society for Neuro-Oncology (SNO), and American Society for Radiation Oncology (ASTRO) brain metastases guideline⁸⁸ recommended nivolumab plus ipilimumab as the most reasonable option for systemic therapy, on the basis of results from a phase II trial⁸⁹ of nivolumab plus ipilimumab in asymptomatic brain metastases. Finally, in all cases, the decision on the choice of therapy should be made jointly with the patient after considering the risk and benefits; patients who prefer more aggressive therapy may wish to receive combination therapy.

A qualifying statement in the 2020 guideline noted that in the relevant randomized trials, nivolumab could be continued beyond 2 years,¹⁴ whereas pembrolizumab was limited to 2 years. It is possible that shorter courses of therapy, as little as 1 year, may be reasonable. However, no high quality data in the melanoma setting address what the duration of therapy should be. The qualifying statement also noted that for longer dosing cycles (eg, up to 6 weeks), appropriate monitoring for toxicity and disease progression is still necessary.

- Recommendation 3.2.1 For patients with BRAF mutant (V600) unresectable and/or metastatic cutaneous melanoma, one of the following treatment options should be offered as first-line therapy: nivolumab plus ipilimumab followed by nivolumab OR

nivolumab plus relatlimab OR nivolumab OR pembrolizumab OR dabrafenib plus trametinib OR encorafenib plus binimetinib OR vemurafenib plus cobimetinib. See Table 2 for recommended dosing and scheduling details. See the Clinical Interpretation section on shared decision making with patients between these options (*Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong*).

- Recommendation 3.2.2 Combination therapy with nivolumab plus ipilimumab is preferred as first-line therapy over BRAF/MEK inhibitor combination therapy. See the Clinical Interpretation section on shared decision making with patients between these options (*Type: Evidence based; Evidence quality: High for dabrafenib plus trametinib, Low for other BRAF/MEK inhibitors; Strength of recommendation: Strong*).

Summary of the 2020 guideline. In addition to the data described for recommendation 3.1 for patients where BRAF mutation status was not considered, the Cochrane review meta-analysis identified a subset of trials in patients with BRAF-mutant metastatic melanoma. The combination of BRAF and MEK inhibitor therapies was associated with statistically significant improvements in OS (HR, 0.70; 95% CI, 0.59 to 0.82; four trials) and PFS (HR, 0.56; 95%CI, 0.44 to 0.71; four trials) compared with BRAF inhibitor therapy alone. Grade 3 and 4 toxicities were similar (RR, 1.01; 95% CI, 0.85 to 1.20; four trials). These results were driven by the coBRIM trial¹⁹ of vemurafenib plus cobimetinib versus vemurafenib alone and the COMBI-D trial,⁹⁰ COMBI-V trial,^{20,91} and the trial by Flaherty et al⁹² investigating dabrafenib plus trametinib. In addition to the trials identified in the Cochrane review, the COLUMBUS trial^{21,81} compared encorafenib plus binimetinib versus encorafenib alone or vemurafenib alone. This trial found significant improvements in PFS of the combination versus vemurafenib (HR, 0.54; 95% CI, 0.41 to 0.71) but not versus encorafenib (HR, 0.75; 95% CI, 0.56 to 1.00). A significant difference in OS between the combination and vemurafenib (HR, 0.61; 95% CI, 0.47 to 0.79) was found. Grade 3 and 4 toxicities were reported at similar rates among the three arms.

Updates for the 2023 guideline. In addition to the RELATIVITY-047 trial¹⁵ described under recommendation 3.1, which included patients regardless of BRAF status, four new randomized trials^{32,34,42,86} were reported in patients with BRAF-mutated melanoma. Of these, the SWOG S1320 trial⁴² compared an intermittent schedule of dabrafenib plus trametinib with the standard continuous schedule. It found no benefits for the intermittent schedule and is not discussed further.

The remaining three trials all investigated the addition of a PD-L1 inhibitor to the combination of BRAF/MEK inhibitor therapy. The Impire150 trial³² compared atezolizumab with placebo in patients who were also receiving vemurafenib and cobimetinib. This trial reported a significant difference in PFS, HR 0.78 (95%CI, 0.63 to 0.97), but not for OS, HR 0.85 (95% CI, 0.64 to 1.11). Note that per protocol, the primary outcome was PFS as assessed by the investigator. PFS was not different between the arms when assessed by independent review (HR, 0.85; 95% CI, 0.67 to 1.07). Similar rates of severe toxicity were reported on each arm. However, 22 patients originally assigned to the triplet combination arm were discontinued on therapy during cycle 1 before receiving atezolizumab and were analyzed as part of the safety population on the placebo arm instead of the atezolizumab arm. This potentially biased toxicity rates in favor of the atezolizumab arm. The KEYNOTE-022 trial compared pembrolizumab with placebo in patients who were receiving dabrafenib plus trametinib and reported no significant difference in PFS, HR 0.66 (95% CI, 0.40 to 1.07). A follow-up publication of KEYNOTE-022³⁵ reported PFS HR 0.58 (95% CI, 0.34 to 0.83) and OS HR 0.64 (95% CI, 0.38 to 1.06) for pembrolizumab compared to placebo. However, given the design of the trial, the authors did not consider the PFS HR to be a statistically significant result. The COMBI-I trial compared spartalizumab versus placebo in patients who were receiving dabrafenib plus trametinib and reported no significant difference in PFS, HR 0.82 (95% CI, 0.66 to 1.03), or OS, HR 0.79 (95% CI, 0.59 to 1.05).

Two other relevant trials were published since 2020 with similar designs that studied BRAF plus MEK inhibition first with nivolumab plus ipilimumab after progression or vice versa. The DREAMseq trial⁴⁰ studied dabrafenib plus trametinib. As proportional hazards were not expected, this trial is unique among identified trials in that its primary outcome was 2-year OS rate and not PFS or OS HR. The two year OS rate was 71.8% in patients who received nivolumab plus ipilimumab first versus 51.5% for those who received dabrafenib plus trametinib first. The difference in OS was significant (log-rank P 5 .01). The median PFS was 11.8 months for nivolumab plus ipilimumab as first line versus 8.5 months for dabrafenib plus trametinib (log rank P 5 .054). The SECOMBIT trial⁴¹ studied encorafenib plus binimetinib. This trial was designed to be noncomparative; HRs and their confidence intervals were considered exploratory. It included a sandwich arm that provided 8 weeks of encorafenib plus binimetinib before nivolumab plus ipilimumab as first-line therapy, which is not further discussed. No significant differences in PFS (HR, 0.71; 95% CI, 0.44 to 1.14) or OS (HR, 0.73; 95% CI, 0.42 to 1.26) were reported.

The exploratory network meta-analysis described in the Data Supplement 2 also investigated whether the available evidence was sufficient to prioritize between the different options for patients with BRAF-mutant unresectable and/or metastatic melanoma. This analysis suggested that

- Addition of PD-L1 inhibitor to the combination of BRAF/ MEK inhibitors might have better PFS but worse serious adverse event frequency than BRAF/MEK inhibitors alone, single-agent nivolumab or pembrolizumab, and two-drug nivolumab plus ipilimumab or nivolumab plus relatlimab.
- BRAF/MEK inhibitor combinations might have higher serious adverse event frequency than single-agent nivolumab, single-agent pembrolizumab, or nivolumab plus relatlimab, but not nivolumab plus ipilimumab.
- BRAF/MEK inhibitor combinations cannot be differentiated on either PFS or adverse events.
- Single-agent nivolumab not only may provide the lowest PFS of all the analyzed options but also might have the lowest frequency of serious adverse events.

However, given the limitations of this analysis described in the Data Supplement 2, none of these points can be considered as good evidence on which to base recommendations and are therefore areas for future research.

Clinical interpretation. Three combinations of BRAF and MEK inhibitors had been shown to be superior to BRAF inhibitor alone in the 2020 guideline: vemurafenib plus cobimetinib in CoBRIM,¹⁹ dabrafenib plus trametinib in COMBI-D90 and COMBI-V,^{20,91} and encorafenib plus binimetinib in COLUMBUS^{21,81} trial investigating encorafenib plus binimetinib. Therefore, in addition to the options described in recommendation 3.1, which now include nivolumab plus relatlimab, these three studied regimens were considered reasonable options for patients with BRAF V600E/K-mutant melanoma.

The COMBI-I, KEYNOTE-022, and Imspire150 trials^{32,34,86} provide evidence regarding the addition of a PD-(L)1 inhibitor to BRAF/MEK inhibitor combination therapy, but the interpretation of this evidence is unclear. Two trials found potential benefits to PFS, but in both cases, those benefits are muddled by other factors. In Imspire150, the discrepancy between investigator- and independently assessed PFS suggests a potential for bias. In KEYNOTE-022, the benefit was only seen after extended follow-up and the authors state that the trial was not intended to be comparative. The Panel recognizes that the US FDA approved atezolizumab for this indication in 2020 on the basis of Imspire150. However, the Expert Panel decided that on the basis of the limited evidence for benefits and the likely increased toxicity that no combination of PD-(L)1 inhibitor with BRAF/MEK inhibitors should be recommended.

The complicated picture for BRAF wild-type melanoma becomes even more complicated for patients with BRAF mutant melanoma; there are seven strongly recommended options that form the new recommendation 3.2.1. The evidence available to prioritize among these options is mixed and difficult to interpret. DREAMseq⁴⁰ reported that a strategy of nivolumab plus ipilimumab first-line followed by dabrafenib plus trametinib after progression had better 2-year OS than the reverse strategy. While RELATIVITY-047 reported better PFS for nivolumab plus relatlimab compared with nivolumab alone, it is unclear how this would compare with BRAF/MEK inhibitor combination therapy. The exploratory network meta-analysis did not provide sufficient information to prioritize among the available regimens. The Expert Panel found it difficult to achieve consensus on this matter as some members believed that a list of options was all that could be provided, whereas others believed that evidence from DREAMseq supported a strong recommendation in favor of nivolumab plus ipilimumab as the best choice for first-line therapy.

Ultimately, the consensus was that a strong recommendation to prefer nivolumab plus ipilimumab over BRAF/ MEK inhibitor therapy could be made, on the basis of the high-quality evidence of DREAMseq in the case of dabrafenib plus trametinib and extrapolating that result to the other BRAF/MEK inhibitor combinations as low-quality evidence given that SECOMBIT trial of encorafenib plus binimetinib was designed to be noncomparative and there is not a similar trial of vemurafenib plus cobimetinib. As noted in recommendation 3.1's Clinical Interpretation, the ASCO-SNO-ASTRO joint brain metastases guidelines⁸⁸ recommended nivolumab plus ipilimumab in patients with brain metastases. In addition, patients who are better able to tolerate toxicity and/or have better performance status may prefer combination therapy over single-agent anti-PD-1 therapy although this does not necessarily help in the decision between nivolumab plus relatlimab compared with BRAF/MEK inhibitor combination. As always, the decision on the choice of therapy should be made jointly with the patient after considering the risks and benefits.

In the 2020 guideline, a qualifying statement suggested that switching between BRAF/MEK inhibitor combinations may be reasonable if patients experience toxicity as each combination can present somewhat different toxicity profiles. In the clinical context of BRAF/MEK inhibitor failure, no prospective data exist regarding the efficacy of switching to a different BRAF/MEK combination. The statement also suggested that for longer dosing cycles for anti-PD-1 regimens (eg, up to 6 weeks), appropriate monitoring for toxicity and disease progression is still necessary.

- Recommendation 3.3 After progression on anti-PD-1-based therapy, patients with unresectable and/or metastatic BRAF wild-type cutaneous melanoma may be offered ipilimumab or ipilimumab containing regimens. Patients should be offered or referred for enrollment in clinical trials where possible (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and analysis. No trials were identified in either the 2020 guideline or the current update that addressed second-line or greater therapy in patients with BRAF wild-type unresectable and/or metastatic melanoma previously treated with the regimens recommended in recommendation 3.1 in first-line therapy. The Cochrane review identified one trial, reported by Hodi et al,⁹³ which investigated ipilimumab in second-line therapy. However, in that trial, patients were previously treated with chemotherapy or interleukin-2 (IL-2) and not anti-PD-1 therapy, so it is unclear how it is relevant to practice on the basis of the recommendations in this guideline and is not further discussed.

Clinical interpretation. Ipilimumab has been associated with improved OS and manageable toxicity in patients who have been treated with chemotherapy or IL-2 compared with a vaccine control. However, assuming that recommendation 3.1 are followed, patients will receive first-line anti-PD-1 therapy, potentially in combination with either ipilimumab or relatlimab. Therefore, the existing evidence is very limited as to the efficacy of ipilimumab after relapse on the recommended initial therapy regimens. However, the consensus of the Expert Panel was that, in the absence of direct trial evidence, ipilimumab- or ipilimumab-containing regimens could be offered to patients. It should be noted that ipilimumab at 3 mg/kg once every 3 weeks for up to four doses has been approved by the US FDA in these patients on the basis of the trial by Hodi et al.⁹³ In addition, ipilimumab-containing regimens could potentially include nivolumab plus ipilimumab in patients who have progressed on single-agent nivolumab or pembrolizumab. In response to external review feedback, a statement encouraging referral to clinical trials where possible was added to the recommendation.

The Panel notes that the results of the M14TIL trial⁹⁴ are relevant to this recommendation. In this trial, patients who had previous systemic treatment were randomly assigned to receive tumor-infiltrating lymphocytes (TILs) versus ipilimumab. TILs were not part of the scope of work for this guideline, so this trial was not included in the systematic review. Because of the nature of TIL therapy, patients had to have 2-3 cm total diameter of lesions that could be surgically resected to generate the TILs. All but 4 of the 168 included patients had previously received anti-PD-1 therapy, 40 as adjuvant therapy and 105 as first-line metastatic therapy. Patients receiving TILs had significantly improved PFS compared with those receiving ipilimumab (7.2 months v 3.1 months, HR, 0.50; 95% CI, 0.35 to 0.72). No significant difference in OS was reported (median 25.8 months with TILs v 18.9 months with ipilimumab, HR, 0.83; 95% CI, 0.54 to 1.27). The grade 3 or worse TRAE rate was 100% on TIL and 57% on ipilimumab. Patients on TILs reported generally better health-related quality-of-life scores.

In 2020, the Panel had recommended T-VEC as a possible option in the patients addressed by recommendation 3.3. At the time, this was based on the indirect data from the OPTIM trial.^{84,95-97} However, given the additional indirect evidence from MASTERKEY-265,³⁹ the Panel no longer believed that T-VEC could be considered a reasonable option and this recommendation was dropped. Both these trials are addressed more fully under recommendation 3.5.

- Recommendation 3.4 After progression on first-line anti-PD-1-based therapy, patients with BRAF mutant (V600) unresectable and/or metastatic cutaneous melanoma may be offered combination BRAF/MEK inhibitor therapy as described in Recommendation 3.2.1. Similarly, those who have progressed after combination BRAF/MEK inhibitor therapy may be offered anti-PD-1-based therapy as described in Recommendation 3.2.1 (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and analysis. In the 2020 guideline, only two randomized trials were identified of second-line or greater therapy that included patients with BRAF-mutant unresectable and/or metastatic melanoma who had received one of the options for first-line therapy in recommendation 3.2.1. The KEYNOTE-002 trial¹⁷ of pembrolizumab versus chemotherapy did not exclude this population, but only included 125 patients with BRAF-mutant disease. It found a PFS benefit in the prespecified subgroup analysis for 10 mg/kg once every three weeks pembrolizumab (HR, 0.44; 95% CI, 0.26 to 0.74) but not 3 mg/kg once every three weeks pembrolizumab (HR, 0.74; 95% CI, 0.46 to 1.18). It was not clear what proportion of these patients had received BRAF/MEK inhibitor therapy versus ipilimumab-based therapy. The KEYNOTE-00698 trial also included patients

who had BRAF-mutant disease and previous therapy with BRAF/MEK inhibitor combination. In the subgroup analysis, a PFS benefit for pembrolizumab every 2 weeks versus ipilimumab was found in patients who had received previous BRAF inhibitor therapy (HR, 0.58; 95% CI, 0.34 to 0.97). No benefits were found with pembrolizumab every 3 weeks. The CheckMate 037 trial⁹⁹ did include second-line or greater patients with BRAF-mutant melanoma, but it required those patients to have progressed on anti-CTLA-4 and anti-BRAF therapy, so it is not clear if any patients received an option that is recommended in 3.2. Since the 2020 guideline, the DREAMseq and SECOMBIT trials have been published and are discussed in the literature review section for recommendation 3.2.

Clinical interpretation. In the absence of direct trial evidence other than small subgroup analyses, the consensus of the Expert Panel in 2020 was that it was reasonable to offer patients with BRAF-mutant disease systemic therapy on relapse on the basis of the indirect evidence of its efficacy in first-line therapy and no known evidence of cross-resistance between these therapies. The DREAMseq and SECOMBIT trials do not directly address this population because those trials addressed a strategy of first-line and second-line therapies and did not randomly assign a population that had all received the same firstline therapy to different second-line options. However, given the evidence in those trials of activity of BRAF/MEK after anti-PD-1 and in the reverse case, the Panel no longer believed that ipilimumab and ipilimumab-containing regimens were reasonable options after progression on first-line therapy, and the recommendation was altered to drop that option. While it is not directly mentioned in recommendation 3.4, the addition of nivolumab plus relatlimab to recommendation 3.2 makes that combination a potential option for patients who have progressed on first-line BRAF/MEK inhibitor combination therapy.

- Recommendation 3.5 For patients with injectable (cutaneous or subcutaneous or nodal) unresectable lesions who are not eligible or do not desire the recommended systemic therapies, T-VEC may be offered as primary therapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and analysis. Two trials have been identified in the original 2020 guideline and for this update. The OPTIM trial^{84,95-97} compared T-VEC with granulocyte macrophage colony-stimulating factor in patients with unresectable and/or metastatic melanoma with injectable lesions. The median time to treatment failure (HR, 0.42; 95% CI, 0.32 to 0.54) was significantly improved, whereas OS (HR, 0.79; 95% CI, 0.62 to 1.00) was not. Grade 3 and 4 toxicities were somewhat increased. Chesney et al⁸⁰ compared T-VEC plus ipilimumab with ipilimumab alone and reported no significant difference in PFS (HR, 0.83; 95% CI, 0.56 to 1.23; P = .35) or OS (HR, 0.80; 95% CI, 0.44 to 1.46). These trials are fully described in the Data Supplement (Supplement 3, Tables 2020-1 to 2020-5). The MASTERKEY-265 trial³⁹ was identified in this full update, compared T-VEC with placebo in patients receiving single-agent pembrolizumab, and reported no significant difference in (HR, 0.86; 95% CI, 0.71 to 1.04) or OS (HR, 0.97; 95% CI, 0.77 to 1.21). It is fully described in the Data Supplement (Supplement 1, Tables 1-5). Given that the MASTERKEY-265 trial compared T-VEC with an option that has been recommended in this guideline, the evidence quality for recommendation 3.5 was downgraded from moderate to weak.

Clinical interpretation. Given the strength of the evidence identified for the options found in recommendations 3.1 and 3.2 and the infrastructure requirements necessary to deliver T-VEC therapy, the Expert Panel in the 2020 guideline felt that it was not possible to list T-VEC as an equivalent option solely on the basis of the OPTIM trial and in light of the trial by Chesney et al. However, in patients in whom those therapy regimens are contraindicated or the patients who are otherwise ineligible, or where the patient refuses the recommended regimens, T-VEC is a reasonable alternative assuming that the patient has injectable lesions. The lack of any PFS or OS benefit reported in MASTERKEY- 265 reinforces this previous consensus.

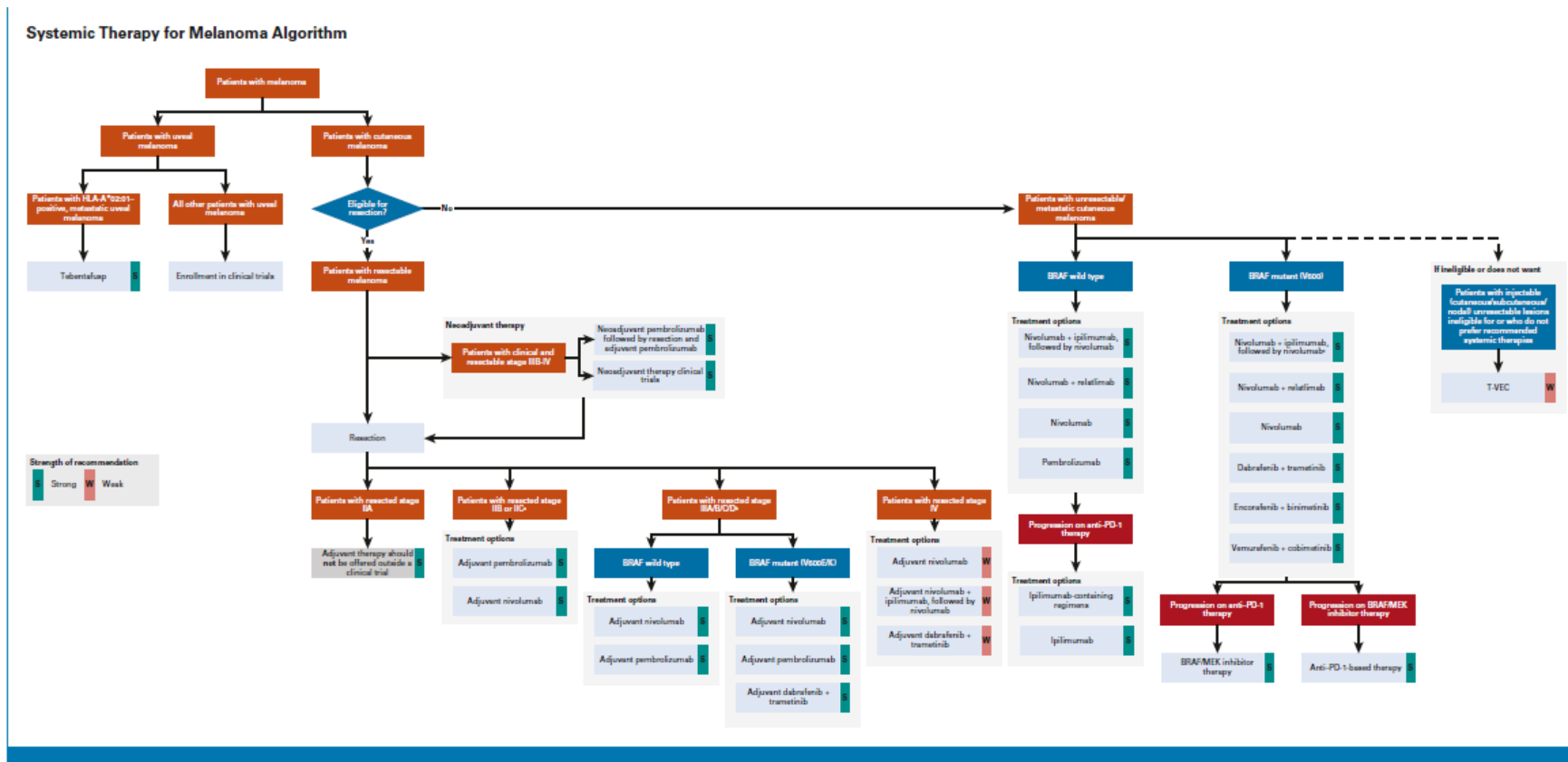


FIG 1. Algorithm for systemic therapy for melanoma. ^aWhile the consensus of the Panel was that a strong recommendation could be made for adjuvant nivolumab or pembrolizumab for these patients, the potential for serious morbidity, both acute and long term, because of immune-related toxicity must be considered and weighed against the lack of overall survival data in stage II disease. Treatment should be individualized after discussing risk-benefit quotient with these patients. ^bPatients with stage IIIA disease with microscopic sentinel nodal metastasis <1 mm in diameter were not included in the randomized trials that studied efficacy of immune checkpoint inhibitors as adjuvant therapy for melanoma. Both nivolumab and pembrolizumab are US Food and Drug Administration–approved adjuvant treatments for patients with melanoma with lymph node involvement who have undergone complete disease resection. Patients with stage IIIA disease with <1 mm involvement in the sentinel lymph node have a relatively better prognosis and lower risk of relapse. Therefore, treatment should be individualized after discussing risk-benefit quotient with these patients. ^cThis option has been found to be superior to dabrafenib plus trametinib in a phase III trial. T-VEC, talimogene laherparepvec.

Scottish Intercollegiate Guidelines Network (SIGN), 2017 [4].

Cutaneous melanoma: a national clinical guideline

Zielsetzung/Fragestellung

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

The update covers new evidence in:

- pathological reporting
- sentinel lymph node biopsy and completion lymphadenectomy
- systemic anticancer therapies
- follow-up surveillance.

Methodik

This guideline was developed according to the 2016 edition of SIGN 50, and the update in 2023 used the 2019 edition

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Informale Konsensusprozesse und externes Begutachtungsverfahren: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität teilweise gesichert: trifft zu.

Recherche/Suchzeitraum:

- 2023 updates include: pathological reporting, in line with the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th edition and the revised edition of the Royal College of Pathology dataset; sentinel lymph node biopsy and completion lymphadenectomy; **advances in systemic anticancer therapies**; revised consensus-based guidance on follow-up surveillance; other minor updates throughout to reflect current practice.
- 2025 update: complete revision of section 3.6 Genetics to reflect update to national genomic testing guidance.

LoE/GoR

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.

Recommendations

Management of advanced (unresectable stage III or IV) melanoma

8.2 Systemic anticancer therapy

8.2.1 Immunotherapy

- ✓ | When choosing systemic anticancer treatment for patients with untreated stage IV or unresectable stage III melanoma, treatment decisions should be based on the following factors:
 - comorbidities and performance status
 - risk of treatment toxicity
 - whether potential treatment toxicity will be tolerated
 - presence of symptomatic brain metastases
 - tumour biology (for example, high disease burden, rapid progression, LDH level).

Treatment decisions should be made after a full assessment of the risks and benefits for the patient by the treating oncologist.⁵⁷
- R** | **In patients with untreated stage IV or unresectable stage III melanoma immunotherapy with immune checkpoint inhibitors is recommended as first-line treatment irrespective of BRAF status.**
- R** | **Nivolumab plus ipilimumab should be considered for patients with untreated stage IV or unresectable stage III melanoma (if suitable for the patient). If nivolumab plus ipilimumab is unsuitable or unacceptable (for example, because of potential toxicity or patient choice), pembrolizumab or nivolumab monotherapy should be offered.**

8.2.2 BRAF and MEK inhibitors

- R** | **Encorafenib plus binimetinib, or dabrafenib plus trametinib should be considered for patients with untreated stage IV or unresectable stage III melanoma with BRAF mutation if nivolumab plus ipilimumab, pembrolizumab or nivolumab monotherapy are contraindicated or it is predicted there is not enough time for an adequate immune response (for example, because of high disease burden or rapid progression).**

8.3 Laser ablation

A carbon dioxide laser delivers short wavelength energy in a focused light beam to destroy tumour nodules. It can be applied under local anaesthetic, can be repeated and provides effective local disease control.¹⁷⁴⁻¹⁷⁶ } 4

- ✓ | Carbon dioxide laser ablation can be considered for multiple lesions of trunk or abdomen and for limb disease.
- ✓ | Laser ablation should be undertaken in a specialist setting by clinicians with experience of the technique and who are in a position to undertake appropriate post-treatment care or offer alternative treatments if laser ablation is not appropriate.

Other similar treatments are available and vary locally.

8.4 Electrochemotherapy

- R** | **Electrochemotherapy should be considered as a treatment option for patients with cutaneous melanoma metastases after multidisciplinary team discussion and careful consideration of alternative systemic therapy options.**

8.5 Radiotherapy

- R** | **Single dose radiotherapy of a least 8 Gy may be considered for palliation of pain from bone metastases.**
- ✓ | If a patient presents with spinal cord compression consideration should be given to available medical oncology options ie *BRAF* testing should be considered if this has not already been done, targeted *BRAF* therapy should be considered in new cases.
 - ✓ | All patients with brain-limited metastasis should be tested for *BRAF* mutations and have their management discussed at a neuro-oncology multidisciplinary team to determine optimal choice of treatment including systemic or targeted therapy, surgery or stereotactic radiosurgery.
- R** | **Patients with good performance status, favourable response to corticosteroid treatment, absence of systemic disease and who have favourable CNS disease should be considered for surgical resection of their CNS disease.**
- ✓ | If surgery is not possible, patients should be considered for systemic therapy (*see section 8.2*) or stereotactic radiotherapy.

National Institute for Health and Care Excellence (NICE), 2015 (Last updated 2022) [2].

National Collaborating Centre for Cancer commissioned by NICE

Melanoma: assessment and management

Zielsetzung/Fragestellung

This guideline covers the assessment and management of melanoma (a type of skin cancer) in **children, young people and adults**. It aims to reduce variation in practice and improve survival.

Methodik

Grundlage der Leitlinie

NICE's original guidance on melanoma: assessment and management was published in 2015 and updated in 2022. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2022.

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: unklar (eindeutige Informationen zur spezifischen Anwendung und Art der Konsensusprozesse in der LL konnten nicht vollständig identifiziert werden);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft teilweise zu (Evidenzgrundlagen beschrieben, jedoch direkte Bezüge zu den spezifischen Empfehlungen sowie die jeweiligen LoE nicht deutlich);
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- The searches were originally run between August 2020 and April 2021 and updated in July 2021.
- The following databases were included in the literature search:
 - The Cochrane Library
 - Medline and Premedline 1946 onwards
 - Excerpta Medica (Embase) 1974 onwards
 - Web of Science [specifically Science Citation Index Expanded
 - (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards]
- Subject specific databases used for certain topics:
 - Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards
 - Psycinfo 1806 onwards

LoE/GoR

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

- The strength of the recommendation is reflected in the wording:
 - ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm
 - ‘Do not offer’ – the intervention will not be of benefit for most patients
 - ‘Consider’ – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for an ‘offer’ recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Sonstige methodische Hinweise

- July 2022: We have reviewed the evidence on assessment, management and follow-up for people with melanoma. These recommendations are marked [2022].
- We amended a heading in section 1.8 to separate treatments for untreated and previously treated stage IV and unresectable stage III melanoma. These recommendations are marked [2022]

Empfehlungen

Systemic anticancer treatments for untreated stage IV and unresectable stage III melanoma

In July 2022, most of the therapies in recommendations 1.8.7 to 1.8.12 were unlicensed for use in the UK in children and young people under 18. See NICE’s information on prescribing medicines. Refer to the summary of product characteristics for the individual treatments because there are differences in their licensed populations.

1.8.6 When choosing systemic anticancer treatment for untreated stage IV or unresectable stage III melanoma, base treatment decisions on the following factors:

- comorbidities and performance status
- risk of treatment toxicity
- whether potential treatment toxicity will be tolerated
- presence of symptomatic brain metastases
- tumour biology (for example, high disease burden, rapid progression, lactate dehydrogenase level).

Treatment decisions should be made after a full assessment of the risks and benefits by the treating oncologist and discussion with the person, in line with NICE’s guideline on shared decision making. **[2022]**

1.8.7 Offer treatment with immunotherapy to people with untreated stage IV or unresectable stage III melanoma, as set out in recommendations 1.8.8 to 1.8.9. If immunotherapy is contraindicated or unsuitable, based on the factors in recommendation 1.8.6, follow recommendations 1.8.10 to 1.8.12 for alternative treatments based on BRAF type. **[2022]** For other guidance on treatments for advanced melanoma, see NICE’s technology appraisal guidance on the NICE topic page for skin cancer.

Immunotherapies

1.8.8 Offer nivolumab plus ipilimumab to people with untreated stage IV or unresectable stage III melanoma if suitable for them based on the factors in recommendation 1.8.6. **[2022]** See NICE's technology appraisal guidance on nivolumab in combination with ipilimumab for treating advanced melanoma.

1.8.9 If nivolumab plus ipilimumab is unsuitable or unacceptable (for example, because of potential toxicity), offer pembrolizumab or nivolumab monotherapy. **[2022]** See NICE's technology appraisal guidance on pembrolizumab for advanced melanoma not previously treated with ipilimumab and nivolumab for treating advanced (unresectable or metastatic) melanoma.

Targeted therapies for BRAF V600 mutation-positive melanoma

1.8.10 Offer encorafenib plus binimetinib, or dabrafenib plus trametinib, to people with untreated BRAF-mutant stage IV or unresectable stage III melanoma if:

- nivolumab plus ipilimumab, pembrolizumab, and nivolumab are contraindicated or
- it is predicted there is not enough time for an adequate immune response (for example, because of high disease burden or rapid progression). **[2022]** See NICE's technology appraisal guidance on encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma and trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma.

1.8.11 If encorafenib plus binimetinib, and dabrafenib plus trametinib, are both unsuitable or unacceptable to the person:

- offer dabrafenib or vemurafenib to people for whom binimetinib and trametinib are contraindicated or
- if targeted treatment is contraindicated, consider treatment with chemotherapy (dacarbazine) or best supportive care. **[2022]** See NICE's technology appraisal guidance on dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma and vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. For other guidance on targeted therapies see NICE's technology appraisal guidance on the NICE topic page for skin cancer.

Alternatives to immunotherapies for BRAF wild-type melanoma

1.8.12 For people with untreated BRAF-wild type stage IV or unresectable stage III melanoma for whom nivolumab plus ipilimumab, pembrolizumab, and nivolumab are contraindicated, consider:

- treatment with chemotherapy (dacarbazine) or
- best supportive care. **[2022]**

Hintergrund:

Managing stage IV and unresectable stage III melanoma

Recommendations 1.8.3 and 1.8.6 to 1.8.16

Why the committee made the recommendations

The committee looked at evidence on immunotherapies (ipilimumab, nivolumab, pembrolizumab, and nivolumab plus ipilimumab) and targeted therapies (encorafenib plus binimetinib, trametinib plus dabrafenib, dabrafenib monotherapy and vemurafenib monotherapy). These therapies were also compared in a health economic model.

The committee noted the complexities and nuances in the treatment pathway. They identified a number of factors that should be taken into account when considering treatment choices to allow appropriate and individualised treatment decisions.

The evidence showed that, overall, the immunotherapies are more clinically effective than the targeted therapies. Within the immunotherapies, nivolumab plus ipilimumab was the most clinically effective. The health economic model demonstrated that it is also the most cost effective.

However, the committee noted evidence showing that the risk of toxicity with immunotherapies is higher than with targeted therapies, and that this risk increases when immunotherapies are used in combination. They therefore agreed that monotherapy should be an option if combination immunotherapy is deemed unsuitable for people, for example those with poor performance status or comorbidities who are less likely to tolerate toxicity. The evidence showed that nivolumab and pembrolizumab have similar clinical effectiveness and cost effectiveness when used as monotherapies so the committee agreed that either of these options should be offered.

The committee noted NICE technology appraisal guidance recommending ipilimumab monotherapy for untreated advanced (unresectable or metastatic) melanoma, but did not include this option in their recommendation because it is not commonly used as first-line treatment and monotherapy with either nivolumab or pembrolizumab is more cost effective in this population. The committee also acknowledged that ipilimumab is licensed for use as monotherapy in adults and young people aged 12 and over. However, based on their clinical experience, its use as a monotherapy is considered to be the same as in

If immunotherapy, either in combination or as monotherapy, is unsuitable, the committee agreed that targeted therapies based on BRAF status are an option. The committee noted that someone with symptomatic brain metastases will usually need steroids, which excludes treatment with immunotherapy. In addition, for people with a high disease burden or rapid progression there may not be enough time to generate the necessary immune response that is associated with immunotherapy. Within the targeted therapies, evidence showed that encorafenib plus binimetinib, or trametinib plus dabrafenib, had similar clinical effectiveness. The health economic model did not demonstrate clear differences in cost effectiveness between these 2 options. Therefore, the committee agreed that either of these options for combination treatment could be recommended. If both of these options are unsuitable, the committee agreed that monotherapy with dabrafenib or vemurafenib should be offered.

If targeted treatment for BRAF-mutated melanoma is unsuitable, or if the melanoma is BRAF-wild type, the committee agreed that the options are limited to chemotherapy with dacarbazine or best supportive care.

The committee also made recommendations on treatments for previously treated stage IV or unresectable stage III melanoma. The evidence for the clinical and cost effectiveness of treatment in this area was limited. Therefore, the committee preferred to list the available treatment options, and to highlight the factors that should be taken into account when considering treatment choices for previously treated melanoma.

No evidence was found for the effectiveness of systemic cancer therapies specific to children and young people. However, the committee agreed that treatment should not differ between children and adults, and that recommendations also apply to children and young people. When treating children and young people, healthcare professionals should refer to the individual summary of product characteristics for the treatment being considered. This is because most of the treatments recommended in this guideline are not licensed for use in the UK in children and young people under 18, but there are differences in their licensed populations.

The committee noted that people with incurable melanoma have a high symptom burden which should be managed at an early stage, and recommended referral to specialist palliative care services.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2026)
am 03.03.2026

#	Suchschritt
1	[mh Melanoma]
2	Melanom*:ti,ab,kw
3	(skin* OR cutaneous):ti
4	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from Mar 2021 to present
8	#7 with Cochrane Library publication date from Mar 2024 to present
9	#7 NOT #8

Leitlinien und systematische Reviews in PubMed am 03.03.2026

verwendete Suchfilter für Leitlinien:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.02.2026

verwendeter Suchfilter für systematische Reviews:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.

#	Suchschritt
	Leitlinien
1	Melanoma[mh]
2	melanom*[tiab]
3	(skin*[ti] OR cutaneous[ti])
4	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab]
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (Guideline[pt] OR Practice Guideline[pt] OR Consensus Statement [pt] OR Consensus Development Conference, NIH[pt] OR guideline*[ti] OR recommendation*[ti])
8	(#7) AND ("2021/03/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews
10	Melanoma/TH [mh]

#	Suchschritt
11	#2 OR #5
12	(#11) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
13	#10 OR #12
14	(#13) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab]))) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR (((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab]))) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebSCO[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
15	(#14) AND ("2021/03/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
18	(#17) NOT (#9)
19	(#18) AND ("2024/03/01"[PDAT] : "3000"[PDAT])
20	#18 NOT #19

Iterative Handsuche nach grauer Literatur, abgeschlossen am 04.03.2026, überprüft am 29.05.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)

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

Referenzen

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- [B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. <https://doi.org/10.1016/j.jclinepi.2016.01.021>