National Institute for Health and Care Excellence

Draft

Melanoma: assessment and management

[F] Evidence reviews for systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma

NICE guideline <number>

Evidence reviews underpinning recommendations 1.7.1 to 1.7.4 and 1.8.6 to 1.8.11 and research recommendations in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by Guideline Updates Team

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ISBN:

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1.1 Review question

RQ 5.1 systemic and localised anticancer treatment for people with stage IV (+ unresectable stage III) melanoma

1.1.1 Introduction

Systemic therapy is playing an ever more important role in the multidisciplinary management of metastatic melanoma. With the development of new targeted treatments and immune therapies the role of chemotherapy has shifted, and selection of the most appropriate therapy must now take into account the mutational status of the tumour, tumour load, pace of disease and treatment availability.

There was a need to update this question in response to new treatment options now being available. In addition, there is a need to sequence the different therapy options to identify the most effective choices for first- and second-line therapy.

1.1.2 Summary of the protocol

Table 1 PICO table for systemic and localised anti-cancer treatment in advanced cancer

Population	People with a diagnosis of stage 4 (or unresectable stage 3) melanoma
Intervention (predictors)	Immunotherapies: • nivolumab • nivolumab + ipilimumab • ipilimumab • pembrolizumab Targeted therapy for BRAF-positive melanoma: • encorafenib + binimetinib • trametinib with dabrafenib • dabrafenib • vemurafenib Localised treatments for people with locoregional disease: • isolated limb infusion (ILI)

	• isolated limb perfusion (ILP) • electrochemotherapy (ECT) • Talimogene laherparepvec (T-VEC)
Comparator (predicted outcome)	Immunotherapies and targeted therapies: • Any Localised treatments for people with locoregional disease: • Interventions compared to each other
Outcomes	• Rate of mortality and time to death • All-cause and melanoma specific mortality; at 1, 2 and 5 years • Progression free survival; at 1, 2 and 5 years • Health related quality of life • Serious adverse events • Time on treatment • Time to second treatment

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

The following modifications were made to this chapter:

- A network meta-analysis (NMA) was conducted to make indirect comparisons of treatments for the outcomes of progression-free survival and overall survival. Pairwise analyses were conducted for the other outcomes listed in the PICO above.
- Pairwise analyses were only conducted for outcomes not reported in the NMA. As NMAs were conducted on all-cause mortality and progression-free survival, these outcomes were not reported in pairwise analyses unless pertaining to specific subgroups (as the NMA used data from the overall trial populations). This was done to avoid duplication of reporting outcomes within the evidence review and because committee discussions surrounding these outcomes relied solely on the evidence from the NMA.

Protocol deviations

- For evidence assessing localised treatments, there were several protocol deviations due to a lack of comparative evidence:
  - Studies comparing localised treatments outlined in the protocol to those not listed in the protocol were included. Although treatments not listed in the protocol are less useful clinically, they were known to the committee and allowed inferences to be made about the efficacy of treatments listed in the protocol.
  - Non-comparative studies were included in this review if they contained prognostic data (predictors of outcomes listed in the protocol). This allowed for

the committee to try to identify groups of people who would benefit most from each of the localised treatments.

- Non-comparative prognostic data was also used to inform discussions surrounding general rates of responses to treatments (complete response, mortality, progressive disease and toxicity). GRADE was not conducted on these outcomes as quality is only assessable for these outcomes when compared to another treatment.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Clinical evidence

1.1.4.1 Included studies

A systematic literature search was conducted for this review on systemic and localised treatment in people with melanoma. This returned 2,324 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocol, 107 references were ordered for screening based on their full texts.

Of the 110 references screened as full texts, 65 references (representing 30 distinct studies across 65 publications) met the inclusion criteria specified in the review protocol for this question (appendix A). 14 RCTs were included for the review pertaining to immunotherapies and targeted treatments. 16 studies (3 RCTs and 13 cohort studies) on localised treatments were included.

The clinical evidence study selection is presented as a diagram in appendix C.

1.1.4.2 Excluded studies

See Appendix I for a list of references for excluded studies, with reasons for exclusion.

1.1.5 Summary of studies included in the clinical evidence

Table 2 Summary of included immunotherapy studies

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
ABC trial	63	• Asymptomatic brain metastases (intracranial lesion of 5–40 mm) • ECOG 0-2 • Naïve to BRAF inhibitor • No previous local brain therapy	• nivolumab + ipilimumab, then nivolumab only • nivolumab only	Up to 2 years	Low *Cohort C excluded as different inclusion criteria.*
CHECK MATE 037	405	• BRAF positive or WT • progression on anti-CTLA-4 treatment (plus BRAFi if mutation positive) • IIIC/V	• nivolumab • dacarbazine or carboplatin	Up to 3 years	High *Open-label* *High level of crossover from ICC arm.*

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
					Large difference in subsequent anti-PD1 therapy between arms.
CHECKMATE 064	140	• BRAF positive • ECOG 0-1 • Naïve or progressed after ≤1 systemic therapy	• nivolumab followed by ipilimumab • ipilimumab followed by nivolumab	Up to 30 months	High *Open-label* *Large difference in subsequent anti-cancer therapy.* *Overall survival was an exploratory endpoint, conducted per protocol.*
CHECKMATE 066	418	• BRAF wild-type • Naïve • ECOG 0-1	• nivolumab • dacarbazine	Up to 6 years	Moderate *Double-blinded however patients crossing over from dacarbazine arm became unblinded.* *Some difference in subsequent anticancer therapy.*
CHECKMATE 067	945	• Unresectable III/IV • BRAF positive or WT • ECOG 0-1 • No prior systemic therapy • No active brain metastases	• nivolumab • ipilimumab	Up to 5 years	Low
CHECKMATE 069	142	• BRAF positive or WT • ECOG 0-1 • Naive	• nivolumab + ipilimumab • ipilimumab alone	Up to 2 years	Low
KEYNOTE 002	540	• BRAF positive or WT • ECOG 0-1 • Progressed on ipilimumab Tx	• pembrolizumab (2mg/kg) • pembrolizumab (10mg/kg) • chemotherapy	Up to 2 years	Moderate *Open-label with large number of participants crossing over from chemotherapy arm.*

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
KEYNOTE 006	834	• BRAF positive or WT • ECOG 0-1 • 0-1 previous systemic therapy	• ipilimumab 3mg/kg every 3 weeks • pembrolizumab every 2 weeks • pembrolizumab every 3 weeks	Up to 5 years	Low

1 **Table 3 Summary of included targeted therapy studies**

Study	Sample size (location)	Inclusion criteria	Interventions	Follow-up time	Risk of bias *notes*
BREAK-3	250	• BRAF positive • ECOG 0-1 • Tx naïve for metastatic melanoma	• dabrafenib • dacarbazine	Up to 9 months	Low
BRIM-3	675	• BRAF positive • Tx naïve • IIIC/IV • ECOG 0-1	• dacarbazine • vemurafenib	Up to 5 years	Low
BRF113222 0	162	• BRAF positive • Tx naïve for BRAF/MEK inhibitor	• dabrafenib + high dose trametinib • dabrafenib + low dose trametinib (1mg) • dabrafenib only	Up to 5 years	Moderate *Open-label* *High number of participants in monotherapy arm subsequently received trametinib during trial.*
COLUMBUS	577	• BRAF positive • Tx naïve or progressed after first-line immunotherapy	• encorafenib + binimetinib • encorafenib only • vemurafenib	Up to 5 years	Low *Open-label*
COMBI-D	423	• BRAF positive • ECOG 0-1	• dabrafenib + trametinib • dabrafenib only	Up to 32 months	Low

Study	Sample size (location)	Inclusion criteria	Interventions	Follow-up time	Risk of bias *notes*
		• Naïve to systemic Tx			
COMBI-V	704	• BRAF positive • ECOG 0-1 • Naïve to systemic Tx	• dabrafenib + trametinib • vemurafenib	Up to 1 year	High *Open-label with differences in subsequent therapies received*

1 **Table 4 Summary of included localised therapy studies (RCTs)**

Study	Trial design	Sample size	Inclusion criteria	Intervention	Follow-up time	Risk of bias (notes)
OPTiM	RCT	436	• Unresectable IIIB-IV • ECOG 0-1	• T-VEC • granulocyte macrophage colony-stimulating factor (GMCSF)	Up to 5 years	Low
Chesney 2018	RCT	198	• Unresectable IIIB-IV • ECOG 0-1	• T-VEC + ipilimumab • ipilimumab only	Up to 3 years	Low
Hughes 2016	RCT	93	• Unresectable melanoma metastatic to the liver • ECOG 0-2	• percutaneous hepatic perfusion • best available care	Up to 20 months	Moderate *Unclear blinding procedures* *Indirectly applicable as intervention not on protocol*

2 **Table 5 Summary of included localised therapy studies (cohort studies)**

Study	Trial design (size)	Treat-ment	Follow up time	% Complete Response (3 months)	% toxicity (3 months)	% Progressive Disease (3 months)	% all-cause mortality (final follow-up)	Risk of bias
Katsarelias 2018	Retrospective (284)	ILP	Up to 10 years	58.8%	32.9%	nr	2y: 64% 5y: 39% 10y: 19%	Moderate *Limited reporting on*

Study	Trial design (size)	Treat-ment	Follow up time	% Complete Response (3 months)	% toxicity (3 months)	% Progressive Disease (3 months)	% all-cause mortality (final follow-up)	Risk of bias
								timing and potential for confounders.
Kenyon-Smith 2020	Retrospective (687)	ILI	Unclear – likely during procedure only	28.9%	29.1%	19.8%	nr	Moderate *Potential for confounders which were not adjusted for.*
Muilenberg 2015	Retrospective (160)	ILI	Up to 4 years	33.8%	31.9%	33.1%	32.5%	Moderate *Potential for confounders which were not adjusted for*
Olofsson 2013	Retrospective (155)	ILP	Median 27 months	65%	36%	20%	2yr: 53% 5yr: 26% 10yr: 8%	Moderate *Potential for confounders which were not adequately adjusted for*
Lidsky 2013/ Sharma 2012	Review of prospectively collected database (215)	ILI Hepatic ILP	Up to 3 years	ILP: 44.4% ILI: 32.1%	ILP: 33.1% ILI: 19.3%	ILP: 11.1% (3-year recurrence: 63.9%) ILI: 29.9% (3-year recurrence: 83.8%)	ILP: 22.2% ILI: 45.9%	Moderate *Potential for confounders which were not adequately adjusted for*
Kroon 2009	Retrospective cohort study (185)	ILI	6 years	38%	42%	46%	70.8%	Moderate *No adjustment for potential confounders*
Beasley 2009	Retrospective cohort study (128)	ILI	3 months	31%	36%	33%	Nr	Moderate *No adjustment for potential confounders*

Study	Trial design (size)	Treat-ment	Follow up time	% Complete Response (3 months)	% toxicity (3 months)	% Progressive Disease (3 months)	% all-cause mortality (final follow-up)	Risk of bias
Steinman 2014	Review of prospectively collected database (62)	ILI	Median 22 months	25%	nr	14.7%	55.9%	Moderate *Limited reporting and potential for confounders*
Read 2019	Review of prospectively collected database (72)	ILI PV-10 therapy	Up to 120 months	22.2%	13.9%	27.8%	38.9%	Moderate *Limited reporting on deviation from protocol.* *Matching was not adequately performed*

See appendix D for full evidence tables.

1.1.6 Summary of clinical pairwise evidence

Pairwise analyses were only conducted on outcomes that were listed in the review protocol (see appendix A) and were not entered into the NMA, as to avoid double counting the data in the present review. NMAs were conducted on overall survival and progression-free survival and as such pairwise analyses were not conducted for these outcomes, except for subgroups.

Table 6 Summary of included localised treatment studies

Study	Sample size	Intervention(s)	Summary of key outcomes *(quality of evidence)*
OPTim	436	• T-VEC • GMCSF	Overall survival up to 5 years was significantly increased in the T-VEC arm, overall (HR: 0.73 (0.59, 0.92)) and in the following subgroups: • Stage IIIB-C: HR 0.48 (0.29, 0.80) *High quality* • Stage IIIB-IVM1a: HR 0.56 (0.40, 0.79) *High quality* • Stage IVM1b: HR 1.06 (0.62, 1.78) *Moderate quality*

Study	Sample size	Intervention(s)	Summary of key outcomes *(quality of evidence)*
			• Stage IVM1c: HR 1.08 (0.68, 1.74) *Moderate quality* • First-line therapy: HR 0.50 (0.35, 0.72) *High quality* • ECOG-0: HR 0.85 (0.63, 1.14) *Moderate quality* • ECOG-1: HR 0.57 (0.36, 0.89) *High quality* • Head and neck cancer only HR 0.38 (0.20, 0.72) *Moderate quality*
Chesney 2018	190	• T-VEC + ipilimumam • Ipilimumab alone	At up to 3 years follow-up (T-VEC+ipi compared to IPI alone): • Overall survival HR 0.80 (0.44, 1.46) *Low quality* • Progression-free survival HR 0.83 (0.56, 1.23) *Moderate quality* • Adverse events leading to treatment discontinuation HR 0.82 (0.43, 1.57) *Low quality* • Grade 3-5 Adverse events HR 1.30 (0.92, 1.86) *Moderate quality* • Adverse events-related mortality HR 7.00 (0.37, 133.70) *Low quality*
Hughes 2016	93	• Percutaneous hepatic infusion • Best available care	At up to 20 months follow-up, hepatic perfusion had improved: • Overall survival HR 0.92 (0.52, 1.62) *Very low quality* • Progression-free survival HR 0.40 (0.25, 0.65) *Moderate quality* • Hepatic progression-free survival HR 0.30 (0.18, 0.50) *Moderate quality*
Lidsky 2013/ Sharma 2012	215	• ILI • ILP	• Increased risk of progression at 3 months in ILI arm: RR 2.89 (1.49, 5.61) *Low quality* • Increased risk of mortality at 3 years in ILI arm: RR 2.07 (1.02, 4.18) *Very low quality*

Study	Sample size	Intervention(s)	Summary of key outcomes *(quality of evidence)*
Read (2019)	72	• ILI • PV-10	At 5 years (ILI compared to PV-10): • melanoma-specific mortality RR 0.61 (0.38, 0.98) *Very low quality* • Grade 3-5 toxicity RR 5.00 (0.61, 40.70) *Very low quality*

1 **Table 7 Summary of included immunotherapy/targeted therapy studies**

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
Nivolumab vs. investigator's choice of chemotherapy – Overall survival at 2 years (HR <1 favour nivolu								
CHECKMATE 037	370	overall	See NMA	See NMA	See NMA	See NMA	RR 1.04 (0.81, 1.34)	Very low
	257	Aged <65 years	HR 1.17 (0.84, 1.63)	Very low	N/A	N/A	N/A	N/A
	148	Aged ≥65 years	HR 0.62 (0.41, 0.94)	Low	N/A	N/A	N/A	N/A
	246	ECOG PF 0	HR 0.95 (0.67, 1.34)	Very low	N/A	N/A	N/A	N/A
	158	ECOG PF 1	HR 0.89 (0.60, 1.31)	Very low	N/A	N/A	N/A	N/A
	211	LDH ≤ULN	HR 0.84 (0.57, 1.23)	Very low	N/A	N/A	N/A	N/A
	191	LDH >ULN	HR 0.78 (0.55, 1.11)	Very low	N/A	N/A	N/A	N/A
	68	LDH > 2x ULN	HR 0.67 (0.38 ,1.18)	Very low	N/A	N/A	N/A	N/A
	73	History of brain metastases	HR 1.42 (0.73, 2.46)	Very low	N/A	N/A	N/A	N/A
Dabrafenib + Trametinib (150/2 dose) vs. dabrafenib alone– Overall survival at 5 years								

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
BRF113220	109	Overall	N/A	N/A	N/A	N/A	RR 1.43 (1.02, 2.00)	Low
	61	LDH ≤ULN	RR 0.76 (0.52, 1.11)	Moderate	RR 0.84 (0.68, 1.04)	Moderate	N/A	N/A
	47	LDH >ULN	RR 1.12 (0.93, 1.34)	Moderate	N/A	N/A	N/A	N/A
Pembrolizumab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumab – Over								
KEYNOTE-006	534	Overall	N/A	N/A	N/A	N/A	Pembro (10mg/2W) vs IPI: RR 0.87 (0.60, 1.24)	Moderate
	533	Overall	N/A	N/A	N/A	N/A	Pembro (10mg/3W) vs IPI: RR 0.85 (0.59, 1.22)	Moderate
	364	Only patients receiving first line therapy	Pembro (10mg/2W) vs IPI: HR 0.74 (0.56, 0.97)	High	Pembro (10mg/2W) vs IPI: HR 0.54 (0.42, 0.69)	High	N/A	N/A
	366		Pembro (10mg/3W) vs IPI: HR 0.72 (0.55, 0.95)	High	Pembro (10mg/3W) vs IPI: HR 0.54 (0.42, 0.69)	High	N/A	N/A
	290	Second line therapy	HR 0.75 (0.55, 1.03)	Low	N/A	N/A	N/A	N/A
	544	BRAF wild-type	HR 0.73 (0.58, 0.93)	Moderate	N/A	N/A	N/A	N/A
	290	BRAF mutated	HR (0.71 (0.48, 1.08)	Low	N/A	N/A	N/A	N/A

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
	167	BRAF mutated and BRAF/MEK inhibitor naïve (also normal LDH as per protocol)	HR 0.70 (0.44, 1.11)	Low	N/A	N/A	N/A	N/A
	147	BRAF mutated and received prior BRAF/MEK inhibitor therapy	HR 0.71 (0.46, 1.08)	Low	N/A	N/A	N/A	N/A
Vemurafenib vs. dacarbazine – overall survival up to 5 years (effect sizes <1 favour vemurafenib)								
BRIM-3	623	Overall	N/A	N/A	N/A	N/A	RR 1.75 (1.51, 2.03)	High
	514	Aged <65 years	RR 0.97 (0.91, 1.03)	High	N/A	N/A	N/A	N/A
	161	Aged ≥65 years	RR 0.92 (0.84, 1.01)	High	N/A	N/A	N/A	N/A
	459	ECOG PF 0	HR 0.86 (0.70–1.07)	Moderate	N/A	N/A	N/A	N/A
	216	ECOG PF 1	HR 0.68 (0.52-0.91)	High	N/A	N/A	N/A	N/A
	284	LDH ≤ULN	HR 0.88 (0.70–1.11)	Moderate	N/A	N/A	N/A	N/A
	391	LDH >ULN	HR 0.66 (0.52–0.85)	High	N/A	N/A	N/A	N/A
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – Overall survival up to 2 yea								
CHECKMATE 064	138	Overall	HR 0·57 (0·33–0·99)	Low	N/A	N/A	RR 1.26 (0.94, 1.70)	Very low

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
	82	Aged <65 years	HR 0.54 (0.29, 1.01)	Very low	N/A	N/A	N/A	N/A
	56	Aged ≥65 years	HR 0.40 (0.16, 0.97)	Low	N/A	N/A	N/A	N/A
	84	ECOG PF 0	HR 0.51 (0.25, 1.06)	Very low	N/A	N/A	N/A	N/A
	54	ECOG PF 1	HR 0.55 (0.27, 1.13)	Very low	N/A	N/A	N/A	N/A
	86	LDH ≤ULN	HR 0.71 (0.33, 1.53)	Very low	N/A	N/A	N/A	N/A
	52	LDH >ULN	HR 0.32 (0.16, 0.64)	Low	N/A	N/A	N/A	N/A
	117	LDH ≤ 2x ULN	HR 0.55 (0.31, 0.98)	Low	N/A	N/A	N/A	N/A
	21	LDH > 2x ULN	HR 0.31 (0.11, 0.90)	Low	N/A	N/A	N/A	N/A
Nivolumab only versus ipilimumab only – overall survival up to 5 years (effect sizes <1 favour nivolum								
CHECKMATE 067	380	Aged <65 years	HR 0.60 (0.47, 0.78)	High	HR 0.56 (0.44, 0.71)	High	N/A	N/A
	252	Aged ≥65 years	HR 0.69 (0.51, 0.93)	High	HR 0.49 (0.37, 0.66)	High	N/A	N/A
	461	ECOG PF 0	HR 0.61 (0.48, 0.78)	High	HR 0.51 (0.41, 0.63)	High	N/A	N/A
	170	ECOG PF 1+	HR 0.74 (0.52, 1.04)	Moderate	HR 0.63 (0.44, 0.89)	High	N/A	N/A
	391	LDH ≤ULN	HR 0.58 (0.44, 0.76)	High	HR 0.50 (0.39, 0.63)	High	N/A	N/A
	227	LDH >ULN	HR 0.71 (0.53, 0.96)	High	HR 0.50 (0.44, 0.80)	High	N/A	N/A
	67	LDH >2x ULN	HR 0.68 (0.41, 1.15)	Moderate	HR 0.57 (0.33, 1.00)	High	N/A	N/A

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
	433	BRAF WT	HR 0.64 (0.50, 0.81)	High	HR 0.46 (0.37, 0.58)	High	N/A	N/A
	198	BRAF mutated	HR 0.63 (0.44, 0.90)	High	HR 0.73 (0.53, 1.01)	Moderate	N/A	N/A
Pembrolizumab (10mg) vs. ICC – up to 2 years (effect sizes <1 favour pembro 2mg)								
KEYNOTE-002	370	Aged <65 years	N/A	N/A	HR 0.42 (0.30, 0.59)	Moderate	N/A	N/A
		Aged ≥65 years	N/A	N/A	HR 0.60 (0.41, 0.88)	Moderate	N/A	N/A
		ECOG PF 0	N/A	N/A	HR 0.50 (0.35, 0.70)	Moderate	N/A	N/A
		ECOG PF 1	N/A	N/A	HR 0.54 (0.38, 0.77)	Moderate	N/A	N/A
		LDH ≤ULN	N/A	N/A	HR 0.43 (0.31, 0.61)	Moderate	N/A	N/A
		LDH >ULN	N/A	N/A	HR 0.62 (0.43, 0.89)	Moderate	N/A	N/A
		BRAF WT	N/A	N/A	HR 0.53 (0.40, 0.69)	Moderate	N/A	N/A
		BRAF M	N/A	N/A	HR 0.44 (0.26, 0.74)	Moderate	N/A	N/A
Pembrolizumbab (2mg) vs. ICC – up to 2 years (effect sizes <1 favour pembro 2mg)								
KEYNOTE-002	370	Aged <65 years	N/A	N/A	HR 0.47 (0.34, 0.66)	Moderate	N/A	N/A
		Aged ≥65 years	N/A	N/A	HR 0.70 (0.48, 1.01)	Low	N/A	N/A
		ECOG PF 0	N/A	N/A	HR 0.55 (0.40, 0.76)	Moderate	N/A	N/A
		ECOG PF 1	N/A	N/A	HR 0.62 (0.43, 0.89)	Moderate	N/A	N/A
		LDH ≤ULN	N/A	N/A	HR 0.50 (0.36, 0.70)	Moderate	N/A	N/A
		LDH >ULN	N/A	N/A	HR 0.65 (0.46, 0.93)	Moderate	N/A	N/A
		BRAF WT	N/A	N/A	HR 0.51 (0.39, 0.67)	Moderate	N/A	N/A
		BRAF M	N/A	N/A	HR 0.74 (0.46, 1.18)	Low	N/A	N/A

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
Nivolumab vs. dacarbazine – Treatment-related events (in those who received at least one dose of stud								
CHECKMATE 066	411	Overall	N/A	N/A	N/A	N/A	RR 0.91 (0.59, 1.40)	Very low
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only – overall survival up to 5								
CHECKMATE 067	626	Overall	N/A	N/A	N/A	N/A	RR 2.20 (1.82, 2.66)	High
	367	Aged <65 years	HR 0.48 (0.37, 0.63)	High	HR 0.41 (0.31, 0.52)	High	N/A	N/A
	262	Aged ≥65 years	HR 0.59 (0.43, 0.81)	High	HR 0.44 (0.33, 0.59)	High	N/A	N/A
	454	ECOG PF 0	HR 0.50 (0.39, 0.64)	High	HR 0.41 (0.33, 0.51)	High	N/A	N/A
	174	ECOG PF 1	HR 0.59 (0.42, 0.85)	High	HR 0.47 (0.32, 0.67)	High	N/A	N/A
	393	LDH ≤ULN	HR 0.48 (0.37, 0.64)	High	HR 0.38 (0.30, 0.49)	High	N/A	N/A
	229	LDH >ULN	HR 0.58 (0.43, 0.79)	High	HR 0.46 (0.34, 0.62)	High	N/A	N/A
	67	LDH >2x ULN	HR 0.50 (0.29, 0.86)	High	HR 0.40 (0.23, 0.70)	High	N/A	N/A
	426	BRAF WT	HR 0.57 (0.45, 0.73)	High	HR 0.41 (0.33, 0.52)	High	N/A	N/A
	203	BRAF mutated	HR 0.44 (0.30, 0.64)	High	HR 0.44 (0.31, 0.62)	High	N/A	N/A
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – overall survival up to 5 y								
CHECKMATE 067	764	Overall	N/A	N/A	N/A	N/A	CHECKMATE 067 and 069 combined RR 2.55	High

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
							(2.04, 3.18)	
	383	Aged <65 years	HR 0.80 (0.60, 1.06)	Moderate	HR 0.73 (0.56, 0.94)	High	N/A	N/A
	247	Aged ≥65 years	HR 0.86 (0.62, 1.20)	Moderate	HR 0.89 (0.65, 1.23)	Moderate	N/A	N/A
	467	ECOG PF 0	HR 0.82 (0.63, 1.06)	Moderate	HR 0.80 (0.63, 1.01)	Moderate	N/A	N/A
	162	ECOG PF 1	HR 0.81 (0.55, 1.18)	Moderate	HR 0.74 (0.51, 1.10)	Moderate	N/A	N/A
	396	LDH ≤ULN	HR 0.83 (0.62, 1.12)	Moderate	HR 0.76 (0.59, 0.99)	High	N/A	N/A
	226	LDH >ULN	HR 0.82 (0.59, 1.13)	Moderate	HR 0.77 (0.56, 1.05)	Moderate	N/A	N/A
	74	LDH >2x ULN	HR 0.73 (0.43, 1.24)	Moderate	HR 0.70 (0.41, 1.17)	Moderate	N/A	N/A
	429	BRAF WT	HR 0.89 (0.69, 1.15)	Moderate	HR 0.89 (0.70, 1.13)	Moderate	N/A	N/A
	201	BRAF mutated	HR 0.70 (0.46, 1.05)	Moderate	HR 0.60 (0.43, 0.86)	High	N/A	N/A
Nivolumab + ipilimumab followed by ipilimumab only vs. ipilimumab only – overall survival up to 2 yea								
CHECKMATE 069	764	Overall	N/A	N/A	N/A	N/A	CHECKMATE 067 and 069 combined RR 2.55 (2.04, 3.18)	High
	68	Aged <65 years	HR 0.52 (0.24, 1.12)	Moderate	HR 0.29 (0.14, 0.60)	High	N/A	N/A
	74	Aged ≥65 years	HR 0.95 (0.45, 2.02)	Moderate	HR 0.43 (0.24, 0.79)	High	N/A	N/A
	116	ECOG PF 0	HR0.79 (0.42, 1.48)	Moderate	HR 0.34 (0.20, 0.56)	High	N/A	N/A

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
	24	ECOG PF 1	HR 0.56 (0.19, 1.67)	Moderate	HR 0.44 (0.15, 1.34)	Moderate	N/A	N/A
	106	LDH ≤ULN	HR 0.72 (0.37, 1.43)	Moderate	HR 0.35 (0.21, 0.60)	High	N/A	N/A
	35	LDH >ULN	HR 0.67 (0.28, 1.60)	Moderate	HR 0.42 (0.16, 1.05)	Moderate	N/A	N/A
	110	BRAF wild-type	0.60 (0.32, 1.11)	Moderate	HR 0.36 (0.21, 0.60)	High	N/A	N/A
	32	BRAF mutated	HR 1.35 (0.43, 4.26)	Moderate	HR 0.36 (0.14, 0.97)	High	N/A	N/A
Encorafenib plus Binimetinib versus vemurafenib – overall survival up to 5 years (effect sizes <1 favou								
COLUMBUS	378	Overall	N/A	N/A	N/A	N/A	RR 1.04 (0.90, 1.20)	High
	272	Aged <65 years	HR 0.65 (0.49, 0.88)	High	N/A	N/A	N/A	N/A
	111	Aged ≥65 years	HR 0.64 (0.41, 1.01)	Moderate	N/A	N/A	N/A	N/A
	279	ECOG PF 0	HR 0.66 (0.49, 0.89)	High	N/A	N/A	N/A	N/A
	104	ECOG PF 1	HR 0.57 (0.36, 0.89)	High	N/A	N/A	N/A	N/A
	276	LDH ≤ULN	HR 0.53 (0.38, 0.73)	High	N/A	N/A	N/A	N/A
	107	LDH >ULN	HR 0.93 (0.62, 1.39)	Moderate	N/A	N/A	N/A	N/A
Debrafenib + Trametinib versus dabrafenib alone – treatment-related adverse events up to 30 days afte								
COMBI-D	420	Overall	N/A	N/A	N/A	N/A	RR 1.06 (0.79, 1.41)	Low
Debrafenib + Trametinib versus Vemurafenib – treatment-related adverse events up to 30 days after las								

Study	Sample size	Analysis	Overall survival effect size	Quality	Progression free survival effect size	Quality	Grade 3-5 adverse events effect size	Quality
COMBI-V	699	Overall	N/A	N/A	N/A	N/A	RR 0.84 (0.73, 0.97)	Very low

1.1.7 Summary of NMA evidence

Table 8 summarises the results from the network meta-analysis (NMA) for overall survival and progression-free survival. Survival over time predicted by the NMA for each comparator is provided in Figure 1 and Figure 2**Error! Reference source not found.**. For further information see the NMA report for the full methods and results of the NMA, and Appendix G for full GRADE tables.

Table 8: Summary of the NMA results

No. of studies	Study design	Sample size	Effect size	Quality	Interpretation of effect
Overall survival					
10	RCT	4,603	See Figure 1: Overall survival (generalized gamma model on location and scale parameters)Figure 1	Moderate	Nivolumab & ipilimumab is most effective treatment
Progression-free survival					
10	RCT	4,603	See **Error! Reference source not found.**	Moderate	Nivolumab & ipilimumab is most effective treatment

Figure 1: Overall survival (generalized gamma model on location and scale parameters)

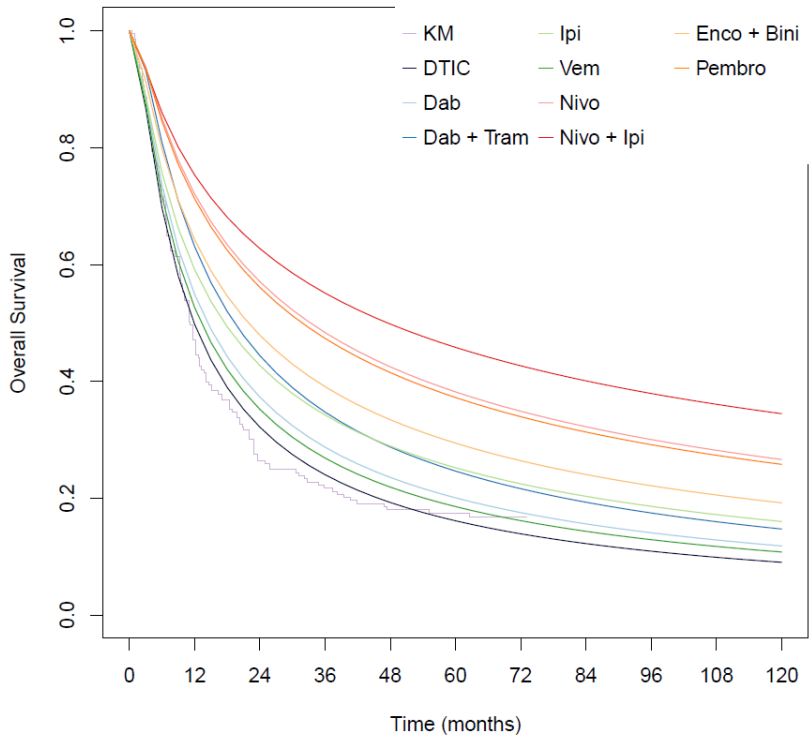
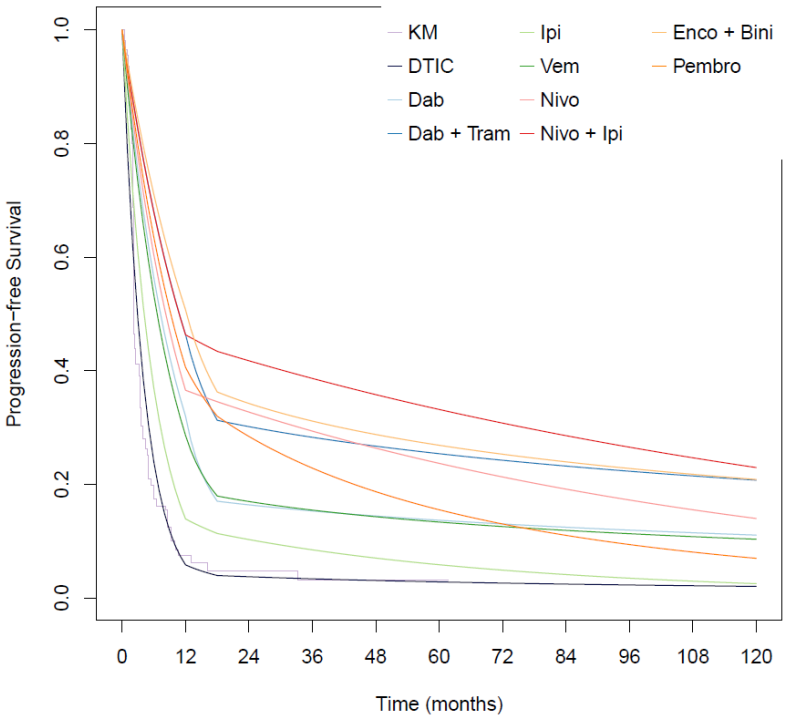


Figure 2: Progression-free survival (piecewise exponential model with 12 and 18-month cut points)



1.1.8 Economic evidence

1.1.8.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 7,545 studies. Based on title and abstract screening, 7,422 of the studies could confidently be excluded for this question, and a further 117 studies were excluded following the full-text review. Thus, the review for this question includes 6 studies from the existing literature.

1.1.8.2 Excluded studies

See Appendix K for a list of references for excluded studies, with reasons for exclusion.

1.1.9 Summary of included economic evidence

Table 4 Summary of included economic evidence

Study	Applicability	Limitations	Comparator	Incremental			Uncertainty[1]
				Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
Fleeman 2017 UK NHS perspective Talimogene laherparepvec People with previously untreated advanced melanoma	Directly applicable	Minor limitations	Ipilimumab	Modified Korn: -£24791 Two-step Korn: -£23,845	Modified Korn: 1.34 Two-step Korn: 0.35	Modified Korn: -£18,501 (Dominant) Two-step Korn: -£68,128 (Dominant)	A range of one-way deterministic sensitivity analyses were conducted which showed that the most influential parameters were the duration of treatment and the drug prices. The probabilistic sensitivity analysis showed that using the modified Korn method the probability of T-VEC being cost-effective compared with ipilimumab was 98.4% and 99.7%, at thresholds of £20,000 and £30,000 respectively. The probabilities of cost-effectiveness at these thresholds were 80.0% and 81.8%, respectively, for the two-step Korn method.
			Dacarbazine	NR	NR	Company[2]: £27,016 ERG[2]: £33,123	
			BSC	NR	NR	Company[2]: £27,242 ERG[2]: £34,394	
Houten 2020 UK NHS perspective Encorafenib plus binimetinib Patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma	Directly applicable	Minor limitations	Dabrafenib plus trametinib	NR – encorafenib plus binimetinib was cost saving	0.453	Dominant (i.e. encorafenib plus binimetinib cost less and was more effective than dabrafenib plus trametinib)	Probabilistic and deterministic sensitivity analyses were conducted. The base-case results were sensitive to the use of an estimated HR for time to treatment discontinuation and dose of Dab+tram. There were only two scenarios where Enco+bini was not dominant; discounted list price of dabrafenib and trametinib, and assuming equal safety and efficacy between Enco+bini and Dab+tram.

Study	Applicability	Limitations	Comparator	Incremental			Uncertainty[1]
				Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
Pike 2017 Norway Healthcare payer perspective Dacarbazine Patients with advanced malignant melanoma aged 18 or older	Partially applicable	Minor limitations	Fully incremental analysis: (1) dacarbazine, (2) trametinib, (3) dabrafenib, (4) vemurafenib, (5) ipilimumab, (6) ipilimumab plus dacarbazine, (7) nivolumab, (8) pembrolizumab, (9) nivolumab plus ipilimumab, (10) vemurafenib plus cobimetinib, (11) dabrafenib plus trametinib	(1) £1,612 (2) +£7,408 (3) +£404 (4) +£16 (5) +£125 (6) +£25 (7) +£1,050 (8) +£227 (9) +£4,228 (10) +£9,667 (11) +£107	(1) 0.88 (2) +0.28 (3) +0.07 (4) -0.04 (5) +0.17 (6) -0.08 (7) +0.42 (8) -0.02 (9) +0.01 (10) +0.08 (11) -0.06	(1) - (2) extended dominated (3) extended dominated (4) dominated (5) extended dominated (6) dominated (7) £11,010 [vs (1)] (8) dominated (9) dominated (10) £201,738 [vs (7)] (11) dominated	A probabilistic sensitivity analysis was conducted, in which all input parameters were randomly drawn from probability distributions and the model was run 10000 times. Scenario analyses were conducted for drug pricing, time horizon and HRQoL weights. An EVPI analysis indicated that the treatment efficacy data was the most influential source of uncertainty, followed by the HRQoL data, costs and SAE hazard ratios.
Quon 2019 Canada Canadian public healthcare system Nivolumab + ipilimumab	Partially applicable	Minor limitations	Fully incremental analysis: (1) Ipilimumab, (2) pembrolizumab 24 months,	(1) £88,970 (2) +£9,430 (3) +£68,836 (4) +£17,098 (5) +£29,682	(1) 1.81 (2) +0.66 (3) +1.01 (4) +0.57 (5) -1.58	(1) - (2) £14,287 (3) extended dominated (4) £54,389 (5) dominated	Multi-way and univariate sensitivity analyses, testing the effect of the high and low ranges of the model parameters were conducted to identify key model drivers. Key drivers included parameters associated with drug costs (e.g., treatment duration, patient weight, and drug wastage), parametric functions for

Study	Applicability	Limitations	Comparator	Incremental			Uncertainty[1]
				Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
Advanced melanoma			(3) nivolumab, (4) nivolumab + ipilimumab, (5) pembrolizumab treat until progression				projecting OS and PFS, relative treatment effect for pembrolizumab, time horizon, discounting, and inclusion of subsequent treatment costs. All scenarios yielded ICERs within the threshold of $CAN50,000–100,000 per QALY gained. The sensitivity analysis did not find that AEs influenced overall results. A probabilistic sensitivity analysis was conducted to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterized using probability distributions and analysed using Monte Carlo simulation (1000 iterations). Mean incremental QALYs and costs were in line with base-case results (vs. nivolumab: 0.558 QALYs, $CAN26,961; vs. ipilimumab: 2.021 QALYs, $CAN149,817; vs. pembrolizumab with a 24-month treatment cap: 1.498 QALYs, $CAN132,936), suggesting that deterministic results were robust in light of uncertainty in all parameters.
Tarhini 2018 US US third-party payer perspective 1L BRAF+MEK inhibitors followed by 2L anti-PD-1 Patients with treatment-naïve BRAF-mutant	Partially applicable	Potentially serious limitations	Fully incremental analysis[3 4]: (1) 1L BRAF + MEK inhibitors followed by 2L anti-PD-1, (2) 1L anti-PD-1 followed by 2L BRAF + MEK inhibitors	(1) £265,906 (2) +£192,326 (3) +£46,894	(1) 2.6 (2) +2.8 (3) +1.1	(1) - (2) extended dominated (3) £61,338	A probabilistic analysis was conducted to estimate the impact of parameter uncertainty on results. The analysis inputs were varied per the standard guidelines by the International Society for Pharmacoeconomics and Outcomes Research – Society for Medical Decision Making task force. Efficacy risk equations used a variance–covariance matrix. Cost inputs assumed gamma distribution, and standard error was assumed to be 20% of the mean. Quality-of-life inputs

Study	Applicability	Limitations	Comparator	Incremental			Uncertainty[1]
				Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
advanced melanoma			(3) 1L anti-PD-1 plus anti-CTLA-4 followed by 2L BRAF + MEK inhibitors				used beta distribution, and standard error was assumed to be 10% of the mean.
Tarhini 2018 US US third-party payer perspective 1L anti-CTLA-4 followed by 2L anti-PD-1 followed by 3L chemo/BSC Patients with advanced melanoma and wild-type BRAF tumours naive to systemic therapies	Partially applicable	Minor limitations	Fully incremental analysis[3 5]: (1) 1L anti-PD-1 followed by 2L anti-CTLA-4 followed by 3L chemotherapy or BSC, (2) 1L anti-CTLA-4 followed by 2L anti-PD-1 followed by 3L chemotherapy or BSC, (3) 1L anti-PD-1 plus anti-CTLA-4 followed by 2L chemotherapy followed by 3L chemotherapy or BSC, (4) 1L anti-PD-1 plus anti-CTLA-4 followed by 2L anti-PD-1 followed by 3L	(1) £245,437 (2) +£18,815 (3) +£4,742 (4) +£77,564	(1) 4.91 (2) -1.27 (3) +2.26 (4) -0.06	(1) - (2) dominated (3) £23,795 (4) dominated	Sensitivity analyses were conducted where inputs were varied as per the standard guidelines by the International Society for Pharmacoeconomics and Outcomes Research — Society for Medical Decision Making task force. The impact of each varied input on the model outcomes was presented as a tornado graph. Probabilistic analyses, based on 1000 Monte Carlo simulations, were presented as cost–effectiveness acceptability curves to capture the impact of uncertainty around the input parameters on the probability of individual sequences being the most cost-effective strategy under various willingness-to-pay thresholds.

Study	Applicability	Limitations	Comparator	Incremental			Uncertainty[1]
				Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
			chemotherapy or BSC				
NICE 2021 UK NHS perspective NICE approved immunotherapies and BRAF/MEK inhibitors People with advanced melanoma	Directly applicable	Minor limitations	Fully incremental analysis: (1) nivolumab, (2) pembrolizumab, (3) ipilimumab + nivolumab, (4) encorafenib + binimetinib, (5) dabrafenib + trametinib	(1) £179,323 (3) £183,360 (2) £187,466 (5) £244,872 (4) £259,792 *absolute costs	(1) 4.320 (3) 5.104 (2) 4.152 (5) 3.091 (4) 3.431 *absolute QALYs	(1) – (3) £5,148 (2) dominated (5) dominated (4) dominated	Probabilistic sensitivity analysis and scenario analyses were conducted to examine uncertainty. The results of the probabilistic analysis indicated that the combination of nivolumab and ipilimumab remained most cost-effective, followed by pembrolizumab rather than nivolumab as the next most cost-effective. In scenario analysis the only parameters that made a substantial difference to the results were those around the data used for second line treatment distribution and time on treatment.

1 Costs were adjusted for purchase price parities and inflated to 2021 British Pounds Sterling using Eppi-Centre Cost Converter. https://eppi.ioe.ac.uk/costconversion/default.aspx
2 The study was based on a NICE Technical Appraisal, and results of both the manufacturer submission and the ERG report were presented.
3 In both Tarhini studies anti-PD-1 agents were represented by nivolumab and pembrolizumab assuming an equal share, and anti-CTLA-4 plus anti-PD-1 were represented by nivolumab plus ipilimumab.
4 BRAF plus MEK inhibitors were represented by dabrafenib plus trametinib.
5 Anti-CTLA-4 agents were represented by ipilimumab, and chemotherapy was represented by a mix of dacarbazine, temozolomide, paclitaxel, and carboplatin plus paclitaxel.

1.1.10 Economic model

A de novo economic model was conducted for this review question.

The economic model is a cost-utility analysis comparing five first-line systemic and targeted treatments for advanced melanoma; nivolumab, pembrolizumab, ipilimumab in combination with nivolumab, encorafenib in combination with binimetinib, and dabrafenib in combination with trametinib. The results of a network meta-analysis were used to inform the survival analysis and clinical inputs in the model.

Ipilimumab, dabrafenib and vemurafenib were also listed in the scope of this analysis, however these strategies were not considered in the economic model as although they have NICE technology appraisals the committee noted that they are not used as first line therapies in current practice as there are more recently approved drugs available, and this is supported by evidence in the SACT database.

In the base-case analysis using list prices for the therapies, it was found that nivolumab in combination with ipilimumab was the most cost-effective of the strategies considered, with an ICER of £5,148 compared with nivolumab monotherapy. The incremental results are presented in Table 9. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each treatment.

The committee was presented with the results of the base case and scenario analyses when the confidential PAS discounts were applied and used these results as the basis for their recommendations. These results cannot be presented here due to their commercially sensitive nature. When these discounts are applied, ipilimumab in combination with nivolumab is still the most cost-effective therapy with an ICER below £20,000, followed by pembrolizumab as the next most cost-effective and nivolumab being extendedly dominated. Additionally when the confidential PAS discounts are applied, encorafenib in combination with binimetinib is dominant over dabrafenib in combination with trametinib.

Table 9: Economic model results (list price analysis)

Strategy	Absolute costs	Absolute QALYs	Incremental costs	Incremental QALYs	ICER
Nivo	£179,323	4.320			
Nivo+ipi	£183,360	5.104	£4,038	0.784	£5,148
Pembro	£187,466	4.152	£4,106*	-0.952*	dominated
Dab+tram	£244,872	3.091	£61,512*	-2.013*	dominated
Enco+bini	£259,792	3.431	£76,432*	-1.673*	dominated

**Incremental costs and QALYs compared with nivo+ipi, excluding the dominated studies.*

Full details of the economic model are presented in the economic model report for review F.

1.1.11 Unit costs

The costs of the drugs included in recommendations for this review question are given below. It should be noted that these are the list prices of the drugs and that confidential patient access schemes are available for all therapies listed below, with the exception of dacarbazine.

Resource	Unit costs	Source
Nivolumab (1x240mg)	£2,633.00	British National Formulary
Pembrolizumab (1x100mg)	£2,630.00	British National Formulary
Ipilimumab (1x50mg)	£3,750.00	British National Formulary

Resource	Unit costs	Source
Nivolumab [with ipi] (1x40mg)	£439.00	British National Formulary
Encorafenib (28x50mg)	£622.22	British National Formulary
Binimetinib (84x15mg)	£2,240.00	British National Formulary
Dabrafenib (28x50mg)	£933.33	British National Formulary
Trametinib (7x2mg)	£1,120.00	British National Formulary
Dacarbazine (1x1000mg)	£70.00	British National Formulary
Talimogene laherparepvec (1x1ml)	£1,670.00	British National Formulary

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1 The outcomes that matter most

The committee advised that in the treatment of localised and advanced disease, mortality, recurrence, and disease progression are all important outcomes.

Adverse events relating to the immunotherapies and targeted therapies are reported in a number of different ways. The committee agreed that serious adverse events and treatment-related adverse events are both important markers of toxicity in the context of treating unresectable III and IV disease. Serious adverse events relate to the any adverse events of grade 3 or greater toxicity, typically only including events occurring whilst the person is on treatment or during a short period after treatment. Treatment-related adverse events include all adverse events determined by the treating physician or investigator to be resulting from the treatment received and is also an important measure of drug safety. Definitions of adverse events were mostly homogenous between studies.

Localised treatments are typically given in advanced disease, when a person cannot tolerate immunotherapies. Adverse events are therefore particularly important in the context of localised therapies, particularly limb toxicity for isolated limb infusion (ILI) and isolated limb perfusion (ILP). Additionally, there is a need to identify characteristics of this population which make someone more likely to benefit from one option over another.

1.1.12.2 The quality of the evidence

Localised treatments

There is very limited good quality evidence for the efficacy of localised therapies. Three RCTs were identified (OPTiM trial, Chesney 2018 and Hughes 2016). The OPTiM trial compared T-VEC to GM-CSF in people with stage IIIB-IVM1c melanoma. Chesney (2018) compared TVEC + ipilimumab to ipilimumab alone. Hughes (2016) compared percutaneous hepatic perfusion to best available care. These trials were of moderate to high quality but only partially applicable to the present review question as the comparators were not listed in the protocol due to not being relevant in clinical practice (see methods and processes section in 1.1.3 for more information).

Numerous case series were also included in the review. These studies were primarily single arm trials assessing complete response rates, progressive disease, mortality and toxicity. As these studies were primarily single armed trails it is unclear which localised treatment would be preferable in populations where two or more options are being considered. Additionally, most studies were retrospective and included a diverse cohort of people treated with localised therapies.

Studies assessing predictors of disease progression, mortality and toxicity also suffered from methodological issues. In particular, the studies typically presented uncontrolled analyses (or univariate analyses) making it difficult to account for the presence of multiple risk factors and

complex disease characteristics typically present in people who undergo localised treatments.

Additionally, there were discrepancies between studies regarding which characteristics are prognostic making it difficult to identify with certainty which groups of people would benefit more from localised treatments.

Immunotherapies and targeted therapies

All studies included in this review were RCTs and were generally at low risk of bias. Some studies suffered from risk of bias due to being open label and, as a result, participants and investigators could modify their behaviour based on the knowledge of the drug they are receiving, which is particularly problematic in intention-to-treat analyses.

Some studies suffered from bias due to deviations from intended interventions; either from a disparity between arms in subsequent treatments received, or participants in one arm switching over to the other arm. This was particularly present in the CHECKMATE-037 trial in which a high proportion of the control arm dropped out as soon as the random assignment occurred (23% compared to 1% in the experimental arm) or went on to receive subsequent therapy after randomized treatment (41% in control arms compared to 11% in experimental arm). This was attempted to be corrected for in sensitivity analyses in which participants were censored at the time of starting subsequent therapy. Although some cross-over is indicative of what would happen in the real world, it is particularly a problem in unblinded studies, in which it is likely that participants will crossover due to knowledge that they are not receiving an experimental drug.

The NMAs conducted for overall and progression-free survival were both assessed as being of moderate quality. Significant evidence from the NMA supported the use of nivolumab and ipilimumab as the most effective treatment with respect to both outcomes. For overall survival, it had an average ranking of 1.04 with a 96% probability of being the best treatment, and for progression-free survival, the average ranking was 1.63 with a 64% probability of being the best treatment. Results from the NMA were downgraded due to precision around estimates for the remaining treatments in analyses of both overall survival and progression-free survival. For the two targeted therapy strategies, encorafenib + binimetinib and dabrafenib + trametinib, there was uncertainty in the evidence, with overlapping 95% credible intervals around the estimates of effect that was observed in both progression-free and overall survival. The evidence also did not identify any meaningful differences between nivolumab and pembrolizumab for overall survival. Additionally, the analysis of progression-free survival found no significant differences between treatment after 12 months. The committee also noted that survival extrapolated beyond the trial periods was less plausible for targeted therapies, and used external data sources to make adjustments to survival on the basis of their clinical experience and knowledge of these treatment strategies. Although there was some evidence of inconsistency in a part of the network, this was not associated with the treatments recommended in this guideline.

1.1.12.3 Benefits and harms

T-VEC

The committee agreed that the evidence and their clinical experience indicates that T-VEC can be very effective for unresectable disease and has a good side effect profile. The OPTiM trial demonstrated improved overall survival compared to granulocyte macrophage colony-stimulating factor (GMCSF) in most subgroups of participants, including those receiving first-line treatment and those with head and neck melanomas. Chesney (2018) could not differentiate any of the outcomes assessed between those people given T-VEC with ipilimumab and those given ipilimumab alone.

However, there are a limited number of centres which offer this treatment and there is a need for referring physicians to be skilled in evaluating who is suitable for T-VEC treatment. Additionally, there are various factors which preclude treatment with T-VEC, such as the person having metastases located on the head, neck or trunk, inadequate vascular supply and when general or regional anaesthesia is unsuitable.

The committee agreed that for people with unresectable, regionally, or distantly metastatic immunotherapies and targeted therapies should be considered first as these are generally considered to be more effective. However, in cases where these treatments are not considered the best option, T-VEC should be considered. The committee made a recommendation to reflect these points.

ILI and ILP

The committee agreed that both ILI and ILP are important for the treatment of people with stage IIIB-IV limb metastases, for both palliative treatment and residual disease control. These treatments have the benefit of being able to be used sequentially and at different stage of disease. However, there is national variability in patient access to these treatment options.

Due to the lack of randomised control trial evidence comparing these options directly, it is difficult to determine exactly when each treatment should be used. The committee agreed that prognostic evidence, assessing which clinical factors affect outcomes following treatment with ILI or ILP is inconclusive and suffers from methodological flaws, namely the diverse treatment populations which are hard to account for in analysis. As such, the committee agreed that treatment with ILI or ILP needs to be individualised and involving a discussion with the specialist skin cancer multidisciplinary team (SSMDT).

The committee agreed that for people with recurrent or unresectable in-transit metastases, ILI and ILP should be considered as treatment options. However, they also noted the need for this to be considered on a case-by-case basis taking into account disease complexities. Both procedures also involve the use of a general anaesthetic. They also noted the lack of awareness of centres offering this treatment regionally and included a link to a list of centres offering ILI or ILP treatment.

ECT

There was no good quality evidence for the efficacy of ECT in the treatment of melanoma. However, the committee agreed that this remains a viable option in the treatment of (recurrent or unresectable) in-transit metastases. Like T-VEC, ECT can be used to treat melanomas across the whole body and therefore does not suffer from the limitations of ILI and ILP which can only be used to treat melanomas on the limbs. ECT is used in current practice and also has the benefit of being available at more centres than T-VEC, which has limited availability.

Immunotherapies and targeted therapies

The committee agreed with the results of the NMA and used this to inform decisions surrounding the efficacy of the different treatments available for unresectable stage III/ stage IV melanoma (see section below on cost-effectiveness and resource use). The committee agreed that evidence from the NMA suggests that in general, immunotherapies are more effective than targeted therapies. Additionally, they agreed that evidence from the NMA suggests that the combination of nivolumab and ipilimumab is the most clinically effective option for treating melanoma, and health economic modelling identified this combination as being the most cost-effective option. Additionally, the modelling showed that, in general, immunotherapies are more cost-effective than targeted therapies.

Within the class of anti-PD1 therapies, efficacy was comparable, but pembrolizumab showed greater cost effectiveness than nivolumab. Efficacy was comparable within the class of BRAF inhibitor combined with MEK inhibitors; since the committee noted that there was less precision around these estimates and greater uncertainty in the cost-effectiveness evidence, they recommended the use of either encorafenib with binimetinib or dabrafenib with trametinib for those who were unsuitable for treatment with immunotherapy.

Single agent ipilimumab is a NICE approved (NICE TA268 and 319) option for both untreated and previously treated melanoma, however it is no longer used as a first-line option due to other options such as nivolumab and pembrolizumab being more cost-effective. People unsuitable for nivolumab or pembrolizumab would also be unsuitable for ipilimumab due to the toxicity associated with this option.

The committee agreed that despite differences in cost-effectiveness and preferences in which options should be tried first, nivolumab with ipilimumab, pembrolizumab, nivolumab, encorafenib with binimetinib, trametinib with dabrafenib, dabrafenib, ipilimumab for untreated advanced melanoma and for previously treated advanced melanoma, and vemurafenib all have a place in the treatment of stage IV and unresectable stage III melanoma.

However, they also noted that immunotherapies have a greater risk of toxicity than targeted therapies. Evidence suggests that ipilimumab is particularly associated with cytotoxicity. Additionally, they noted that toxicity is greatest when using multi-agent immunotherapies. As a result, the use of a combination of nivolumab and ipilimumab may be deemed unsuitable for some people due to toxicity risk. The committee therefore agreed that although this combination of treatment should be offered as the first choice for people with untreated stage IV or unresectable stage III disease, pembrolizumab or nivolumab monotherapy should be considered if a combination of nivolumab and ipilimumab is considered unsuitable.

The committee agreed that these recommendations apply to all people with melanoma but made some key exceptions and additional recommendations based on the person's BRAF status. For people with BRAF-mutated disease, economic modelling suggests that if the above options are contraindicated or there is insufficient time for an immune response due to high disease burden and/or rapid progression, encorafenib with binimetinib or dabrafenib with trametinib are the most suitable options. The committee made recommendations to offer these combination of treatments in these circumstances.

There are limited options for people with untreated BRAF wild type stage IV or unresectable stage III melanoma when the main options (nivolumab in combination with ipilimumab, pembrolizumab and nivolumab monotherapy) are contraindicated. The committee agreed that in these circumstances the person should be encouraged to enrol in a clinical trial assessing a new treatment option, or to consider chemotherapy treatment or best supportive care.

1.1.12.4 Cost effectiveness and resource use

The committee considered the cost-effectiveness evidence found in the literature for systemic treatments and felt that, although some studies were directly applicable, the key piece of evidence for making recommendations on this type of treatment would be the *de novo* economic model, since this analysis was conducted specifically to answer the question in the review and contained direct comparisons between all interventions of interest in the decision problem. The studies that were directly applicable did not include all relevant comparators so could not be used to answer the review question. The key difference between the *de novo* model and the existing economic analyses is that all of the relevant comparators for the UK NHS setting are compared in an incremental analysis, and the NMA utilised as much of the relevant clinical trial data as possible.

All modelling decisions, assumptions and inputs used in the model were presented to the committee and informed by their expertise. The majority of the inputs in the models were taken from previous technology appraisals, the relevant clinical trials or large nationally representative databases of cancer patients (e.g. SACT), which the committee considered appropriate to use. The committee agreed that using a partitioned survival model informed by an NMA would be an appropriate use of the data available, and was in line with existing analyses and technology appraisals. The recommendation making was supported by the committee's clinical expertise and experience of the circumstances where different treatments may be required. The committee felt that the ranking of treatments by cost-effectiveness in the model base-case and scenario analyses was appropriate to use to inform the strength of recommendations for each of the systemic immuno- and targeted therapies that are approved by NICE.

The committee was presented the results from a number of NMAs that estimated relative treatment effects for each treatment strategies in the decision problem. The NMA used in the base case analysis included both immunotherapy and targeted therapy strategies, and combined both *BRAF* wild type and *BRAF* mutant populations. The committee noted that *BRAF* status is not expected to be an effect modifier for treatment efficacy of immunotherapies so the effectiveness of these treatments was considered to be consistent across the mixed *BRAF* population. We also explored alternative networks that considered only immunotherapies, or only people with *BRAF* wild type melanoma, although it was not possible to conduct an analysis of a *BRAF* mutant population only because there was not sufficient data to provide a connected network of evidence. Given that the trials did not follow all of the cohort for their remaining lifetime, it was necessary to make assumptions about the long-term survival rate and extrapolate the evidence beyond the trial period. The best fitting curves and extrapolations from the NMA were selected by using a combination of model fit statistics and visual inspection, with the committee providing clinical insight on what the PFS and OS over time are expected to look like. In the majority of trials in the network, the proportional hazard assumption was not met, and therefore we explored more complex models that captured the change in hazard over time. These included the piecewise exponential model with a number of different cut points at different time points, a fractional polynomial model and two forms of the generalised gamma model (one with one treatment effect and the other with two treatment effects). The best fitting PFS model was the 2-cut point piecewise exponential model with cut points at 12 & 18 months, and the best fitting OS model was generalized gamma model with two treatment effects.

Results from the NMA showed that nivolumab + ipilimumab was the best treatment consistently within each network that we explored, for improving both progression-free survival and overall survival in people with advanced melanoma. Notably, this result held for people with *BRAF* mutant as well as *BRAF* wild type melanoma. The other two immunotherapies in the analysis, pembrolizumab and nivolumab, showed very similar outcomes to each other, being ranked just below nivolumab + ipilimumab for the majority of networks. Targeted treatment dual strategies, dabrafenib + trametinib and encorafenib + binimetinib, were less effective than nivolumab + ipilimumab and the immunotherapies for progression-free survival and overall survival. However, uncertainty around the data meant that differences between these two options were not significant.

Evaluating the changing event hazard over time of treatment strategies each with different modes of action and corresponding response patterns led to challenges in selecting a single NMA model that was a good fit to every single treatment in the network. That is to say, certain models may have provided plausible extrapolations for one treatment, but implausible extrapolations for another. Therefore, in selecting the best model, the committee had to evaluate which model had the best fit overall, rather than selecting a model for fitting a specific treatment best. This was further compounded by small numbers of patients and events in the latter period of some of the trials, which had implications for the extrapolation of survival. As such, based on their clinical experience the committee noted that the long-term

survival projections could lack plausibility and determined that adjustments to the curves were necessary. The curves for encorafenib+binimetinib and dabrafenib+trametinib were adjusted by gradually changing the per-cycle hazard to that of ipilimumab, which the committee believed was most representative of what patients would receive upon discontinuation. We also adjusted the survival curves with general population mortality, which was applied from 10 years onwards because the committee considered that patients that survive for 10 years are generally considered to be cured and are unlikely to die from melanoma.

The principal finding of the *de novo* model was that ipilimumab in combination with nivolumab is the most cost-effective strategy for first line treatment of advanced melanoma when compared with the other licensed immunotherapies and *BRAF*/MEK inhibitors. Both combination *BRAF*/MEK inhibitor strategies were more costly and less effective than the immunotherapies in the base-case, all scenario analyses and the probabilistic analysis. The most influential assumptions tested in scenario analyses were around the distribution of therapies used as second line treatment and the duration of treatment; however, the committee agreed that the alternative sources of this data were not as applicable to current practice as the data selected for the base-case. The committee agreed that the uncertainty had been explored and were confident in making the recommendations based on the model results.

Although *BRAF*/MEK inhibitors are not as cost-effective as the immunotherapies in the overall melanoma population, there are factors that we were not able to include in the economic model that mean that patients may prefer to receive treatment with them, for example where the clinician has judged the patient to be at risk of rapid progression, or there is a preference due to concerns around side effects of immunotherapies. Therefore, the committee felt that it was appropriate to recommend the use of targeted therapy in people who were not suitable for immunotherapy. Although the results of the economic analysis suggested that there were some differences in costs and QALYs between the two targeted treatment strategies, they considered that these results were less certain than those for the immunotherapies. Firstly, this is because we cannot estimate duration of treatment (a very important parameter) in the same robust way as we did for the immunotherapies because we do not have the SACT data, we only have median months on treatment, which we have had to convert to mean months by making a few assumptions about how this input is distributed. This means we are less sure that there is a difference in treatment duration (and therefore costs) between the two strategies. Secondly, because the results of the NMA show overlapping credible intervals around the estimate of effect for each of these options, we are less sure that there is a difference in effectiveness between the two strategies. Therefore, the committee decided that should a person wish to receive treatment with targeted therapy, each of the two strategies are equally valid options.

The economic model did not include the localised treatment talimogene laherparepvec since it is NICE approved for a slightly different population (for example, talimogene laherparepvec is only recommended in people for whom immunotherapies are not considered the best option by a multidisciplinary team) and there was sufficient economic evidence in the Fleeman 2017 study based on the NICE technology appraisal to inform a recommendation. Fleeman et al. found that talimogene laherparepvec was cost-effective against ipilimumab but not against dacarbazine, however the committee noted that dacarbazine is much less commonly used in current practice, so the comparison is not as useful for decision making. The committee recommended that talimogene laherparepvec be considered for treating unresectable, regional/distant nodal or skin subcutaneous metastases in line with the NICE TA recommendation and felt that this approach to treatment would be an effective use of NHS resources based on the evidence presented. This recommendation is not expected to impact practice as talimogene laherparepvec is already used and is available on the NHS.

1.1.12.5 Other factors the committee took into account

The committee agreed that the management of in-transit disease is very specialised and consideration on a case-by-case basis. As a result, when treatment in this area is being considered, it should always involve discussion with the specialised skin multidisciplinary team and should be performed in regional specialised centres. The committee made a recommendation to reflect this.

The committee also agreed that due to the limited good quality evidence available for localised therapies (see section 1.1.11.2 on the quality of the evidence) it would be useful to include a table within the recommendations providing information on when the different localised therapies can be considered.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1 to 1.7.4 and 1.8.6 to 1.8.11, and the research recommendation on localised therapies.

1.1.14 References – included studies

1.1.14.1 Clinical evidence

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1.1.14.2 Economic

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Larkin J, Chiarion-Sileni V, Gonzalez R et al. (2019) Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 381:1535-46.

Pike E, Hamidi V, Saeterdal I et al. (2017) Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting. BMJ Open. 7(8):e014880.

Quon P, Xiao Y, Sorensen S et al. (2019) Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada. PharmacoEcon Open 3:321–331.

Tarhini A, McDermott D, Ambavane A et al. (2018) Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma. Immunotherapy 11(4), 283–295.

1 Tarhini A, Benedict A, McDermott D et al. (2018) Sequential treatment approaches in the
2 management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis.
3 Immunotherapy 10(14), 1241–1252.

Appendices

Appendix A – Review protocols

Review protocol for systemic and localised anticancer treatment in advanced melanoma

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Systemic and localised anticancer treatment for advanced melanoma
2.	Review question	RQ 5.1 What is the most effective systemic and localised anticancer treatment for people with stage 4 (+ unresectable stage 3) melanoma?
3.	Objective	To sequence the systemic and localised anticancer treatments with existing NICE technology appraisals for people with stage 4 (+ unresectable stage 3) melanoma.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		Searches will be restricted by: • None The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	• Stage 4 melanoma • Unresectable stage 3 melanoma
6.	Population	People with a diagnosis of stage 4 (or unresectable stage 3) melanoma
7.	Intervention/Test	Immunotherapies: • Nivolumab • Nivolumab + ipilimumab • Ipilimumab • Pembrolizumab

		Targeted therapy for BRAF-positive melanoma: • Encorafenib + binimetinib • Trametinib with dabrafenib • Dabrafenib • Vemurafenib Localised treatments for people with locoregional disease: • isolated limb infusion • isolated limb perfusion • electrochemotherapy • Talimogene laherparepvec
8.	Comparator/Reference standard	Immunotherapies and targeted therapies: • Any Localised treatments for people with locoregional disease: • Interventions compared to each other

9.	Types of study to be included	For systemic and localised anticancer treatments for stage 4 melanoma (and unresectable stage 3): • RCTs For localised treatments for locoregional disease: • RCTs if available • Prospective cohort studies which have adjusted for baseline differences
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2015). This guideline covers adults and children with melanoma. Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need to update this question in response to new treatment options now being available. In addition, there is a need to attempt to sequence the different options available to identify the most effective options for first- and second-line therapy

12.	Primary outcomes (critical outcomes)	• Rate of mortality and time to death • All-cause and melanoma specific mortality; at 1, 2 and 5 years • Progression free survival; at 1, 2 and 5 years • Health related quality of life • Serious adverse events • Time on treatment • Time to second treatment
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline

		characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane risk of bias tool (version 2) for RCTs and the ROBINS-I checklist for cohort studies, as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted,

		random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. Meta-analyses will be performed in Cochrane Review Manager V5.3. Where sufficient data is available, a network meta-analysis will be conducted. Analysis will be performed in R. The PFS and OS curves of different systemic anticancer treatments will come from the clinical reviews for RQ 5.1 and evidence used in past TAs. Kaplan-Meier curves for PFS and OS will be extracted from the evidence and digitized using the engauage digitizer software (also can be done in R). Next, individual patient level data will be reconstructed either within STATA using the 'ipdfc' command or within R using available code. This data will then be synthesized in a network-meta analysis (NMA), using one of five methods: standard parametric models, restricted mean survival time (RMST), piecewise exponential models, fractional polynomials, or flexible parametric models. Standard parametric models use a survival function consisting of a scale and shape parameter to describe the datasets created from the digitized KM curves. The differences between these parameters are then synthesized and indirectly compared across trials. This approach has been used in prior melanoma research (Dequen et al. 2012) and is further described in additional papers (Jansen 2011 and Ouwens et al. 2010). RMST uses the difference in the restricted mean survival time to obtain an estimate of the survival function. This method was utilized in the Lung Cancer N2

		model. In this method, the area under the KM curve is calculated up until time T, 'and the treatment effect estimated as the difference in AUCs between treatments'. Piecewise exponential models are limited in that they assume a constant hazard in the final interval. Fractional polynomial models are dependent on the choice of powers. Flexible parametric models are limited in that they are restricted to being linear beyond the boundary knots. All methods do not rely on the proportional hazards assumption, which is important as this assumption is unlikely to be met with the available data. We will liaise with the TSU in determining which method is the most suitable way to conduct our NMA.
17.	Analysis of sub-groups	**Subgroups (to be investigated irrespective of presence of statistical heterogeneity):** • Pregnant women. • People with a compromised immune system. • Location of metastases • Desmoplastic melanoma • Oligometastatic disease • Age (including children and young people, and elderly) • Tumour mutation status • Number and type of previous treatments • Number of type of subsequent treatments • Performance status • AJCC stage 4 subgroup (presence of brain metastases)
18.	Type and method of review	☒Intervention

19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	TBC
22.	Anticipated completion date	TBC
23.	Stage of review at time of this submission	Review stage
		Preliminary searches
		Piloting of the study selection process
		Formal screening of search results against eligibility criteria
		Data extraction
		Risk of bias (quality) assessment
		Data analysis
24.	Named contact	a. Named contact Guideline updates team b Named contact e-mail skincancer@nice.nhs.uk

		c Organisational affiliation of the review **National Institute for Health and Care Excellence (NICE)**
25.	Review team members	From the Guideline Updates Team • Caroline Mulvihill • Thomas Jarratt • Brett Doble • Steph Armstrong • Jeremy Dietz • Jenny Craven
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10155
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	• Localised • Systemic • Melanoma • Skin cancer

		• Skin tumour
33.	Details of existing review of same topic by same authors	Update of question 2.5 in NICE Guideline NG14 Melanoma: assessment and management
34.	Current review status	☒Completed
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
36.	Details of final publication	www.nice.org.uk

1

Appendix B – Literature search strategies

Searches were run on the 2nd December 2020 and updated on 13th July 2021 in Medline, Medline in Process, Medline epub, the Cochrane Database of Systematic Reviews (CRD/CENTRAL) and DARE (Wiley platform). These searches are presented below.

Database: Ovid MEDLINE(R) <1946 to December 02, 2020>

1 exp Melanoma/ (96197)
2 Skin Neoplasms/ (122179)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (104932)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (62202)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (25240)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (69)
7 dubreuilh*.tw. (74)
8 (maligna* adj2 lentigo*).tw. (1077)
9 LMM.tw. (896)
10 or/1-9 (253749)
11 nivolumab/ (2740)
12 (nivolumab* or 31yo63lbsn or bms 936558 or mdx 1106 or ono 4538 or opdivo*).tw. (2935)
13 ipilimumab/ (1985)
14 (ipilimumab* or 6t8c155666 or anti ctla 4 mab* or "mdx 010" or mdx ctla 4 or yervoy*).tw. (2292)
15 Vemurafenib/ (1357)
16 (vemurafenib* or zelboraf* or rg-7204 or plx 4032 or r05185426 or 207smy3fqt).tw. (1556)
17 (pembrolizumab* or keytruda* or mk 3475 or sch 900475 or lambrolizumab*).tw. (2153)
18 or/11-17 (8153)
19 (encorafenib* or braftovi* or lgx 818 or nvp lgx 818).tw. (67)
20 (binimetinib* or mektovi* or arry 162 or arry 438162 or balimek or mek 162).tw. (99)
21 (trametinib* or mekinist* or gsk 1120212* or jtp 74057).tw. (785)
22 (dabrafenib* or tafinlar* or gsk 2118436*).tw. (720)
23 or/19-22 (1187)
24 ((regional or locoregional or "isolated limb*") adj2 (chemotherap* or infusion* or perfusion*)).tw. (5567)
25 (ili or ilp).tw. (2716)
26 Electrochemotherapy/ (656)
27 (electrochemotherap* or electroporation*).tw. (9601)
28 tvec.tw. (22)
29 "Talimogene laherparepvec*".tw. (129)
30 Imlygic*.tw. (18)
31 (diphencyprone* or diphenylcyclopropenone* or DPCP).tw. (315)
32 or/24-31 (18053)
33 18 or 23 (8910)
34 10 and 33 (4411)
35 10 and 32 (1436)
36 animals/ not humans/ (4728824)
37 34 not 36 (4367)
38 35 not 36 (1283)
39 limit 37 to english language (4163)
40 limit 38 to english language (1182)
41 limit 39 to (letter or historical article or comment or editorial or news or case reports) (1534)

Database: Ovid MEDLINE(R) <1946 to December 02, 2020>	
42	limit 40 to (letter or historical article or comment or editorial or news or case reports) (180)
43	39 not 41 (2629)
44	40 not 42 (1002)
45	randomized controlled trial.pt. (518015)
46	randomi?ed.mp. (814966)
47	placebo.mp. (198182)
48	or/45-47 (867208)
49	Observational Studies as Topic/ (5662)
50	Observational Study/ (88863)
51	Epidemiologic Studies/ (8484)
52	exp Case-Control Studies/ (1123667)
53	exp Cohort Studies/ (2061901)
54	Cross-Sectional Studies/ (345417)
55	Controlled Before-After Studies/ (573)
56	Historically Controlled Study/ (192)
57	Interrupted Time Series Analysis/ (1050)
58	Comparative Study.pt. (1876925)
59	case control$.tw. (114689)
60	case series.tw. (61390)
61	(cohort adj (study or studies)).tw. (179159)
62	cohort analy$.tw. (7049)
63	(follow up adj (study or studies)).tw. (45782)
64	(observational adj (study or studies)).tw. (90368)
65	longitudinal.tw. (210803)
66	prospective.tw. (507642)
67	retrospective.tw. (459022)
68	cross sectional.tw. (296503)
69	or/49-68 (4450196)
70	43 and 48 (379)
71	44 and 69 (293)
72	limit 70 to ed=20130101-20201202 (330)
73	limit 71 to ed=20130101-20201202 (119)

1

Database: MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 02, 2020>	
1	exp Melanoma/ (0)
2	Skin Neoplasms/ (0)
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (12400)
4	((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (6833)
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (3198)
6	(hutchinson* adj2 (freckle* or melano*)).tw. (1)
7	dubreuilh*.tw. (0)
8	(maligna* adj2 lentigo*).tw. (79)
9	LMM.tw. (181)
10	or/1-9 (20279)
11	nivolumab/ (0)

Database: MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 02, 2020>

12 (nivolumab* or 31yo63lbsn or bms 936558 or mdx 1106 or ono 4538 or opdivo*).tw. (1574)
13 ipilimumab/ (0)
14 (ipilimumab* or 6t8c155666 or anti ctla 4 mab* or "mdx 010" or mdx ctla 4 or yervoy*).tw. (818)
15 Vemurafenib/ (0)
16 (vemurafenib* or zelboraf* or rg-7204 or plx 4032 or r05185426 or 207smy3fqt).tw. (376)
17 (pembrolizumab* or keytruda* or mk 3475 or sch 900475 or lambrolizumab*).tw. (1383)
18 or/11-17 (3111)
19 (encorafenib* or braftovi* or lgx 818 or nvp lgx 818).tw. (41)
20 (binimetinib* or mektovi* or arry 162 or arry 438162 or balimek or mek 162).tw. (43)
21 (trametinib* or mekinist* or gsk 1120212* or jtp 74057).tw. (306)
22 (dabrafenib* or tafinlar* or gsk 2118436*).tw. (248)
23 or/19-22 (432)
24 ((regional or locoregional or "isolated limb*") adj2 (chemotherap* or infusion* or perfusion*)).tw. (307)
25 (ili or ilp).tw. (388)
26 Electrochemotherapy/ (0)
27 (electrochemotherap* or electroporation*).tw. (1348)
28 tvec.tw. (4)
29 "Talimogene laherparepvec*".tw. (77)
30 Imlygic*.tw. (9)
31 (diphencyprone* or diphenylcyclopropenone* or DPCP).tw. (60)
32 or/24-31 (2158)
33 18 or 23 (3417)
34 10 and 33 (1133)
35 10 and 32 (177)
36 animals/ not humans/ (1)
37 34 not 36 (1133)
38 35 not 36 (177)
39 limit 37 to english language (1124)
40 limit 38 to english language (175)
41 limit 39 to (letter or historical article or comment or editorial or news or case reports) (259)
42 limit 40 to (letter or historical article or comment or editorial or news or case reports) (15)
43 39 not 41 (865)
44 40 not 42 (160)
45 randomized controlled trial.pt. (277)
46 randomi?ed.mp. (78435)
47 placebo.mp. (18506)
48 or/45-47 (85006)
49 Observational Studies as Topic/ (0)
50 Observational Study/ (91)
51 Epidemiologic Studies/ (0)
52 exp Case-Control Studies/ (1)
53 exp Cohort Studies/ (1)
54 Cross-Sectional Studies/ (0)
55 Controlled Before-After Studies/ (0)
56 Historically Controlled Study/ (0)
57 Interrupted Time Series Analysis/ (0)
58 Comparative Study.pt. (47)

Database: MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 02, 2020>

59 case control$.tw. (15331)
60 case series.tw. (14156)
61 (cohort adj (study or studies)).tw. (30821)
62 cohort analy$.tw. (1071)
63 (follow up adj (study or studies)).tw. (3657)
64 (observational adj (study or studies)).tw. (18779)
65 longitudinal.tw. (36419)
66 prospective.tw. (66935)
67 retrospective.tw. (79335)
68 cross sectional.tw. (64462)
69 or/49-68 (266987)
70 43 and 48 (57)
71 44 and 69 (20)
72 limit 70 to dt=20130101-20201202 (54)
73 limit 71 to dt=20130101-20201202 (20)

1

Database: MEDLINE EPub Ahead of Print

---
1 exp Melanoma/ (0)
2 Skin Neoplasms/ (0)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (1748)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (985)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (432)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (1)
7 dubreuilh*.tw. (0)
8 (maligna* adj2 lentigo*).tw. (27)
9 LMM.tw. (31)
10 or/1-9 (2841)
11 nivolumab/ (0)
12 (nivolumab* or 31yo63lbsn or bms 936558 or mdx 1106 or ono 4538 or opdivo*).tw. (274)
13 ipilimumab/ (0)
14 (ipilimumab* or 6t8c155666 or anti ctla 4 mab* or "mdx 010" or mdx ctla 4 or yervoy*).tw. (133)
15 Vemurafenib/ (0)
16 (vemurafenib* or zelboraf* or rg-7204 or plx 4032 or r05185426 or 207smy3fqt).tw. (58)
17 (pembrolizumab* or keytruda* or mk 3475 or sch 900475 or lambrolizumab*).tw. (267)
18 or/11-17 (536)
19 (encorafenib* or braftovi* or lgx 818 or nvp lgx 818).tw. (14)
20 (binimetinib* or mektovi* or arry 162 or arry 438162 or balimek or mek 162).tw. (11)
21 (trametinib* or mekinist* or gsk 1120212* or jtp 74057).tw. (58)
22 (dabrafenib* or tafinlar* or gsk 2118436*).tw. (52)
23 or/19-22 (85)
24 ((regional or locoregional or "isolated limb*") adj2 (chemotherap* or infusion* or perfusion*)).tw. (47)
25 (ili or ilp).tw. (63)
26 Electrochemotherapy/ (0)
27 (electrochemotherap* or electroporation*).tw. (117)

Database: MEDLINE EPub Ahead of Print	
28	tvec.tw. (1)
29	"Talimogene laherparepvec*".tw. (7)
30	Imlygic*.tw. (2)
31	(diphencyprone* or diphenylcyclopropenone* or DPCP).tw. (12)
32	or/24-31 (244)
33	18 or 23 (596)
34	10 and 33 (168)
35	10 and 32 (14)
36	animals/ not humans/ (0)
37	34 not 36 (168)
38	35 not 36 (14)
39	limit 37 to english language (166)
40	limit 38 to english language (14)
41	limit 39 to (letter or historical article or comment or editorial or news or case reports) (14)
42	limit 40 to (letter or historical article or comment or editorial or news or case reports) (1)
43	39 not 41 (152)
44	40 not 42 (13)

1

Database: Embase <1974 to 2020 December 04>	
1	exp melanoma skin cancer/ or melanoma/ or cutaneous melanoma/ or metastatic melanoma/ or superficial spreading melanoma/ or skin carcinoma/ (158486)
2	skin tumor/ or skin cancer/ or epithelium tumor/ (67484)
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (164864)
4	((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (93912)
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (39993)
6	(hutchinson* adj2 (freckle* or melano*)).tw. (80)
7	dubreuilh*.tw. (73)
8	(maligna* adj2 lentigo*).tw. (1691)
9	LMM.tw. (1531)
10	or/1-9 (334254)
11	nivolumab/ (19459)
12	(nivolumab* or 31yo63lbsn or bms 936558 or mdx 1106 or ono 4538 or opdivo*).tw. (12494)
13	ipilimumab/ (14994)
14	(ipilimumab* or 6t8c155666 or anti ctla 4 mab* or "mdx 010" or mdx ctla 4 or yervoy*).tw. (8242)
15	Vemurafenib/ (7671)
16	(vemurafenib* or zelboraf* or rg-7204 or plx 4032 or r05185426 or 207smy3fqt).tw. (4911)
17	Pembrolizumab/ (17230)
18	(pembrolizumab* or keytruda* or mk 3475 or sch 900475 or lambrolizumab*).tw. (10593)
19	or/11-18 (41160)
20	(encorafenib* or braftovi* or lgx 818 or nvp lgx 818).tw. (355)
21	Encorafenib/ (592)
22	binimetinib/ (918)
23	(binimetinib* or mektovi* or arry 162 or arry 438162 or balimek or mek 162).tw. (596)
24	Trametinib/ (5387)
25	(trametinib* or mekinist* or gsk 1120212* or jtp 74057).tw. (2982)
26	dabrafenib/ (4491)
27	(dabrafenib* or tafinlar* or gsk 2118436*).tw. (2460)

Database: Embase <1974 to 2020 December 04>
28 or/20-27 (7758)
29 ((regional or locoregional or "isolated limb*") adj2 (chemotherap* or infusion* or perfusion*)).tw. (7464)
30 (ili or ilp).tw. (4013)
31 Electrochemotherapy/ (1305)
32 (electrochemotherap* or electroporation*).tw. (14839)
33 Talimogene laherparepvec/ (922)
34 tvec.tw. (87)
35 "Talimogene laherparepvec*".tw. (391)
36 Imlygic*.tw. (122)
37 Diphencyprone/ (873)
38 (diphencyprone* or diphenylcyclopropenone* or DPCP).tw. (576)
39 or/29-38 (27891)
40 10 and 39 (2717)
41 19 or 28 (45051)
42 10 and 41 (18693)
43 nonhuman/ not human/ (4763479)
44 40 not 43 (2481)
45 42 not 43 (18295)
46 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4703694)
47 44 not 46 (1924)
48 45 not 46 (12430)
49 limit 47 to english language (1800)
50 limit 48 to english language (12092)
51 Clinical study/ (156781)
52 Case control study/ (165162)
53 Family study/ (26235)
54 Longitudinal study/ (148902)
55 Retrospective study/ (1001533)
56 comparative study/ (881924)
57 Prospective study/ (647781)
58 Randomized controlled trials/ (192444)
59 57 not 58 (640742)
60 Cohort analysis/ (644618)
61 cohort analy$.tw. (13728)
62 (Cohort adj (study or studies)).tw. (320798)
63 (Case control$ adj (study or studies)).tw. (142572)
64 (follow up adj (study or studies)).tw. (65105)
65 (observational adj (study or studies)).tw. (178812)
66 (epidemiologic$ adj (study or studies)).tw. (109361)
67 (cross sectional adj (study or studies)).tw. (235704)
68 case series.tw. (109821)
69 prospective.tw. (895147)
70 retrospective.tw. (931444)
71 or/51-56,59-70 (4224846)
72 random:.tw. (1613350)
73 placebo:.mp. (467313)
74 double-blind:.tw. (216432)
75 or/72-74 (1872845)

Database: Embase <1974 to 2020 December 04>

76 49 and 71 (267)
77 50 and 75 (1228)
78 limit 76 to dc=20130101-20201202 (173)
79 limit 77 to dc=20130101-20201202 (966)

1

Database: Cochrane

ID Search Hits
#1 MeSH descriptor: [Melanoma] explode all trees 1806
#2 MeSH descriptor: [Skin Neoplasms] this term only 1560
#3 ((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)):ti,ab,kw 5403
#4 (((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))):ti,ab,kw 3979
#5 (((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*))):ti,ab,kw 686
#6 ((hutchinson* NEAR/2 (freckle* or melano*))):ti,ab,kw 9
#7 (dubreuilh*):ti,ab,kw 0
#8 (maligna* NEAR/2 lentigo*) 54
#9 (LMM):ti,ab,kw 118
#10 {or #1-#9} 8502
#11 MeSH descriptor: [Nivolumab] this term only 433
#12 ((nivolumab* or 31yo63lbsn or bms 936558 or mdx 1106 or ono 4538 or opdivo*)):ti,ab,kw 1763
#13 MeSH descriptor: [Ipilimumab] this term only 181
#14 ((ipilimumab* or 6t8c155666 or anti ctla 4 mab* or "mdx 010" or mdx ctla 4 or yervoy*)):ti,ab,kw 1222
#15 MeSH descriptor: [Vemurafenib] this term only 43
#16 ((vemurafenib* or zelboraf* or rg-7204 or plx 4032 or r05185426 or 207smy3fqt)):ti,ab,kw 204
#17 ((pembrolizumab* or keytruda* or mk 3475 or sch 900475 or lambrolizumab*)):ti,ab,kw 1552
#18 #11 or #12 or #13 or #14 or #15 or #16 or #17 3671
#19 ((encorafenib* or braftovi* or lgx 818 or nvp lgx 818)):ti,ab,kw 59
#20 ((binimetinib* or mektovi* or arry 162 or arry 438162 or balimek or mek 162)):ti,ab,kw 89
#21 ((trametinib* or mekinist* or gsk 1120212* or jtp 74057)):ti,ab,kw 259
#22 ((dabrafenib* or tafinlar* or gsk 2118436*)):ti,ab,kw 215
#23 #19 or #20 or #21 or #22 364
#24 (((regional or locoregional or "isolated limb*") near/2 (chemotherap* or infusion* or perfusion*))):ti,ab,kw 685
#25 ((ili or ilp)):ti,ab,kw 2427
#26 MeSH descriptor: [Electrochemotherapy] this term only 8
#27 ((electrochemotherap* or electroporation*)):ti,ab,kw 223
#28 ("Talimogene laherparepvec"):ti,ab,kw 68
#29 (tvec):ti,ab,kw 45
#30 (Imlygic*):ti,ab,kw 3
#31 ((diphencyprone* or diphenylcyclopropenone* or DPCP)):ti,ab,kw 55
#32 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 3430

Database: Cochrane

#33 #18 or #23 or #32 7314

#34 #10 and #33 with Cochrane Library publication date Between Jan 2013 and Jan 2020, in Cochrane Reviews, Trials 1153

1

Database: CRD DARE

1 MeSH DESCRIPTOR melanoma EXPLODE ALL TREES 221 Delete

2 MeSH DESCRIPTOR Skin Neoplasms 193 Delete

3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*) 329 Delete

4 (((skin or derm* or cutaneous* or epitheli* or epiderm*) near1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))) 386 Delete

5 (((maligna* or melano*) near2 (freckle* or lesion* or mole* or nev* or naev*))) 102 Delete

6 ((hutchinson* near2 (freckle* or melano*))) 0 Delete

7 (dubreuilh*) 0 Delete

8 (maligna* near2 lentigo*) 0 Delete

9 (LMM) 0 Delete

10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 630 Delete

11 (nivolumab* or 31yo63lbsn or bms 936558 or mdx 1106 or ono 4538 or opdivo*) 47 Delete

12 (ipilimumab* or 6t8c155666 or anti ctla 4 mab* or "mdx 010" or mdx ctla 4 or yervoy*) 32 Delete

13 (vemurafenib* or zelboraf* or rg-7204 or plx 4032 or r05185426 or 207smy3fqt) 13 Delete

14 (pembrolizumab* or keytruda* or mk 3475 or sch 900475 or lambrolizumab*) 24 Delete

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17 (binimetinib* or mektovi* or arry 162 or arry 438162 or balimek or mek 162) 2 Delete

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18	(trametinib* or mekinist* or gsk 1120212* or jtp 74057)	10	Delete	
19	(dabrafenib* or tafinlar* or gsk 2118436*)	16	Delete	
20	#16 OR #17 OR #18 OR #19	21	Delete	
21	MeSH DESCRIPTOR Electrochemotherapy	7	Delete	
22	(electrochemotherap* or electroporation*)	18	Delete	
23	(tvec)	0	Delete	
24	(Talimogene laherparepvec)	2	Delete	
25	(Imlygic*)	1	Delete	
26	(diphencyprone* or diphenylcyclopropenone* or DPCP)	3	Delete	
27	#21 or #22 OR #23 OR #24 OR #25 OR #26	23	Delete	
28	#15 OR #20 OR #27	144	Delete	
29	#10 AND #28	63	Delete	
30	* IN DARE FROM 2013 TO 2020	17124	Delete	
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34	* IN NHSEED FROM 2013 TO 2020	3345	Delete	
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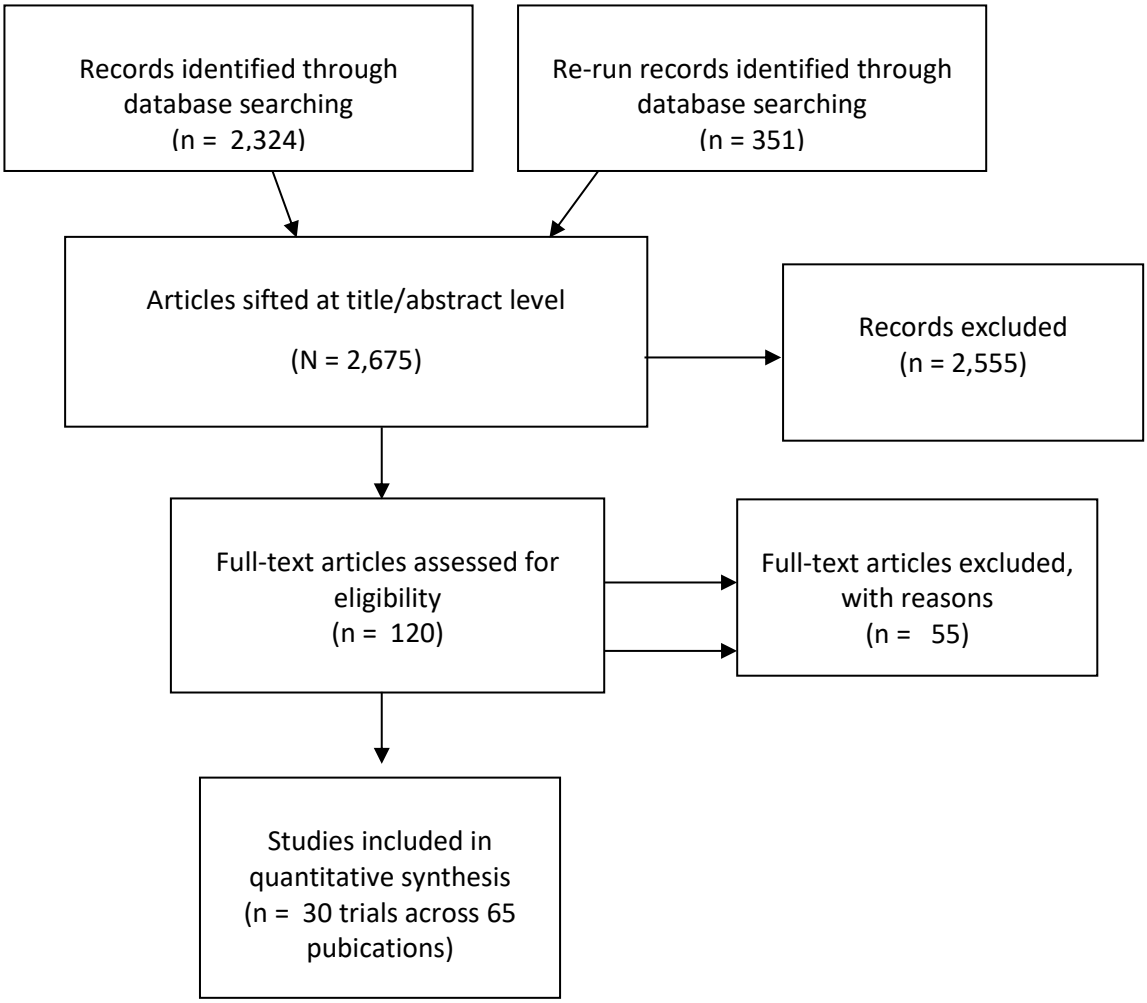
1
2

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence

Immunotherapy and targeted therapy trials

ABC

ABC trial

Bibliographic Reference	Long, Georgina V; Atkinson, Victoria; Lo, Serigne; Sandhu, Shahneen; Guminski, Alexander D; Brown, Michael P; Wilmott, James S; Edwards, Jarem; Gonzalez, Maria; Scolyer, Richard A; Menzies, Alexander M; McArthur, Grant A; Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study.; The Lancet. Oncology; 2018; vol. 19 (no. 5); 672-681

Study details

Trial registration number and/or trial name	NCT02374242
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Four cancer centres
Study dates	2014 - 2017
Sources of funding	Melanoma Institute Australia and Bristol-Myers Squibb
Inclusion criteria	Age at least 18 years Eastern Cooperative Oncology Group performance status (ECOG PS)

	0 to 2 At least one target intracranial lesion of 5–40 mm on Gadolinium-enhanced MRI No history of severe autoimmune disease Previous BRAF inhibitor therapy with or without MEK inhibitor therapy was allowed if intracranial RECIST 1.1 progression occurred
Exclusion criteria	Active brain metastases Melanoma brain metastasis >40mm Previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways Pregnancy or breastfeeding Ocular melanoma History or current Active autoimmune disease Patients with active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol Condition requiring corticosteroids or immunosuppressive medication Current systemic treatment with corticosteroids, with the exception of prednisone at non-immunosuppressive doses of ≤ 10 mg/day (or equivalent). Past treatment for non-neurological symptoms allowed, if this was ceased 2 weeks prior to commencement of study treatment. dose). Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the patient is on a stable dose. Non-absorbed intra-articular steroid injections were permitted Known history of HIV infection Active hepatitis B virus or hepatitis C virus infection History of other malignancy or a concurrent malignancy unless the patient has been disease-free for 3 years Other exclusion criteria

	Any serious or unstable pre-existing medical conditions (aside from the malignancy exceptions specified), psychiatric disorders, or other conditions that, in the opinion of the treating clinician, could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures Any investigational drug or other systemic drug therapy for melanoma within 28 days or 5 half-lives from baseline
Intervention(s)	Nivolumab combined with ipilimumab
Comparator	Nivolumab
Outcome measures	Melanoma specific mortality Progression free survival Overall progression-free survival was calculated from the first dose of study treatment until earliest intracranial and extracranial progression or death. Overall survival calculated from the first dose of study treatment until death Serious adverse events
Number of participants	79
Duration of follow-up	24 months
Loss to follow-up	
Additional comments	Patients who neither progressed nor died by the data cutoff date were censored at their last tumour assessment. Post-hoc survival analyses were done for BRAF and MEK inhibitor treatment-naive patients.

1 **Study arms**

Nivolumab combined with ipilimumab (cohort A) (N = 36)
Intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks. Cohort A: patients with asymptomatic melanoma brain metastases who had no previous local brain therapy (surgery, stereotactic radiosurgery, or whole-brain radiotherapy).

Nivolumab (cohort B) (N = 27)
Intravenous nivolumab 3 mg/kg every 2 weeks. Cohort B: patients with asymptomatic melanoma brain metastases who had no previous local brain therapy (surgery, stereotactic radiosurgery, or whole-brain radiotherapy).

Nivolumab (cohort C) (N = 16)
Intravenous nivolumab 3 mg/kg every 2 weeks. Cohort C: patients with melanoma brain metastases, who either failed local therapy (ie, had developed new brain metastases or had RECIST 1.1 progression in treated brain metastases with new lesions or a ≥20% increase in sum of diameters of previously treated lesions and an absolute increase of ≥5 mm for existing lesions), had symptoms related to brain metastases, or had leptomeningeal disease, or any combination of these.

1 **Arm-level characteristics**

	Nivolumab combined with ipilimumab (cohort A) (N = 36)	**Nivolumab (cohort B) (N = 27)**	**Nivolumab (cohort C) (N = 16)**
% Female			
Sample Size	n = 6 ; % = 17	n = 6 ; % = 24	n = 5 ; % = 31
Mean age (SD)			
MedianIQR	59 (53 to 68)	63 (52 to 74)	51 (48 to 56)
Number of intracranial metastases (target and non-target)			
one			
Sample Size	n = 11 ; % = 31	n = 6 ; % = 24	n = 1 ; % = 6
2 - 4			

	Nivolumab combined with ipilimumab (cohort A) (N = 36)	Nivolumab (cohort B) (N = 27)	Nivolumab (cohort C) (N = 16)
Sample Size	n = 10 ; % = 29	n = 14 ; % = 56	n = 7 ; % = 44
>4			
Sample Size	n = 14 ; % = 40	n = 5 ; % = 20	n = 8 ; % = 50
Target intracranial RECIST sum of diameters, mm			
MedianIQR	19 (13 to 37)	17 (12 to 29)	34 (21 to 53)
Presence of extracranial metastases			
Sample Size	n = 30 ; % = 86	n = 21 ; % = 84	n = 12 ; % = 75
Target extracranial RECIST sum of diameters, mm			
MedianIQR	90 (47 to 120)	46 (28 to 89)	37 (22 to 82)
No previous combined BRAF and MEK inhibitor therapy received			
Sample Size	n = 22 ; % = 77	n = 19 ; % = 76	n = 4 ; % = 25
Previous combined BRAF and MEK inhibitor therapy received			
Sample Size	n = 8 ; % = 23	n = 6	n = 12 ; % = 75
BRAFV600 mutation			

	Nivolumab combined with ipilimumab (cohort A) (N = 36)	Nivolumab (cohort B) (N = 27)	Nivolumab (cohort C) (N = 16)
BRAFV600E			
Sample Size	n = 14 ; % = 40	n = 11 ; % = 44	n = 11 ; % = 69
BRAFV600K			
Sample Size	n = 4 ; % = 11	n = 2 ; % = 8	n = 1 ; % = 6
BRAFV600R			
Sample Size	n = 1 ; % = 3	n = 1 ; % = 4	n = 1 ; % = 6
Previous local brain therapy			
Any surgery			
Sample Size	n = 0	n = 0	n = 9 ; % = 56
Any stereotactic radiosurgery			
Sample Size	n = 0	n = 0	n = 8 ; % = 50
Any whole brain radiotherapy			
Sample Size	n = 0	n = 0	n = 7 ; % = 44
Leptomeningeal melanoma			
Sample Size	n = 0	n = 0	n = 4 ; % = 25

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable

Section	Question	Answer
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No information
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes

Section	Question	Answer
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes

Section	Question	Answer
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1 **BREAK-3**

BREAK-3 trial

2

Bibliographic Reference	Grob, J-J; Amonkar, M M; Martin-Algarra, S; Demidov, L V; Goodman, V; Grotzinger, K; Haney, P; Kampgen, E; Karaszewska, B; Mauch, C; Miller, W H Jr; Millward, M; Mirakhur, B; Rutkowski, P; Chiarion-Sileni, V; Swann, S; Hauschild, A; Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine.; Annals of oncology : official journal of the European Society for Medical Oncology; 2014; vol. 25 (no. 7); 1428-1436

3

4

5 **Study details**

Other publications associated with this study included in review	Hauschild, A, Grob, JJ, Demidov, LV et al. (2012) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet (London, England) 380(9839): 358-365 Hauschild, A., Ascierto, P. A., Schadendorf, D., Grob, J. J., Ribas, A., Kiecker, F., ... & Chapman, P. B. (2020). Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib monotherapy: Analysis from phase 2 and 3 clinical trials. European Journal of Cancer, 125, 114-120 Latimer, N. R., Abrams, K. R., Amonkar, M. M., Stapelkamp, C., & Swann, R. S. (2015). Adjusting for the confounding effects of treatment switching—the BREAK-3 trial: dabrafenib versus dacarbazine. The oncologist, 20(7), 798 Santiago-Walker, A., Gagnon, R., Mazumdar, J., Casey, M., Long, G. V., Schadendorf, D., ... & Martin, A. M. (2016). Correlation of BRAF mutation status in circulating-free DNA and tumor and association with clinical outcome across four BRAFi and MEKi clinical trials. Clinical Cancer Research, 22(3), 567-574
Trial registration number and/or trial name	BREAK-3 trial NCT01227889
Study type	Randomised controlled trial (RCT)
Study location	Australia, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Russian Federation, Spain, US
Study setting	Multicentre
Study dates	2010 - 2016
Sources of funding	GlaxoSmithKline
Inclusion criteria	Age at least 18 years Melanoma histologically confirmed advanced (unresectable stage III) or metastatic (stage IV) BRAF V600E mutation-positive melanoma Eastern Cooperative Oncology Group performance status (ECOG PS)

	0 (fully active and able to carry on all performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) Adequate haematological function Adequate hepatic function $BRAFV^{600}$ mutation-positive tumour BRAFV600E mutation by central testing using an investigational-use-only assay Adequate organ function Measurable disease according to RECIST 1.1 criteria Treatment naive for metastatic disease except for interleukin-2 treatment, surgery, or radiotherapy Women of child-bearing potential must have a negative pregnancy test within 14 days prior to the first dose of study treatment Women with reproductive potential must be willing to practice acceptable methods of birth control during the study and for up to 4 weeks after the last dose of study medication Men with reproductive potential must be willing to practice acceptable methods of birth control during the study and for up to 16 weeks after the last dose of study medication Adequate cardiac function
Exclusion criteria	Known history of HIV infection Currently receiving cancer therapy chemotherapy, radiation therapy, immunotherapy, biologic therapy or surgery within 4 weeks Evidence of active central nervous system disease Previous treatment for metastatic melanoma including treatment with BRAF or MEK inhibitor History of other malignancy

	Subjects who have been disease-free for 5 years or subjects with a history of complete resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible Certain cardiac abnormalities Glucose-6-dehydrogenase deficiency Central nervous system metastasis unless they were without evidence of active CNS metastases for more than 3 months after surgery or stereotactic radiosurgery Other exclusion criteria corrected QT interval of 480 ms or more; acute coronary syndrome, coronary angioplasty, placement of stents, or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks; abnormal cardiac valve morphology grade 2 or higher on ECHO cardiography, or known cardiac metastases
Intervention(s)	Dabrafenib
Comparator	Dacarbazine
Outcome measures	Progression free survival defined as the interval of time between the date of randomisation and the earlier of the date of disease progression or the date of death due to any cause. Overall survival defined as the interval of time between the date of randomisation and the date of death due to any cause. For participants who did not die, overall survival was censored at the date of last contact. Health related quality of life European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
Number of participants	250
Duration of follow-up	Median follow-up of 10.5 months
Loss to follow-up	

Additional comments	Patients randomised to dacarbazine treatment were allowed to receive dabrafenib after initial progression was confirmed by independent review

Study arms

Dabrafenib (N = 187)
oral dabrafenib 150 mg twice daily

Loss to follow-up	2

Dacarbazine (N = 63)
intravenous dacarbazine1000 mg/m2 every 3 weeks

Loss to follow-up	1

Arm-level characteristics

	Dabrafenib (N = 187)	**Dacarbazine (N = 63)**
% Female		
Sample Size	n = 75 ; % = 40	n = 26 ; % = 41
Mean age (SD)		
Custom value	Median 53.0 years (range 22 to 93)	Median 50.0 years (range 21 to 82)
M-status at screening		
M0		

	Dabrafenib (N = 187)	Dacarbazine (N = 63)
Sample Size	n = 6 ; % = 3	n = 1 ; % = 2
M1a		
Sample Size	n = 23 ; % = 12	n = 10 ; % = 16
M1b		
Sample Size	n = 34 ; % = 18	n = 12 ; % = 19
M1c		
Sample Size	n = 124 ; % = 66	n = 40 ; % = 63
Previous treatment		
No previous therapy		
Sample Size	n = 6 ; % = 3	n = 1 ; % = 2
Previous therapy		
Sample Size	n = 181 ; % = 97	n = 62 ; % = 98
Immunotherapy		
Sample Size	n = 52 ; % = 28	n = 15 ; % = 24
Radiotherapy		
Sample Size	n = 37 ; % = 20	n = 10 ; % = 16

	Dabrafenib (N = 187)	Dacarbazine (N = 63)
Adjuvant biologic therapy (monoclonal antibody, vaccines)		
Sample Size	n = 3 ; % = 2	n = 3 ; % = 5
Adjuvant chemotherapy		
Sample Size	n = 1 ; % = 1	n = 4 ; % = 6

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes

Section	Question	Answer
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes

Section	Question	Answer
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1 **BRIM-3**

BRIM-3 trial

2

Bibliographic Reference	Chapman, P B; Robert, C; Larkin, J; Haanen, J B; Ribas, A; Hogg, D; Hamid, O; Ascierto, P A; Testori, A; Lorigan, P C; Dummer, R; Sosman, J A; Flaherty, K T; Chang, I; Coleman, S; Caro, I; Hauschild, A; McArthur, G A; Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study.; Annals of oncology : official journal of the European Society for Medical Oncology; 2017; vol. 28 (no. 10); 2581-2587

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2 **Study details**

Other publications associated with this study included in review	Ascierto, P. A., Ribas, A., Larkin, J., McArthur, G. A., Lewis, K. D., Hauschild, A., ... & Dréno, B. (2020). Impact of initial treatment and prognostic factors on postprogression survival in BRAF-mutated metastatic melanoma treated with dacarbazine or vemurafenib±cobimetinib: a pooled analysis of four clinical trials. Journal of translational medicine, 18(1), 1-12 McArthur, Grant A, Chapman, Paul B, Robert, Caroline et al. (2014) Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. The Lancet. Oncology 15(3): 323-32
Trial registration number and/or trial name	BRIM-3 trial NCT01006980
Study type	Randomised controlled trial (RCT)
Study location	Australia, Canada, France, Germany, Israel, Italy, Netherlands, New Zealand, Sweden, Switzerland, UK, USA
Study setting	Multicentre
Study dates	2010 - 2016
Sources of funding	This work was supported by F. Hoffmann-La Roche Ltd. There are no grant numbers associated with this funding. The authors also acknowledge partial support from an NCI Cancer Center Support Grant (CCSG, P30 CA08748).
Inclusion criteria	Age ≥18 years Melanoma previously untreated, unresectable stage IIIC or stage IV melanoma with a BRAFV600 mutation Life expectancy ≥3 months Eastern Cooperative Oncology Group performance status (ECOG PS)

	0 or 1 Adequate haematological function Adequate hepatic function Adequate renal function
Intervention(s)	Vemurafenib
Comparator	Dacarbazine
Outcome measures	Progression free survival defined as the time from randomisation to documented disease progression or death Overall survival defined as the time from randomisation to death from any cause Serious adverse events
Number of participants	675

Study arms

Vemurafenib (N = 337)
960 mg orally twice daily

Intervention(s)	
Duration of follow-up	The median duration of follow-up for the ITT population was 13.4 months (range 0.4–59.6) for patients in the vemurafenib arm
Loss to follow-up	Not reported

Dacarbazine (N = 338)
1000 mg/m2 as an intravenous infusion every 3 weeks

Intervention(s)	
Duration of follow-up	The median duration of follow-up for the ITT population was 9.2 months (range 0–56.2) for patients in the dacarbazine arm
Loss to follow-up	Not reported

1 **Arm-level characteristics**

	Vemurafenib (N = 337)	**Dacarbazine (N = 338)**
% Female		
Sample Size	n = 137 ; % = 41	n = 157 ; % = 46
Mean age (SD)		
Custom value	Median 56 years (range 21 to 86)	Median 52 years (range 17 to 86)
Stage		
Unresectable IIIC		
Sample Size	n = 20 ; % = 6	n = 13 ; % = 4
M1a		
Sample Size	n = 34 ; % = 10	n = 40 ; % = 12
M1b		

	Vemurafenib (N = 337)	Dacarbazine (N = 338)
Sample Size	n = 62 ; % = 18	n = 65 ; % = 19
M1c		
Sample Size	n = 221 ; % = 66	n = 220 ; % = 65

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Yes/Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Yes
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes

Section	Question	Answer
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1 **BRF113220**

BRF113220 trial

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Bibliographic Reference	Long, Georgina V; Eroglu, Zeynep; Infante, Jeffrey; Patel, Sapna; Daud, Adil; Johnson, Douglas B; Gonzalez, Rene; Kefford, Richard; Hamid, Omid; Schuchter, Lynn; Cebon, Jonathan; Sharfman, William; McWilliams, Robert; Sznol, Mario; Redhu, Suman; Gasal, Eduard; Mookerjee, Bijoyesh; Weber, Jeffrey; Flaherty, Keith T; Long-Term Outcomes in Patients With BRAF V600-Mutant Metastatic Melanoma Who Received Dabrafenib Combined With Trametinib.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2018; vol. 36 (no. 7); 667-673

Study details

Other publications associated with this study included in review	Flaherty, KT, Infante, JR, Daud, A et al. (2012) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. New England Journal of Medicine 367(18): 1694-1703 Johnson, D. B., Flaherty, K. T., Weber, J. S., Infante, J. R., Kim, K. B., Kefford, R. F., ... & Gonzalez, R. (2014). Combined BRAF (Dabrafenib) and MEK inhibition (Trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. Journal of Clinical Oncology, 32(33), 3697 Latimer, N. R., Amonkar, M. M., Stapelkamp, C., & Sun, P. (2015). Adjusting for confounding effects of treatment switching in a randomized phase II study of dabrafenib plus trametinib in BRAF V600+ metastatic melanoma. Melanoma research, 25(6), 528-536 Long, G. V., Weber, J. S., Infante, J. R., Kim, K. B., Daud, A., Gonzalez, R., ... & Flaherty, K. T. (2016). Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. Journal of Clinical Oncology, 34(8), 871-878.
Trial registration number and/or trial name	NCT01072175 BRF113220
Study type	Randomised controlled trial (RCT)
Study location	Australia, US
Study setting	Multicentre
Study dates	2010 - 2016
Sources of funding	Supported by GlaxoSmithKline
Inclusion criteria	Age 18 years of age or older

	Melanoma histologically confirmed metastatic melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 (with 0 indicating asymptomatic and 1 ambulatory but restricted in strenuous activity) BRAFV^{600} mutation-positive tumour either BRAF V600E or BRAF V600K mutations BRAFi and MEKi treatment naïve Adequate organ function Measurable disease Without brain metastases or have undergone treatment for brain metastases Patients with treated brain metastases and at least a 3-month history of stable disease were eligible for inclusion. Brain metastases were considered stable if they met the following criteria: asymptomatic with no corticosteroids and/or enzyme-inducing anticonvulsants for ≥30 days, confirmed stable with two consecutive MRI or CT scans ≥90 days apart, and previously treated with surgery or stereotactic radiosurgery.
Exclusion criteria	Untreated brain metastases History of cardiovascular disease History of interstitial lung disease Evidence or risk of retinal vein occlusion Central serous retinopathy
Intervention(s)	Dabrafenib 150mg plus trametinib 2mg
Comparator	Dabrafenib 150mg plus trametinib 1mg Dabrafenib 150mg
Outcome measures	All-cause mortality

	Progression free survival For randomised participants staying in their assigned treatment, progression free survival was defined as the time from randomisation to the first documented radiological progression or death, based on investigator assessment. For crossover participants, progression free survival was defined as the time from the first dose of study medication to the first documented radiological progression or death, based on investigator assessment. Overall survival defined as the interval of time between the date of randomisation until the date of death due to any cause. For the participants who did not die, overall survival was censored at the date of last contact. When calculating overall survival, deaths following crossover were included. Time on treatment Time to second treatment
Subgroup analysis	Melanoma stage Progression free survival was reported by baseline disease stage • IIIcM0, IVM1a, or IVM1b • IVM1c
Number of participants	162
Duration of follow-up	5 years
Additional comments	Patients who had disease progression while receiving dabrafenib monotherapy could cross over to receive combination with trametinib 2mg. There were 45 crossover participants from dabrafenib 150mg monotherapy to dabrafenib 150mg in combination with trametinib 2mg.

Study arms

Dabrafenib 150mg plus trametinib 2mg (N = 54)

150 mg of dabrafenib twice daily plus once-daily trametinib, at a dose of 2 mg	
Loss to follow-up	2
Dabrafenib 150mg plus trametinib 1mg (N = 54) 150 mg of dabrafenib twice daily plus once-daily trametinib, at a dose of 1 mg	
Loss to follow-up	2
Dabrafenib 150mg (N = 54) 150 mg of dabrafenib monotherapy twice daily	
Loss to follow-up	2

1 **Arm-level characteristics**

	Dabrafenib 150mg plus trametinib 2mg (N = 54)	**Dabrafenib 150mg plus trametinib 1mg (N = 54)**	**Dabrafenib 150mg (N = 54)**
% Female			
Sample Size	n = 20 ; % = 37	n = 24 ; % = 44	n = 25 ; % = 46
Mean age (SD)			
Custom value	Median 58 years (range 27 to 79)	Median 49 years (range 23 to 85)	Median 50 years (range 18 to 82)
Metastatic status			
M0			

	Dabrafenib 150mg plus trametinib 2mg (N = 54)	Dabrafenib 150mg plus trametinib 1mg (N = 54)	Dabrafenib 150mg (N = 54)
Sample Size	n = 0 ; % = 0	n = 1 ; % = 2	n = 1 ; % = 2
M1a			
Sample Size	n = 6 ; % = 11	n = 9 ; % = 17	n = 11 ; % = 20
M1b			
Sample Size	n = 10 ; % = 19	n = 11 ; % = 20	n = 5 ; % = 9
M1c			
Sample Size	n = 38 ; % = 70	n = 33 ; % = 61	n = 37 ; % = 69
History of brain metastases			
Sample Size	n = 2 ; % = 4	n = 7 ; % = 13	n = 4 ; % = 7
BRAF mutation			
V600E			
Sample Size	n = 47 ; % = 87	n = 45	n = 45 ; % = 83
V600K			
Sample Size	n = 7 ; % = 13	n = 9 ; % = 17	n = 9 ; % = 17
No. of organ sites with metastasis			

	Dabrafenib 150mg plus trametinib 2mg (N = 54)	Dabrafenib 150mg plus trametinib 1mg (N = 54)	Dabrafenib 150mg (N = 54)
≥3			
Sample Size	n = 28 ; % = 52	n = 27 ; % = 50	n = 34 ; % = 63
≥3			
Sample Size	n = 26 ; % = 48	n = 27 ; % = 50	n = 20 ; % = 37
Previous immunotherapy			
Sample Size	n = 13 ; % = 24	n = 16 ; % = 30	n = 8 ; % = 15

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Probably yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate (unblinded with a high level of crossover from monotherapy arm)
	Overall Directness	Directly applicable

CHECKMATE-037

CHECKMATE-037

Bibliographic Reference	Larkin, James; Minor, David; D'Angelo, Sandra; Neyns, Bart; Smylie, Michael; Miller, Wilson H Jr; Gutzmer, Ralf; Linette, Gerald; Chmielowski, Bartosz; Lao, Christopher D; Lorigan, Paul; Grossmann, Kenneth; Hassel, Jessica C; Sznol, Mario; Daud, Adil; Sosman, Jeffrey; Khushalani, Nikhil; Schadendorf, Dirk; Hoeller, Christoph; Walker, Dana; Kong, George; Horak, Christine; Weber, Jeffrey; Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2018; vol. 36 (no. 4); 383-390

Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Weber, Jeffrey S, D'Angelo, Sandra P, Minor, David et al. (2015) Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. The Lancet. Oncology 16(4): 375-84
Trial registration number and/or trial name	CheckMate 037 trial NCT01721746
Study type	Randomised controlled trial (RCT)

Study location	Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, UK, US
Study setting	Multicentre
Study dates	2012 - 2016
Sources of funding	The study was funded by Bristol-Myers Squibb.
Inclusion criteria	Age • 18 years or older Melanoma • histologically confirmed, unresectable stage IIIC or IV metastatic melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) • 0 or 1 Progressed after anti-CTLA-4 treatment • BRAF wild-type tumours patients must have had progression after anti-CTLA-4 treatment, such as ipilimumab • $BRAFV^{600}$ mutation-positive tumour patients must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor
Exclusion criteria	Active brain metastases Previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies Those who had grade 4 toxic effects Used infliximab to manage adverse events from previous ipilimumab treatment Patients with a primary ocular melanoma
Intervention(s)	Nivolumab
Comparator	Investigator's choice chemotherapy (either dacarbazine or carboplatin plus paclitaxel)
Outcome measures	Progression free survival

	Defined as the time from randomization to first documented disease progression as determined by the independent radiological review committee Overall survival Defined as the time from randomisation to death Health related quality of life Assessed at baseline, every cycle (ICC), or every other cycle (nivolumab) for the first 6 months, then every 6 weeks and at follow-up and survival visits; assessments were EORTC QLQ-C30 version 3 and EuroQoL EQ-5D summary index and visual analog scale. Serious adverse events
Subgroup analysis	Melanoma stage Overall survival at 2 years follow-up was reported by melanoma stage • M0 • M1A • M1B • M1C
Number of participants	405
Duration of follow-up	2 years
Loss to follow-up	1

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2 **Study arms**

Nivolumab (N = 272) 3 mg/kg every 2 weeks	
Loss to follow-up	

Investigator's choice chemotherapy (N = 133)
either dacarbazine 1000 mg/m² every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m² every 3 weeks, by intravenous infusion

1 **Characteristics**

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	Nivolumab (N = 272)	**Investigator's choice chemotherapy (N = 133)**
% Female		
Sample Size	n = 96 ; % = 35	n = 48 ; % = 36
Mean age (SD)		
Custom value	Median 59 years (range 23 to 88)	Median 62 years (29 to 85)
Stage M1c at study entry		
Sample Size	n = 203 ; % = 75	n = 102 ; % = 77
AJCC stage IV at study entry		
Sample Size	n = 261 ; % = 96	n = 131 ; % = 99
History of brain metastases		
Sample Size	n = 55 ; % = 20	n = 18 ; % = 14
BRAF mutant		

	Nivolumab (N = 272)	**Investigator's choice chemotherapy (N = 133)**
Sample Size	n = 60 ; % = 22	n = 29 ; % = 22
Tumour size at baseline		
Custom value	Median 96 mm (range 10 to 422)	Median 87 mm (range 13 to 400)
Number of previous systemic treatments In metastatic disease setting		
one		
Sample Size	n = 77 ; % = 28	n = 34 ; % = 26
two		
Sample Size	n = 139 ; % = 51	n = 68 ; % = 51
≤2		
Sample Size	n = 56 ; % = 21	n = 31 ; % = 23
Type of previous treatment In metastatic disease setting		
Ipilimumab		
Sample Size	n = 271 ; % = 99	n = 133 ; % = 100
Vemurafenib		

	Nivolumab (N = 272)	Investigator's choice chemotherapy (N = 133)
Sample Size	n = 49 ; % = 18	n = 23 ; % = 17
Chemotherapy		
Sample Size	n = 145 ; % = 53	n = 72 ; % = 54
Other immunotherapy Excluding previous ipilimumab treatment (documented previous interferon α2a and b, interleukin 2 and 21, and T-cell infusion immunotherapies)		
Sample Size	n = 37 ; % = 14	n = 35 ; % = 26

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No

Section	Question	Answer
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Yes/Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Yes
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable

Section	Question	Answer
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(41% of patients in the ICC group versus 11% in the nivolumab group received a subsequent anti–PD-1/PDL1 agent; a numeric survival difference was observed between treatment groups with censoring at the start of anti–PD-1/PD-L1 treatment after assigned therapy in the ICC group)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No
	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
	2.5. Did study participants adhere to the assigned intervention regimen?	No
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(A high proportion of patients who were randomly assigned to ICC compared with those who were randomly assigned to nivolumab (23% v 1%) dropped out as soon as the random assignment occurred before receiving assigned chemotherapy treatments. Many of these patients went on to receive*

Section	Question	Answer
		pembrolizumab in available phase I studies, which may have skewed the results.)
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably yes

Section	Question	Answer
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(More patients in the ICC group received a subsequent anti–PD-1/PDL1 agent compared to patients in the nivolumab group; a numeric survival difference was observed between treatment groups with censoring at the start of anti–PD-1/PD-L1 treatment after assigned therapy in the ICC group; a*

Section	Question	Answer
		high proportion of patients who were randomly assigned to ICC compared with those who were randomly assigned to nivolumab dropped out as soon as the random assignment occurred before receiving assigned chemotherapy treatments. Many of these patients went on to receive pembrolizumab in available phase I studies, which may have skewed the results.)
	Overall Directness	Directly applicable

CHECKMATE-064

CHECKMATE-064

Bibliographic Reference	Weber, Jeffrey S; Gibney, Geoff; Sullivan, Ryan J; Sosman, Jeffrey A; Slingluff, Craig L Jr; Lawrence, Donald P; Logan, Theodore F; Schuchter, Lynn M; Nair, Suresh; Fecher, Leslie; Buchbinder, Elizabeth I; Berghorn, Elmer; Ruisi, Mary; Kong, George; Jiang, Joel; Horak, Christine; Hodi, F Stephen; Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial.; The Lancet. Oncology; 2016; vol. 17 (no. 7); 943-955

Study details

Trial registration number and/or trial name	CheckMate 064 NCT01783938
Study type	Randomised controlled trial (RCT)

Study location	US
Study setting	Academic medical centres
Study dates	2013 - 2020
Sources of funding	Bristol-Myers Squibb
Inclusion criteria	Age at least 18 years of age Melanoma histologically confirmed unresectable stage III or stage IV melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 Know BRAF mutation status or consent to BRAFV600E mutation testing during the screening period Measurable disease by CT or MRI scan within 28 days prior to randomisation as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria Previously untreated or had progressed after no more than one previous systemic therapy Criteria for determining progression on previous systemic therapy were based on investigator-assessed radiographic imaging Suitable lesions available for biopsies at baseline and at week 13 (eg, assessment of PD-L1)
Exclusion criteria	Active brain metastases Previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies Active autoimmune disease Condition requiring corticosteroids or immunosuppressive medication

Intervention(s)	Nivolumab followed by ipilimumab
Comparator	Ipilimumab followed by nivolumab
Outcome measures	Overall survival
Subgroup analysis	Melanoma stage Overall survival by melanoma stage at study entry • M1a/M1b • M1c
Number of participants	140
Duration of follow-up	2 years
Loss to follow-up	Not reported
Additional comments	The time interval between drug sequences was 2 weeks for nivolumab followed by ipilimumab whereas it was 3 weeks for ipilimumab followed by nivolumab (dosing intervals were different for the two strategies because the agents have different frequencies of administration). After induction, all patients in both groups who completed the second induction period with the second immunotherapy agent and had clinical benefit were eligible to enter the continuation period and receive nivolumab 3 mg/kg every 2 weeks for up to 2 years or longer until progression, unacceptable toxicity, or withdrawal of consent.

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2 **Study arms**

Nivolumab followed by ipilimumab (N = 70) Nivolumab at 3 mg/kg as a 60-min intravenous infusion every 2 weeks for up to six doses during weeks 1 to 13 in the first induction period, followed by a planned switch to ipilimumab 3 mg/kg as a 90-min intravenous infusion every 3 weeks for up to four doses during weeks 13–25 in the second induction period

Duration of follow-up	Median follow-up in the nivolumab followed by ipilimumab group was 19.8 months (IQR 12.8–25.7)

Ipilimumab followed by nivolumab (N = 70)
Ipilimumab 3 mg/kg as a 90-min intravenous infusion every 3 weeks for up to four doses during weeks 1 to 13 in the first induction period, followed by a planned switch to nivolumab at 3 mg/kg as a 60-min intravenous infusion every 2 weeks for up to six doses during weeks 13–25 in the second induction period

Duration of follow-up	Median follow-up in the ipilimumab followed by nivolumab group was 14.7 months (5.6–23.9)

1 **Arm-level characteristics**

	Nivolumab followed by ipilimumab (N = 70)	**Ipilimumab followed by nivolumab (N = 70)**
% Female		
Sample Size	n = 22 ; % = 32	n = 24 ; % = 34
Mean age (SD)		
MedianIQR	60.5 (46.5 to 70)	63 (52 to 73)
AJCC stage at study entry		
III		
Sample Size	n = 6 ; % = 9	n = 12 ; % = 17
IV		
Sample Size	n = 62 ; % = 91	n = 58 ; % = 83
M stage		

	Nivolumab followed by ipilimumab (N = 70)	Ipilimumab followed by nivolumab (N = 70)
M0		
Sample Size	n = 0 ; % = 0	n = 3 ; % = 4
M1a		
Sample Size	n = 3 ; % = 4	n = 7 ; % = 10
M1b		
Sample Size	n = 14 ; % = 21	n = 8 ; % = 11
M1c		
Sample Size	n = 45 ; % = 66	n = 43 ; % = 61
Not reported		
Sample Size	n = 6 ; % = 9	n = 9 ; % = 13
BRAF status		
BRAFV600E mutant		
Sample Size	n = 19 ; % = 28	n = 20 ; % = 29
Wild type		
Sample Size	n = 44 ; % = 65	n = 43 ; % = 61
Not reported		

	Nivolumab followed by ipilimumab (N = 70)	Ipilimumab followed by nivolumab (N = 70)
Sample Size	n = 5 ; % = 7	n = 7 ; % = 10
History of brain metastases		
Yes		
Sample Size	n = 9 ; % = 13	n = 2 ; % = 3
No		
Sample Size	n = 53 ; % = 78	n = 60 ; % = 86
Not reported		
Sample Size	n = 6 ; % = 9	n = 8 ; % = 11
Any previous systemic therapy for metastatic disease		
Sample Size	n = 10 ; % = 15	n = 8 ; % = 11

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

Section	Question	Answer
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes

Section	Question	Answer
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Overall survival was an exploratory endpoint; per-protocol analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
	2.5. Did study participants adhere to the assigned intervention regimen?	No information
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(There was an imbalance between groups in patients who received subsequent anticancer therapy, which was possibly indicative of the difference between groups in survival)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes

Section	Question	Answer
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Overall survival was an exploratory endpoint; per-protocol analysis. There was an imbalance between groups in patients who received subsequent anticancer therapy, which was possibly indicative of the difference between groups in survival.)*
	Overall Directness	Directly applicable

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2 **CHECKMATE-066**

CHECKMATE-066

3

Bibliographic Reference	Robert, C.; Long, G.V.; Brady, B.; Dutriaux, C.; Di Giacomo, A.M.; Mortier, L.; Rutkowski, P.; Hassel, J.C.; McNeil, C.M.; Kalinka, E.A.; Lebbe, C.; Charles, J.; Hernberg, M.M.; Savage, K.J.; Chiarion-Sileni, V.; Mihalcioiu, C.; Mauch, C.; Arance, A.; Cognetti, F.; Ny, L.; Schmidt,

H.; Schadendorf, D.; Gogas, H.; Zoco, J.; Re, S.; Ascierto, P.A.; Atkinson, V.; Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2020; vol. 38 (no. 33); 3937-3946

Study details

Other publications associated with this study included in review	Ascierto, Paolo A, Long, Georgina V, Robert, Caroline et al. (2019) Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. JAMA oncology 5(2): 187-194 Long, G V, Atkinson, V, Ascierto, P A et al. (2016) Effect of nivolumab on health-related quality of life in patients with treatment-naive advanced melanoma: results from the phase III CheckMate 066 study. Annals of oncology : official journal of the European Society for Medical Oncology 27(10): 1940-6 Robert, Caroline, Long, Georgina V, Brady, Benjamin et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation. The New England journal of medicine 372(4): 320-30
Trial registration number and/or trial name	CheckMate 066 trial NCT01721772
Study type	Randomised controlled trial (RCT)
Study location	Argentina, Australia, Canada, Chile, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, Norway, Poland, Spain, Sweden,
Study setting	Multicentre
Study dates	2013 - 2020
Sources of funding	Bristol Myers Squibb
Inclusion criteria	Age

	at least 18 years Melanoma untreated, histologically confirmed, unresectable stage III or IV wild-type BRAF melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1
Exclusion criteria	Active brain metastases Uveal melanoma History of serious autoimmune disease
Intervention(s)	Nivolumab
Comparator	Dacarbazine
Outcome measures	All-cause mortality Progression free survival Investigator-assessed PFS defined as the time from randomisation to the date of the first documented progression, as determined by the investigator, or death due to any cause, whichever occurred first. Patients who died without progressing were considered to have progressed on the date of their death. Those who did not progress or die were censored on the date of their last evaluable tumor assessment. Patients who did not have any on-study tumor assessments and did not die were censored on their date of randomisation. Those who started any subsequent anticancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment prior to initiation of subsequent anticancer therapy. Overall survival defined as the time between the date of randomisation and the date of death. For those without documentation of death, OS was censored on the last date the participant was known to be alive. Health related quality of life EORTC QLQ-C30 and the EQ-5D 3L Serious adverse events

	a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalisation.
Subgroup analysis	Melanoma stage Overall survival was reported by melanoma stage at study entry • M0/M1A/M1B • M1C
Number of participants	418
Duration of follow-up	5 years
Loss to follow-up	None
Additional comments	Patients who had received adjuvant therapy previously were not excluded. A protocol amendment on July 9, 2014, after unmasking of the study and based on recommendations of the data monitoring committee, allowed patients who discontinued dacarbazine to cross over to receive nivolumab in an open-label extension phase, in which they were treated until progression or unacceptable toxic effects.

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2 **Study arms**

Nivolumab (N = 210) intravenous infusion 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks 3 mg/kg every 2 weeks plus placebo every 3 weeks

Dacarbazine (N = 208)
intravenous infusion 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks

1 **Arm-level characteristics**

	Nivolumab (N = 210)	Dacarbazine (N = 208)
% Female		
Sample Size	n = 89 ; % = 42.4	n = 83 ; % = 39.9
Mean age (SD)		
Custom value	Median 64 years (range 18 to 86)	Median 66 years (range 25 to 87)
M stage		
M0/M1a/M1b		
Sample Size	n = 82 ; % = 39	n = 81 ; % = 38.9
M1c		
Sample Size	n = 128 ; % = 61	n = 127 ; % = 61.1
History of brain metastases		
Yes		
Sample Size	n = 7 ; % = 3.3	n = 8 ; % = 3.8

	Nivolumab (N = 210)	Dacarbazine (N = 208)
No		
Sample Size	n = 203 ; % = 96.7	n = 200 ; % = 96.2
BRAF status		
Mutation		
Sample Size	n = 0	n = 0
No mutation		
Sample Size	n = 202 ; % = 96.2	n = 204 ; % = 98.1
Not reported		
Sample Size	n = 8 ; % = 3.8	n = 4 ; % = 1.9
Prior systemic therapy		
Adjuvant therapy		
Sample Size	n = 32 ; % = 15.2	n = 36 ; % = 17.3
Neoadjuvant therapy		
Sample Size	n = 1 ; % = 0.5	n = 1 ; % = 0.5

Risk of bias

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Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable

Section	Question	Answer
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Trial started as double-blind but on the basis of recommendation of the data safety monitoring committee, a protocol amendment was done in 2014 that allowed dacarbazine-treated patients to cross over to receive on-study open-label nivolumab until progression or unacceptable toxicity.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no

Section	Question	Answer
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Some of the participants who discontinued study treatment received subsequent therapy (more than one type of subsequent therapy may have received, including radiotherapy, surgery or systemic therapy): nivolumab arm (59%) and dacarbazine arm (74%).)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Trial started as double-blind but on the basis of recommendation of the data safety monitoring committee, a protocol amendment was done in 2014 that allowed dacarbazine-treated patients to cross over to receive on-study open-label nivolumab until progression or unacceptable toxicity. Some of the participants who discontinued study treatment received subsequent therapy (more than one type of subsequent therapy may have received, including radiotherapy, surgery or systemic therapy): nivolumab arm (59%) and dacarbazine arm (74%).)*
	Overall Directness	Directly applicable

1 **CHECKMATE-067**

CHECKMATE-067

2

Bibliographic Reference	Larkin, James; Chiarion-Sileni, Vanna; Gonzalez, Rene; Grob, Jean-Jacques; Rutkowski, Piotr; Lao, Christopher D; Cowey, C Lance; Schadendorf, Dirk; Wagstaff, John; Dummer, Reinhard; Ferrucci, Pier F; Smylie, Michael; Hogg, David; Hill, Andrew; Marquez-Rodas, Ivan; Haanen, John; Guidoboni, Massimo; Maio, Michele; Schoffski, Patrick; Carlino, Matteo S; Lebbe, Celeste; McArthur, Grant; Ascierto, Paolo A; Daniels, Gregory A; Long, Georgina V; Bastholt, Lars; Rizzo, Jasmine I; Balogh, Agnes; Moshyk, Andriy; Hodi, F Stephen; Wolchok, Jedd D; Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.; The New England journal of medicine; 2019; vol. 381 (no. 16); 1535-1546

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Study details

Other publications associated with this study included in review	Hodi, Frank Stephen, Chiarion-Sileni, Vanna, Gonzalez, Rene et al. (2018) Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. The Lancet. Oncology 19(11): 1480-1492 Larkin, James, Chiarion-Sileni, Vanna, Gonzalez, Rene et al. (2015) Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine 373(1): 23-34 Schadendorf, Dirk, Larkin, James, Wolchok, Jedd et al. (2017) Health-related quality of life results from the phase III CheckMate 067 study. European journal of cancer (Oxford, England : 1990) 82: 80-91 Wolchok, Jedd D, Chiarion-Sileni, Vanna, Gonzalez, Rene et al. (2017) Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. The New England journal of medicine 377(14): 1345-1356
Trial registration number and/or trial name	CheckMate 067 trial NCT01844505
Study type	Randomised controlled trial (RCT)
Study location	Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Spain, Sweden, Switzerland, UK, US
Study setting	Multicentre
Study dates	2013 - 2018
Sources of funding	This study was funded by Bristol-Myers Squibb (Princeton, NJ, USA).
Inclusion criteria	Age 18 years or older

	Melanoma histologically confirmed, unresectable stage III or stage IV metastatic melanoma No prior systemic therapy for advanced disease Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 Know BRAF mutation status (WT or M) Measurable disease by CT or MRI scan in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Sufficient tumour tissue available for biomarker analyses assessment of PD-L1 expression
Exclusion criteria	Active brain metastases Pregnancy or breastfeeding Leptomeningeal metastases Ocular melanoma mucosal melanoma was allowed Active autoimmune disease Condition requiring corticosteroids or immunosuppressive medication within 14 days of study drug administration
Intervention(s)	Nivolumab plus ipilimumab
Comparator	Nivolumab plus ipilimumab-matched placebo Ipilimumab plus nivolumab-matched placebo
Outcome measures	Progression free survival

	defined as time from randomisation to progression or death from any cause, whichever occurred first Overall survival defined as time from randomisation to death from any cause Health related quality of life HRQoL was collected, as available, in all randomised patients and assessed at weeks 1 and 5 of each 6-week cycle for the first 6 months and then once every 6 weeks thereafter as well as at two visits in the follow-up period. Secondary end-point assessment was European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire Version 3; European Quality of Life-5 Dimensions (EQ-5D) Summary Index and Visual Analogue Scale (VAS). Serious adverse events
Subgroup analysis	Melanoma stage Progression free survival and overall survival at 5 years follow-up were reported by melanoma stage • M0/M1a/M1b • M1c
Number of participants	945
Duration of follow-up	5 years
Loss to follow-up	
Additional comments	Previous adjuvant or neoadjuvant treatment for melanoma was allowed if it was completed at least 6 weeks before randomisation, and all treatment-related adverse events had either returned to baseline or had stabilised.

Study arms

Nivolumab plus ipilimumab (N = 314) intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses (induction phase), then nivolumab 3 mg/kg every 2 weeks

Duration of follow-up	Median follow-up was 54.6 months
Loss to follow-up	None

Nivolumab plus ipilimumab-matched placebo (N = 316)
intravenous nivolumab 3 mg/kg every 2 weeks plus ipilimumab-matched placebo

Duration of follow-up	Median follow-up was 36.0 months
Loss to follow-up	1

Ipilimumab plus nivolumab-matched placebo (N = 315)
intravenous ipilimumab 3 mg/kg every 3 weeks for four doses plus nivolumab-matched placebo

Duration of follow-up	Median follow-up was 18.6 months
Loss to follow-up	None

1 **Arm-level characteristics**

	Nivolumab plus ipilimumab (N = 314)	**Nivolumab plus ipilimumab-matched placebo (N = 316)**	**Ipilimumab plus nivolumab-matched placebo (N = 315)**
% Female			
Sample Size	n = 108 ; % = 34	n = 114 ; % = 36	n = 113 ; % = 36
Mean age (SD)			
Custom value	Median 61 years (range 18 to 88)	Median 60 years (range 25 to 90)	Median 62 years (range 18 to 89)

	Nivolumab plus ipilimumab (N = 314)	Nivolumab plus ipilimumab-matched placebo (N = 316)	Ipilimumab plus nivolumab-matched placebo (N = 315)
M stage			
M1c			
Sample Size	n = 181 ; % = 58	n = 184 ; % = 58	n = 183 ; % = 58
M0, M1a, or M1b			
Sample Size	n = 133 ; % = 42	n = 132 ; % = 42	n = 132 ; % = 42
Brain metastases at baseline			
Yes			
Sample Size	n = 11 ; % = 4	n = 7 ; % = 2	n = 15 ; % = 5
No			
Sample Size	n = 303 ; % = 97	n = 309 ; % = 98	n = 300 ; % = 95
BRAF status			
Mutant			
Sample Size	n = 101 ; % = 32	n = 100 ; % = 32	n = 97 ; % = 31
Wild-type			
Sample Size	n = 213 ; % = 68	n = 216 ; % = 68	n = 218 ; % = 69

	Nivolumab plus ipilimumab (N = 314)	Nivolumab plus ipilimumab-matched placebo (N = 316)	Ipilimumab plus nivolumab-matched placebo (N = 315)
Sum of reference diameters of target lesions (mm)			
Custom value	Median 54.5 (range 10 to 372)	Median 54.0 (range 10 to 384)	Median 55.0 (range 10 to 283)
Number of lesion sites			
one			
Sample Size	n = 89 ; % = 28	n = 80 ; % = 25	n = 84 ; % = 27
2-3			
Sample Size	n = 165 ; % = 53	n = 176 ; % = 56	n = 170 ; % = 54
≥3			
Sample Size	n = 60 ; % = 19	n = 59 ; % = 19	n = 61 ; % = 19

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

Section	Question	Answer
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable

Section	Question	Answer
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
	Overall Directness	Directly applicable

1 **CHECKMATE-069**

CHECKMATE-069

2

Bibliographic Reference	Hodi, F Stephen; Chesney, Jason; Pavlick, Anna C; Robert, Caroline; Grossmann, Kenneth F; McDermott, David F; Linette, Gerald P; Meyer, Nicolas; Giguere, Jeffrey K; Agarwala, Sanjiv S; Shaheen, Montaser; Ernstoff, Marc S; Minor, David R; Salama, April K; Taylor, Matthew H; Ott, Patrick A; Horak, Christine; Gagnier, Paul; Jiang, Joel; Wolchok, Jedd D; Postow, Michael A; Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial.; The Lancet. Oncology; 2016; vol. 17 (no. 11); 1558-1568

3

4

5 **Study details**

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Postow, Michael A, Chesney, Jason, Pavlick, Anna C et al. (2015) Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. The New England journal of medicine 372(21): 2006-17

Trial registration number and/or trial name	CheckMate 069 trial NCT01927419
Study type	Randomised controlled trial (RCT)
Study location	France, US
Study setting	Multicentre
Study dates	2013 - 2016
Sources of funding	Bristol-Myers Squibb
Inclusion criteria	Age 18 years or older Melanoma histologically confirmed, unresectable stage III or stage IV metastatic melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 Measurable disease by CT or MRI scan per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) criteria Sufficient tumour tissue available for biomarker analyses assessment of PD-L1 Treatment naive Known BRAFV600 mutation status
Exclusion criteria	Active brain metastases Leptomeningeal metastases

	Ocular melanoma
Intervention(s)	Nivolumab plus ipilimumab
Comparator	Ipilimumab
Outcome measures	All-cause mortality Progression free survival defined as the time between the date of randomization and the first date of documented progression, as assessed by the investigator, or death due to any cause, whichever occurs first Overall survival Serious adverse events Time to second treatment
Number of participants	142
Duration of follow-up	2 years
Loss to follow-up	Not reported
Additional comments	Patients with mucosal melanoma were allowed to enroll. Prior adjuvant or neoadjuvant treatment for melanoma was permitted (if completed at least 6 weeks prior to the date of first dose), and all related adverse events either returned to baseline or stabilized.

1

2 **Study arms**

Nivolumab plus ipilimumab (N = 95)

In the combination group, nivolumab was administered intravenously at a dose of 1 mg/kg over a period of 60 minutes, once every 3 weeks for four doses. Thirty minutes after the completion of each nivolumab infusion, patients received ipilimumab at 3 mg/kg over a period of 90 minutes. After the fourth dose of both agents (induction phase), ipilimumab was discontinued and nivolumab was then administered as a single agent at 3 mg/kg over a period of 60 minutes, once every 2 weeks (maintenance phase).

Loss to follow-up	

Ipilimumab (N = 47)
In the ipilimumab alone group, the same dosing schedule was used, except that nivolumab was replaced with matched placebo during both the combination and maintenance portions of the trial.

1 **Arm-level characteristics**

	Nivolumab plus ipilimumab (N = 95)	**Ipilimumab (N = 47)**
% Female		
Sample Size	n = 32 ; % = 33.7	n = 15 ; % = 31.9
Mean age (SD)		
Custom value	Median 64 years (range 27 to 87)	Median 67 years (range 31 to 80)
AJCC stage at study entry		
Stage III		
Sample Size	n = 10 ; % = 10.5	n = 9 ; % = 19.1
Stage IV		
Sample Size	n = 85 ; % = 89.5	n = 38 ; % = 80.9

	Nivolumab plus ipilimumab (N = 95)	Ipilimumab (N = 47)
Metastasis stage at study entry		
M0		
Sample Size	n = 8 ; % = 8.4	n = 5 ; % = 10.6
M1a		
Sample Size	n = 15 ; % = 15.8	n = 8 ; % = 17
M1b		
Sample Size	n = 27 ; % = 28.4	n = 12 ; % = 25.5
M1c		
Sample Size	n = 44 ; % = 46.3	n = 21 ; % = 44.7
Not reported		
Sample Size	n = 1 ; % = 1.1	n = 1 ; % = 2.1
History of brain metastases		
Yes		
Sample Size	n = 4 ; % = 4.2	n = 0
No		

	Nivolumab plus ipilimumab (N = 95)	Ipilimumab (N = 47)
Sample Size	n = 90 ; % = 94.7	n = 47 ; % = 100
BRAF V600 Mutation		
Sample Size	n = 23 ; % = 24.2	n = 10 ; % = 21.3

1 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable

Section	Question	Answer
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

COLUMBUS

COLUMBUS trial

Bibliographic Reference	Ascierto, Paolo A; Dummer, Reinhard; Gogas, Helen J; Flaherty, Keith T; Arance, Ana; Mandala, Mario; Liszkay, Gabriella; Garbe, Claus; Schadendorf, Dirk; Krajsova, Ivana; Gutzmer, Ralf; de Groot, Jan Willem B; Loquai, Carmen; Gollerkeri, Ashwin; Pickard, Michael D; Robert, Caroline; Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma.; European journal of cancer (Oxford, England : 1990); 2020; vol. 126; 33-44

1 **Study details**

Other publications associated with this study included in review	Dummer, Reinhard, Ascierto, Paolo A, Gogas, Helen J et al. (2018) Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. The Lancet. Oncology 19(10): 1315-1327 Dummer, Reinhard, Ascierto, Paolo A, Gogas, Helen J et al. (2018) Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. The Lancet. Oncology 19(5): 603-615
Trial registration number and/or trial name	COLUMBUS trial NCT01909453
Study type	Randomised controlled trial (RCT)
Study location	Argentina, Australia, Brazil, Canada, Colombia, Czechia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Mexico, Netherlands, Norway, Poland, Portugal, Russian Federation, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Turkey, UK, US
Study setting	Multicentre
Study dates	2013 - 2018
Sources of funding	This study was sponsored by Pfizer Inc. (formerly Array BioPharma, Inc).
Inclusion criteria	Age at least 18 years of age Melanoma histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma classified as American Joint Committee on Cancer (AJCC) stage IIIB, IIIC or IV Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 $BRAFV^{600}$ mutation-positive tumour

	BRAF V600E or BRAF V600K mutation or both in tumour tissue as ascertained by central genetic mutation analysis with the bioMerieux THxID BRAF diagnostic test before enrolment Treatment naive or had progressed on or after previous first-line immunotherapy Adequate bone marrow Adequate organ function Adequate laboratory parameters At least one measurable lesion in accordance with guidelines based on Response Evaluation Criteria in Solid Tumors
Exclusion criteria	Leptomeningeal metastases Untreated central nervous system lesions Uveal melanoma Mucosal melanoma Gilbert syndrome History, current evidence or risk of retinal vein occlusion Previous BRAF inhibitor treatment Previous MEK inhibitor treatment Previous use of systemic chemotherapy Extensive radiotherapy An investigational agent other than previous immunotherapy for locally advanced, unresectable or metastatic melanoma
Intervention(s)	Encorafenib plus binimetinib
Comparator	Encorafenib

	Vemurafenib
Outcome measures	Progression free survival defined as the time from randomisation to first documented progression or death from any cause (whichever occurred first) Overall survival time from randomisation to death from any cause
Subgroup analysis	Melanoma stage Overall survival and progression free survival reported by tumour stage • IIIb, IIIc, IVM1a or IVM1b • IVM1c
Number of participants	577
Duration of follow-up	Median follow-up for overall survival was 48.8 months Median follow-up for progression free survival was 16.6 months
Loss to follow-up	Lost to follow-up was reported combined with protocol violation and new therapy for study indication

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2 **Study arms**

Encorafenib plus binimetinib (N = 192) encorafenib 450 mg once a day plus binimetinib 45 mg twice daily	
Loss to follow-up	2 (1.0%) which included lost to follow-up, protocol violation and new therapy for study indication
Encorafenib (N = 194)	

encorafenib 300 mg once a day	
Loss to follow-up	1 (0.5%) which included lost to follow-up, protocol violation and new therapy for study indication
Vemurafenib (N = 191) vemurafenib 960 mg twice daily	
Duration of follow-up	
Loss to follow-up	1 (0.5%) which included lost to follow-up, protocol violation and new therapy for study indication

1 **Arm-level characteristics**

	Encorafenib plus binimetinib (N = 192)	**Encorafenib (N = 194)**	**Vemurafenib (N = 191)**
% Female			
Sample Size	n = 77 ; % = 40	n = 86 ; % = 44	n = 80 ; % = 42
Mean age (SD)			
Mean/SD	56 (14)	55 (13)	55 (14)
BRAF mutation status			
BRAFV600E			
Sample Size	n = 170 ; % = 89	n = 173 ; % = 89	n = 168 ; % = 88
BRAFV600K			
Sample Size	n = 22 ; % = 11	n = 19 ; % = 10	n = 23 ; % = 12

	Encorafenib plus binimetinib (N = 192)	Encorafenib (N = 194)	Vemurafenib (N = 191)
AJCC tumour stage at study entry			
IIIB/IIIC			
Sample Size	n = 9 ; % = 5	n = 6 ; % = 3	n = 11 ; % = 6
IVM1a			
Sample Size	n = 26 ; % = 14	n = 29 ; % = 15	n = 24 ; % = 13
IVM1b			
Sample Size	n = 34 ; % = 18	n = 39 ; % = 20	n = 31 ; % = 16
IVM1c			
Sample Size	n = 123 ; % = 64	n = 120 ; % = 62	n = 125 ; % = 65
Number of organs involved			
one			
Sample Size	n = 47 ; % = 24	n = 56 ; % = 29	n = 45 ; % = 24
two			
Sample Size	n = 58 ; % = 30	n = 52 ; % = 27	n = 59 ; % = 31
≥3			

	Encorafenib plus binimetinib (N = 192)	Encorafenib (N = 194)	Vemurafenib (N = 191)
Sample Size	n = 87 ; % = 45	n = 86 ; % = 44	n = 87 ; % = 46
Previous immunotherapy			
Sample Size	n = 57 ; % = 30	n = 58 ; % = 30	n = 57 ; % = 30
Ipilimumab			
Sample Size	n = 7 ; % = 4	n = 10 ; % = 5	n = 7 ; % = 4
Ipilimumab adjuvant			
Sample Size	n = 2 ; % = 1	n = 1 ; % = 1	n = 2 ; % = 1
Ipilimumab advance or metastatic			
Sample Size	n = 5 ; % = 3	n = 9 ; % = 5	n = 5 ; % = 3

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes

Section	Question	Answer
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1

1 **COMBI-D**

COMBI-D trial

2

Bibliographic Reference	Long, Georgina V; Stroyakovskiy, Daniil; Gogas, Helen; Levchenko, Evgeny; de Braud, Filippo; Larkin, James; Garbe, Claus; Jouary, Thomas; Hauschild, Axel; Grob, Jean-Jacques; Chiarion-Sileni, Vanna; Lebbe, Celeste; Mandala, Mario; Millward, Michael; Arance, Ana; Bondarenko, Igor; Haanen, John B A G; Hansson, Johan; Utikal, Jochen; Ferraresi, Virginia; Kovalenko, Nadezhda; Mohr, Peter; Probachai, Volodymr; Schadendorf, Dirk; Nathan, Paul; Robert, Caroline; Ribas, Antoni; DeMarini, Douglas J; Irani, Jhangir G; Swann, Suzanne; Legos, Jeffrey J; Jin, Fan; Mookerjee, Bijoyesh; Flaherty, Keith; Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial.; Lancet (London, England); 2015; vol. 386 (no. 9992); 444-51

3 **Study details**

Other publications associated with this study included in review	Long, Georgina V, Stroyakovskiy, Daniil, Gogas, Helen et al. (2014) Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. The New England journal of medicine 371(20): 1877-88 Long, G. V., Grob, J. J., Nathan, P., Ribas, A., Robert, C., Schadendorf, D., ... & Davies, M. A. (2016). Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. The lancet oncology, 17(12), 1743-1754 Menzies, A. M., Ashworth, M. T., Swann, S., Kefford, R. F., Flaherty, K., Weber, J., ... & Daud, A. (2015). Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. Annals of Oncology, 26(2), 415-421 Robert, C., Grob, J. J., Stroyakovskiy, D., Karaszewska, B., Hauschild, A., Levchenko, E., ... & Long, G. V. (2019). Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. New England Journal of Medicine, 381(7), 626-636 Schadendorf, Dirk, Amonkar, Mayur M, Stroyakovskiy, Daniil et al. (2015) Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. European journal of cancer (Oxford, England: 1990) 51(7): 833-40 Schadendorf, D., Robert, C., Dummer, R., Flaherty, K. T., Tawbi, H. A., Menzies, A. M., ... & Long, G. V. (2021). Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in BRAF-mutant cancers. European Journal of Cancer, 153, 234-241 Syeda, M. M., Wiggins, J. M., Corless, B. C., Long, G. V., Flaherty, K. T., Schadendorf, D., ... & Polsky, D. (2021). Circulating tumour DNA in patients with advanced melanoma treated with dabrafenib or dabrafenib plus trametinib: a clinical validation study. The Lancet Oncology, 22(3), 370-380

Trial registration number and/or trial name	COMBI-d NCT01584648
Study type	Randomised controlled trial (RCT)
Study location	Argentina, Australia, Canada, France, Germany, Greece, Italy, Netherlands, Russian Federation, Spain, Sweden, Ukraine, UK, US
Study setting	Multicentre
Study dates	2012 - 2015
Sources of funding	This study was funded by GlaxoSmithKline
Inclusion criteria	Age at least 18 years old Melanoma histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF Val600Glu or Val600Lys mutations, as determined by PCR (ThxID BRAF Assay, bioMérieux) done at a central reference laboratory *Patients with brain metastases were eligible if they had been definitively treated and stable for at least 12 weeks*
Exclusion criteria	Previous systemic treatment for advanced or metastatic cancer
Intervention(s)	Dabrafenib and trametinib
Comparator	Dabrafenib and placebo
Outcome measures	All-cause mortality Progression free survival investigator-assessed progression-free survival, defined as the time from randomisation until progression or death of any cause Overall survival

	defined as the time from randomisation to death of any cause Health related quality of life Using the European Organisation for Research and Treatment of Cancer QOL Questionnaire-C30 (EORTC-QLQ-C30) Serious adverse events
Subgroup analysis	Melanoma stage Overall survival and progression free survival was reported by melanoma stage • IIIc, IVM1a, or IVM1b • IVM1c
Number of participants	423
Duration of follow-up	32 months

1

2 **Study arms**

Dabrafenib and trametinib (N = 211)
Oral dabrafenib (150 mg twice daily) and oral trametinib (2 mg once daily)

Loss to follow-up	0

Dabrafenib and placebo (N = 212)
Oral dabrafenib (150 mg twice daily) and placebo

Loss to follow-up	1

3 **Arm-level characteristics**

	Dabrafenib and trametinib (N = 211)	Dabrafenib and placebo (N = 212)
% Female		
Sample Size	n = 100 ; % = 47	n = 98 ; % = 46
Mean age (SD)		
Custom value	Median 55.0 years (range 22 to 89)	Median 56.5 years (range 22 to 86)
Previous immunotherapy		
Sample Size	n = 57 ; % = 27	n = 61 ; % = 29
Val600E		
Sample Size	n = 179 ; % = 85	n = 181 ; % = 85
Val600K		
Sample Size	n = 32 ; % = 15	n = 30 ; % = 14
IVM1c		
Sample Size	n = 142 ; % = 67	n = 138 ; % = 65
IIIc, IVM1a, or IVM1b		
Sample Size	n = 69 ; % = 33	n = 73 ; % = 34
M0		
Sample Size	n = 5 ; % = 2	n = 10 ; % = 5
M1a		

	Dabrafenib and trametinib (N = 211)	Dabrafenib and placebo (N = 212)
Sample Size	n = 19 ; % = 9	n = 31 ; % = 15
M1b		
Sample Size	n = 45 ; % = 21	n = 32 ; % = 15
M1c		
Sample Size	n = 142 ; % = 67	n = 138 ; % = 65
≤2		
Sample Size	n = 109 ; % = 52	n = 119 ; % = 56
≥3		
Sample Size	n = 101 ; % = 48	n = 92 ; % = 44

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3 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
	Overall Directness	Directly applicable

1 **COMBI-V**

COMBI-V

2

Bibliographic Reference	Robert, C., Grob, J. J., Stroyakovskiy, D., Karaszewska, B., Hauschild, A., Levchenko, E., ... & Long, G. V. (2019). Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. New England Journal of Medicine, 381(7), 626-636

3

4

5 **Study details**

Other publications associated with this study included in review	Grob, Jean Jacques, Amonkar, Mayur M, Karaszewska, Boguslawa et al. (2015) Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. The Lancet. Oncology 16(13): 1389-98 Robert, Caroline; Karaszewska, Boguslawa; Schachter, Jacob; Rutkowski, Piotr; Mackiewicz, Andrzej; Stroiakovski, Daniil; Lichinitser, Michael; Dummer, Reinhard; Grange, Florent; Mortier, Laurent; Chiarion-Sileni, Vanna; Drucis, Kamil; Krajsova, Ivana; Hauschild, Axel; Lorigan, Paul; Wolter, Pascal; Long, Georgina V; Flaherty, Keith; Nathan, Paul; Ribas, Antoni; Martin, Anne-Marie; Sun, Peng; Crist, Wendy; Legos, Jeff; Rubin, Stephen D; Little, Shonda M; Schadendorf, Dirk; Improved overall survival in melanoma with combined dabrafenib and trametinib.; The New England journal of medicine; 2015; vol. 372 (no. 1); 30-9
Trial registration number and/or trial name	COMBI-v NCT01597908

Study type	Randomised controlled trial (RCT)
Study location	Argentina, Australia, Austria, Belgium, Brazil, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Korea, Netherlands, New Zealand, Norway, Poland, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Ukraine, UK, US
Study setting	Multicentre
Study dates	2012 - 2019
Sources of funding	GlaxoSmithKline
Inclusion criteria	Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and higher numbers reflecting greater disability) BRAFV^{600} mutation-positive tumour The presence of BRAF V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux). Measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 Undergone treatment for brain metastases with no increase in lesion size for at least 12 weeks
Exclusion criteria	History or evidence of cardiovascular risk including any of the following: • QTcB ≥480 ms • History or evidence of current clinically significant uncontrolled arrhythmia, with the exception that patients with controlled atrial fibrillation for >30 days prior to randomization were eligible • History of (within 6 months prior to randomization) of acute coronary syndromes (including myocardial infarction and unstable angina) or coronary angioplasty • History or evidence of current ≥ class II congestive heart failure as defined by the New York Heart Association • Treatment-refractory hypertension defined as a blood pressure of systolic >140 mm Hg and/or diastolic >90 mm Hg that cannot be controlled by antihypertensive therapy

	• Intracardiac defibrillators or permanent pacemakers • Known cardiac metastases • Abnormal cardiac valve morphology (≥ grade 2) documented by ECG (patients with grade 1 abnormalities [i.e., mild regurgitation/stenosis] were permitted to enroll). Patients with moderate valvular thickening were excluded
Intervention(s)	Dabrafenib plus trametinib
Comparator	Vemurafenib
Outcome measures	Progression free survival defined as time from randomisation until radiologic disease progression or death due to any cause Overall survival defined as the time from randomisation until death from any cause Health related quality of life HRQoL was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30), the EuroQoL-5D (EQ-5D), and the Melanoma Subscale of the Functional Assessment of Cancer Therapy—Melanoma (FACT-M) questionnaire Time on treatment Reported as median
Subgroup analysis	Melanoma stage Overall survival and progression free survival were reported by tumour stage • IIIc, IVM1a, IVM1b • IVM1c
Number of participants	704
Duration of follow-up	12 months

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2 **Study arms**

Dabrafenib plus trametinib (N = 352) dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily)	
Loss to follow-up	4
Vemurafenib (N = 352) vemurafenib (960 mg orally twice daily)	
Loss to follow-up	9

3 **Arm-level characteristics**

	Dabrafenib plus trametinib (N = 352)	**Vemurafenib (N = 352)**
% Female		
Sample Size	n = 144 ; % = 41	n = 172 ; % = 49
Mean age (SD)		
Custom value	Median 55 years (range 18 to 91)	Median 54 years (range 18 to 88)
Tumor stage at screening		
IVM1c		
Sample Size	n = 221 ; % = 63	n = 208 ; % = 59

	Dabrafenib plus trametinib (N = 352)	Vemurafenib (N = 352)
IIIc, IVM1a, or IVM1b		
Sample Size	n = 130 ; % = 37	n = 143 ; % = 41
Metastasis stage at screening		
M0		
Sample Size	n = 14 ; % = 4	n = 26 ; % = 7
M1a		
Sample Size	n = 55 ; % = 16	n = 50 ; % = 14
M1b		
Sample Size	n = 61 ; % = 17	n = 67 ; % = 19
M1c		
Sample Size	n = 221 ; % = 63	n = 208 ; % = 59
BRAF mutation		
V600E		
Sample Size	n = 312 ; % = 90	n = 317 ; % = 90
V600K		

	Dabrafenib plus trametinib (N = 352)	Vemurafenib (N = 352)
Sample Size	n = 34 ; % = 10	n = 34 ; % = 10
Previous immunotherapy		
Sample Size	n = 61 ; % = 17	n = 93 ; % = 26
Number of disease sites at baseline		
Fewer than 3		
Sample Size	n = 177 ; % = 50	n = 201 ; % = 57
3 or more		
Sample Size	n = 174 ; % = 50	n = 151 ; % = 43

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable

Section	Question	Answer
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably no
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Probably no
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(After progression, more patients in the vemurafenib group received subsequent anticancer therapy than in the combination-therapy group (43% vs. 20%).The most common post-progression therapy in the two groups was ipilimumab, which is known to prolong survival in patients with metastatic melanoma. Median duration of exposure to vemurafenib was 4 months shorter than that for the combination therapy; this might partly explain why*

Section	Question	Answer
		more patients in the vemurafenib group received post-progression therapy at this point. However, with more patients in the vemurafenib group having received a therapy that is known to affect overall survival, there is no evidence that differences in post-progression therapy contributed to the survival benefit seen in the combination-therapy group.)
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no

Section	Question	Answer
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(After progression, more patients in the vemurafenib group received subsequent anticancer therapy than in the combination-therapy group (43% vs. 20%). The most common post-progression therapy in the two groups was ipilimumab, which is known to prolong survival in patients with metastatic melanoma. Median duration of exposure to vemurafenib was 4 months shorter than that for the combination therapy; this might partly explain why more patients in the vemurafenib group received post-progression therapy at this point. However, with more patients in the vemurafenib group having received a therapy that is known to affect overall survival, there is no evidence that differences in post-progression therapy contributed to the survival benefit seen in the combination-therapy group.)*
	Overall Directness	Directly applicable

1 **KEYNOTE-002**

KEYNOTE-002

2

Bibliographic Reference	Hamid, Omid; Puzanov, Igor; Dummer, Reinhard; Schachter, Jacob; Daud, Adil; Schadendorf, Dirk; Blank, Christian; Cranmer, Lee D; Robert, Caroline; Pavlick, Anna C; Gonzalez, Rene; Hodi, F Stephen; Ascierto, Paolo A; Salama, April K S; Margolin, Kim A; Gangadhar, Tara C; Wei, Ziwen; Ebbinghaus, Scot; Ibrahim, Nageatte; Ribas, Antoni; Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma.; European journal of cancer (Oxford, England : 1990); 2017; vol. 86; 37-45

3 **Study details**

Other publications associated with this study included in review	Robert, C., Hwu, W. J., Hamid, O., Ribas, A., Weber, J. S., Daud, A. I., ... & Joshua, A. M. (2021). Long-term safety of pembrolizumab monotherapy and relationship with clinical outcome: A landmark analysis in patients with advanced melanoma. European Journal of Cancer, 144, 182-191

	Ribas, Antoni, Puzanov, Igor, Dummer, Reinhard et al. (2015) Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. The Lancet. Oncology 16(8): 908-18 Schadendorf, Dirk, Dummer, Reinhard, Hauschild, Axel et al. (2016) Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma. European journal of cancer (Oxford, England: 1990) 67: 46-54
Trial registration number and/or trial name	KEYNOTE-002 trial NCT01704287
Study type	Randomised controlled trial (RCT)
Study location	Argentine, Australia, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, US
Study setting	Multicentre
Study dates	2012 - 2019
Sources of funding	Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
Inclusion criteria	Age • 18 years or older Melanoma • histologically or cytologically confirmed unresectable stage III or stage IV melanoma not amenable to local therapy Eastern Cooperative Oncology Group performance status (ECOG PS) • 0 or 1 Measurable disease

	• per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) Previous BRAF inhibitor therapy or MEK inhibitor therapy or both (if BRAFV600 mutant-positive) Confirmed disease progression • within 24 weeks of the last ipilimumab dose (minimum two doses, 3 mg/kg once every 3 weeks) Resolution or improvement of ipilimumab-related adverse events to grade 0–1 Prednisone dose 10 mg/day or less for at least 2 weeks before the first dose of study drug Values within the prespecified range for absolute neutrophil count (≥1500 cells per mL), platelets (≥100 000 cells per mL), haemoglobin (≥90 g/L), serum creatinine (≤1·5 upper limit of normal [ULN]), serum total bilirubin (≤1·5 ULN or direct bilirubin ≤ULN for patients with total bilirubin concentrations >1·5 ULN), aspartate and alanine aminotransferases (≤2·5 ULN or ≤5 ULN for patients with liver metastases), international normalised ratio or prothrombin time (≤1·5 ULN if not using anticoagulants), and activated partial thromboplastin time (≤1·5 ULN if not using anticoagulants)
Exclusion criteria	Active brain metastases or carcinomatous meningitis Active autoimmune disease Active infection requiring systemic therapy Known history of HIV infection Active hepatitis B virus or hepatitis C virus infection History of grade 4 ipilimumab-related adverse events or grade 3 ipilimumab-related adverse events lasting longer than 12 weeks Previous treatment with any other anti-PD-1 or anti-PD-L1 therapy

Intervention(s)	Pembrolizumab 2mg/kg Pembrolizumab 10mg/kg
Comparator	Chemotherapy
Outcome measures	Progression free survival time from randomisation to first documented disease progression per RECIST v1.1 by independent central review or death from any cause, whichever occurred first. Overall survival time from randomisation to death from any cause. Health related quality of life European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 instrument (QLQ-C30) Serious adverse events †Results in death; or †is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or †results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or †results in or prolongs an existing inpatient hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or †is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis); or is a new cancer; (that is not a condition of the study) or is an overdose (Whether accidental or intentional). Other important medical events that may not result in death, not be life threatening, or not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Number of participants	540
Duration of follow-up	Median follow-up 28 months (range 24.1 to 35.5)
Loss to follow-up	Not reported

Additional comments	Patients had a washout period of at least 4 weeks between the last dose of the most recent therapy and the first dose of pembrolizumab. Patients in the chemotherapy group with documented and verified disease progression at or after week 12 who met the relevant eligibility criteria could cross over to receive pembrolizumab after a washout period of at least 28 days from the last dose of chemotherapy; patients who crossed over were randomly assigned to one of the two pembrolizumab doses in a double-blind manner.

1 **Study arms**

Pembrolizumab 2mg/kg (N = 180) Pembrolizumab 2 mg/kg intravenously every 3 weeks
Pembrolizumab 10mg/kg (N = 181) Pembrolizumab 10 mg/kg intravenously every 3 weeks
Chemotherapy (N = 179) Investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin [eliminated with protocol amendment one], dacarbazine, or oral temozolomide)

2 **Arm-level characteristics**

	Pembrolizumab 2mg/kg (N = 180)	**Pembrolizumab 10mg/kg (N = 181)**	**Chemotherapy (N = 179)**
% Female			
Sample Size	n = 76 ; % = 42	n = 72 ; % = 40	n = 65 ; % = 36
Mean age (SD)			

	Pembrolizumab 2mg/kg (N = 180)	Pembrolizumab 10mg/kg (N = 181)	Chemotherapy (N = 179)
Custom value	Median 62 years (range 15 to 87)	Median 60 years (range 27 to 89)	Median 63 years (range 27 to 87)
BRAFV600 status			
Mutant			
Sample Size	n = 44 ; % = 24.4	n = 40 ; % = 22.1	n = 42 ; % = 23.5
Wild type			
Sample Size	n = 136 ; % = 75.6	n = 141 ; % = 77.9	n = 137 ; % = 76.5
Tumour size			
Custom value	Median 99.4 mm (range 10 to 428)	Median 98.6 mm (range 12 to 560)	Median 101.3 mm (range 11 to 568)
Metastatic stage			
M0			
Sample Size	n = 2 ; % = 1.1	n = 2 ; % = 1.1	n = 2 ; % = 1.1
M1a			
Sample Size	n = 8 ; % = 4.4	n = 13 ; % = 7.2	n = 15 ; % = 8.4
M1b			

	Pembrolizumab 2mg/kg (N = 180)	Pembrolizumab 10mg/kg (N = 181)	Chemotherapy (N = 179)
Sample Size	n = 22 ; % = 12.2	n = 17 ; % = 9.4	n = 15 ; % = 8.4
M1c			
Sample Size	n = 148 ; % = 82.2	n = 149 ; % = 82.3	n = 147 ; % = 82.1
Number of lines of previous systemic therapies			
None Patients with no previous systemic therapies received neoadjuvant or adjuvant therapy only			
Sample Size	n = 1 ; % = 0.6	n = 0	n = 0
one			
Sample Size	n = 40 ; % = 22.2	n = 55 ; % = 30.4	n = 47 ; % = 26.3
two			
Sample Size	n = 79 ; % = 43.9	n = 65 ; % = 35.9	n = 78 ; % = 43.6
three			
Sample Size	n = 32 ; % = 17.8	n = 36 ; % = 19.9	n = 32 ; % = 17.9
Four			
Sample Size	n = 12 ; % = 6.7	n = 18 ; % = 9.9	n = 11 ; % = 6.1

	Pembrolizumab 2mg/kg (N = 180)	Pembrolizumab 10mg/kg (N = 181)	Chemotherapy (N = 179)
≥5			
Sample Size	n = 16 ; % = 18.9	n = 7 ; % = 3.9	n = 11 ; % = 6.1
Previous therapy			
Ipilimumab			
Sample Size	n = 180 ; % = 100	n = 181 ; % = 100	n = 179 ; % = 100
Interleukin 2			
Sample Size	n = 21 ; % = 12	n = 16 ; % = 9	n = 12 ; % = 7
Immunotherapy, excluding ipilimumab and interleukin 2			
Sample Size	n = 25 ; % = 14	n = 18 ; % = 10	n = 23 ; % = 13
Chemotherapy			
Sample Size	n = 90 ; % = 50	n = 84 ; % = 46	n = 86 ; % = 48
BRAF or MEK inhibitor			
Sample Size	n = 46 ; % = 26	n = 45 ; % = 25	n = 43 ; % = 24

1 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable

Section	Question	Answer
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable

Section	Question	Answer
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (moderate) *(At final analysis, no patients remained on chemotherapy, and over half (98 of 179 [55%]) of the patients had crossed over to pembrolizumab; six patients also received antiePD-1 therapy off-study, for an effective crossover rate of 58% (104 of 179).)*
	Overall Directness	Directly applicable

1 **KEYNOTE-006**

KEYNOTE-006	
Bibliographic Reference	Robert, Caroline; Ribas, Antoni; Schachter, Jacob; Arance, Ana; Grob, Jean-Jacques; Mortier, Laurent; Daud, Adil; Carlino, Matteo S; McNeil, Catriona M; Lotem, Michal; Larkin, James M G; Lorigan, Paul; Neyns, Bart; Blank, Christian U; Petrella, Teresa M; Hamid, Omid; Su, Shu-Chih; Krepler, Clemens; Ibrahim, Nageatte; Long, Georgina V; Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study.; The Lancet. Oncology; 2019; vol. 20 (no. 9); 1239-1251

2 **Study details**

Other publications associated with this study included in review	Carlino, M. S., Long, G. V., Schadendorf, D., Robert, C., Ribas, A., Richtig, E., ... & Daud, A. (2018). Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: a randomised clinical trial. European Journal of Cancer, 101, 236-243. Schachter, J., Ribas, A., Long, G. V., Arance, A., Grob, J. J., Mortier, L., ... & Robert, C. (2017). Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). The Lancet, 390(10105), 1853-1862 Robert, C., Hwu, W. J., Hamid, O., Ribas, A., Weber, J. S., Daud, A. I., ... & Joshua, A. M. (2021). Long-term safety of pembrolizumab monotherapy and relationship with clinical outcome: A landmark analysis in patients with advanced melanoma. European Journal of Cancer, 144, 182-191
Trial registration number and/or trial name	KEYNOTE-006 trial NCT01866319
Study type	Randomised controlled trial (RCT)
Study location	Australia, Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, and US
Study setting	Multicentre

Study dates	2013 - 2018
Sources of funding	Merck Sharp & Dohme
Inclusion criteria	Age 18 years or older Melanoma histologically confirmed unresectable stage III or IV melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 At least one measurable lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) Up to one previous systemic therapy for advanced disease with known BRAFV600 status; excluding anti-CTLA-4, PD-1, or PD-L1 agents Known BRAF status previous treatment with BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase [LDH] and no clinically significant tumour-related symptoms or evidence of rapidly progressing disease Provision of a tumour sample for determination of PD-L1 status by immunohistochemistry using the 22C3 anti-PD-L1 antibody (Merck & Co, Kenilworth, NJ, USA) at a central laboratory
Exclusion criteria	Active brain metastases patients with previously-treated stable brain metastases without evidence of progression by magnetic resonance imaging at least 4 weeks before the first dose of pembrolizumab were permitted Ocular melanoma Active autoimmune disease requiring systemic steroids

Intervention(s)	pembrolizumab every 2 weeks
Comparator	pembrolizumab every 3 weeks ipilimumab
Outcome measures	All-cause mortality Progression free survival defined as the time from randomisation to first documented disease progression based on immune-related response criteria by investigator review or death from any cause Overall survival defined as time from randomisation to death from any cause Health related quality of life European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) EuroQoL EQ-5D questionnaire Serious adverse events Time on treatment
Number of participants	834
Duration of follow-up	5 years
Additional comments	line of therapy (first vs second)

1 **Study arms**

Pembrolizumab every 2 weeks (N = 279)
intravenous pembrolizumab 10 mg/kg every 2 weeks. Treatment was given for 2 years or until disease progression, intolerable toxicity, complete response, patient withdrawal of consent, or investigator decision to discontinue treatment.

Loss to follow-up	0

Pembrolizumab every 3 weeks (N = 277)
intravenous pembrolizumab 10 mg/kg every 3 weeks. Treatment was given for 2 years or until disease progression, intolerable toxicity, complete response, patient withdrawal of consent, or investigator decision to discontinue treatment.

Loss to follow-up	1

Ipilimumab (N = 278)
intravenous ipilimumab 3 mg/kg every 3 weeks for four doses.

Duration of follow-up	
Loss to follow-up	1

1 **Arm-level characteristics**

	Pembrolizumab every 2 weeks (N = 279)	Pembrolizumab every 3 weeks (N = 277)	Ipilimumab (N = 278)
% Female	42%	37%	42%
Mean age (SD)	Median 61 years (range 18 to 89)	Median 63 years (range 22 to 89)	Median 62 years (range 18 to 88)
BRAFV600E/K status			
Wild-type	63%	64%	61%
Mutant	35%	35%	39%

	Pembrolizumab every 2 weeks (N = 279)	Pembrolizumab every 3 weeks (N = 277)	Ipilimumab (N = 278)
M staging of the extent of metastasis			
M0 no distant metastasis	3%	3%	5%
M1	2%	1%	2%
M1a metastasis to skin, subcutaneous tissues, or distant lymph nodes	8%	13%	11%
M1b metastasis to lung	23%	15%	19%
M1c metastasis to all other visceral sites or distant metastases at any site associated with elevated serum concentrations of LDH	64%	68%	64%
Lines of previous therapy			
0	66%	67%	65%
1	34%	33%	35%
2	0%	1%	0%
Previous BRAF or MEK inhibitor	18%	16%	20%
Previous immunotherapy	3%	2%	4%
Baseline tumour size	Median 58.5 mm (range 10 to 390)	Median 63.4 mm (range 11 to 554)	Median 55.6 mm (range 10 to 465)

	Pembrolizumab every 2 weeks (N = 279)	Pembrolizumab every 3 weeks (N = 277)	Ipilimumab (N = 278)
Brain metastases	9%	10%	10%
Previous (neo)adjuvant therapy	15%	11%	13%

1 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable

Section	Question	Answer
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes

Section	Question	Answer
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes

Section	Question	Answer
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1 **Localised therapy trials**

2 **Chesney (2018)**

Chesney, 2018

3

Bibliographic Reference	Chesney, Jason; Puzanov, Igor; Collichio, Frances; Singh, Parminder; Milhem, Mohammed M; Glaspy, John; Hamid, Omid; Ross, Merrick; Friedlander, Philip; Garbe, Claus; Logan, Theodore F; Hauschild, Axel; Lebbe, Celeste; Chen, Lisa; Kim, Jenny J; Gansert, Jennifer; Andtbacka, Robert H I; Kaufman, Howard L; Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination With Ipilimumab Versus Ipilimumab Alone in Patients With Advanced, Unresectable Melanoma.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2018; vol. 36 (no. 17); 1658-1667

4 **Study details**

Trial registration number and/or trial name	NCT01740297

Study type	Randomised controlled trial (RCT)
Study location	France, Germany, US
Study setting	Multicentre
Study dates	2013 - 2016
Sources of funding	Funded by Amgen
Inclusion criteria	Age ≥18 years Melanoma histologically confirmed stages IIIB to IVM1c malignant melanoma not suitable for surgical resection, but suitable for injection ($ 1 cutaneous/subcutaneous/nodal lesion ≥5 mm in longest diameter) Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1 Adequate haematological function Adequate hepatic function Adequate renal function Measurable disease per contrast-enhanced or spiral computed tomography (CT; visceral lesions) or callipers (cutaneous/subcutaneous lesions)
Exclusion criteria	Active autoimmune disease history of inflammatory bowel disease and/or other symptomatic autoimmune disease Uveal melanoma Mucosal melanoma History of melanoma in an immunodeficient state

	Clinically active cerebral metastases Active herpetic lesions that require systemic treatment with antiherpetic drugs Evidence of clinically significant immunosuppression Prior exposure to talimogene laherparepvec and/or other oncolytic immunotherapy
Intervention(s)	Talimogene Laherparepvec plus Ipilimumab
Comparator	Ipilimumab
Outcome measures	All-cause mortality Progression free survival defined as time from random assignment to the earlier of disease progression or death Overall survival Serious adverse events
Number of participants	198
Loss to follow-up	Not reported
Methods of analysis	
Additional comments	Patients were initially required to be treatment naive; however, a protocol amendment that was intended to account for the availability of new melanoma therapies allowed the enrolment of patients who had received one line of systemic anticancer therapy if BRAF wild-type or ≤2 lines if BRAF mutant (one must have been a BRAF inhibitor).

1 **Study arms**

Talimogene Laherparepvec plus Ipilimumab (N = 98)

Talimogene laherparepvec was injected intralesionally on day 1 of week 1 at a dose of 10^6 plaque-forming units/mL (≤4.0 mL total injection volume; new and larger lesions were prioritized) followed by administration on day 1 of week 4, and every 2 weeks thereafter at 10^8 plaque-forming units/mL (≤4.0 mL); ipilimumab (3 mg/kg) was administered intravenously every 3 weeks beginning on day 1 of week 6 for up to four infusions	
Duration of follow-up	Median follow-up time was 68 weeks (range, 0 to 156 weeks)
Ipilimumab (N = 100) Ipilimumab (3 mg/kg) was administered intravenously every 3 weeks beginning on day 1 of week 1 for up to four infusions	
Duration of follow-up	Median follow-up time was 58 weeks (range, 0 to 152 weeks)

1 **Arm-level characteristics**

	Talimogene Laherparepvec plus Ipilimumab (N = 98)	**Ipilimumab (N = 100)**
% Female	37%	45%
Mean age (SD)	Median 65 years (range 23 to 93)	Median 64 years (range 23 to 90)
Disease substage, AJCC classification		
IIIB	5%	9%
IIIC	30%	31%
IVM1a	16%	17%
IVM1b	20%	10%
IVM1c	29%	33%

	Talimogene Laherparepvec plus Ipilimumab (N = 98)	Ipilimumab (N = 100)
BRAF status		
Mutant	36%	34%
Wild-type	63%	60%
Prior surgery	95%	89%
Prior anticancer therapy Among patients who had previously received anticancer therapy, seven had received systemic therapy for advanced melanoma	26%	29%
Radiotherapy	12%	13%
Immunotherapy	10%	16%
PD-1 inhibitors	2%	3%
Chemotherapy	4%	4%
Targeted small molecules	2%	0%
BRAF inhibitors	2%	0%
MEK inhibitors	1%	0%
Biochemotherapy	2%	1%
Isolated limb perfusion	0%	2%
Other	3%	2%

1 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Probably yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes

Section	Question	Answer
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable

Section	Question	Answer
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes

Section	Question	Answer
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

1 **Guadagni (2021)**

Guadagni, 2021

Bibliographic Reference	Guadagni, S., Zoras, O., Fiorentini, G., Masedu, F., Lasithiotakis, K., Sarti, D., ... & Clementi, M. (2021). A Prospective Study of Intraarterial Infusion Chemotherapy in Advanced WT BRAF Melanoma Patients. *Journal of Surgical Research*

2 **Study details**

Trial registration number and/or trial name	Not reported
Study type	Prospective cohort study - analysis of patients prospectively enrolled as pre-defined subset of a larger trial database of CM patients treated with melphalan locoregional chemotherapy

Study location	Italy
Study setting	Unclear
Study dates	2012-2020
Sources of funding	None
Inclusion criteria	• locoregional metastases (local recurrences,in-transit and satellite metastases, and regional lymph node metastases) located in inferior limbs, or in limbs and pelvis/including inguinal region (synchronous metastases) • BRAF wild-type status • Progression following novel immunotherapy or ineligibility for clinical or non-clinical reasons, including: the absence of National Health System approval, administrative problems or for economic reasons. Patients with acral melanomas or upper limbs lesions were excluded from this study
Intervention(s)	**ILI** - for patients > 75 y old and/or with ≥ 2 ECOG performance status and locoregional limb metastases **HILP** - for patients < 76 y old with < 2 ECOG performance status and locoregional limb metastases **How procedures were performed** - HILP was performed with oxygenation, high flow rates (150-1000 ml/min) and circuit hyperthermia to maintain tissue normothermia or mild tissue hyperthermia (39˚C). - ILI and HPLP were performed under hypoxic conditions with low flow-rates (50-150 ml/min) and mild circuit hyperthermia to maintain tissue normothermia, with the option of chemofiltration. - Both HILP and HPLP procedures require specialized surgical skill, the HPLP procedure can also be performed percutaneously, whereas the ILI procedure requires an interventional radiologist. A percutaneous approach was chosen to minimize invasiveness and was contraindicated if: (1) iliac access was necessary in relation to fibrosis of the femoral vessel area; (2) lymphadenectomy was required, or (3) if the diameter of the common femoral artery was ≤ 7 mm, making vessel dissection risky

Comparator	Each other
Outcome measures	Overall survival Recurrence-free survival Adverse events
Number of participants	62
Duration of follow-up	Unclear
Predictors	- Age - Gender - Stage - Mitotic rate of metastatic cells - Burden
Multivariate analyses	Multivariate variables were included based on criteria influencing choice of locoregional chemotherapy procedure and collinearity of variables: - Location of locoregional metastases (Inferior limbs plus pelvis vs. inferior limbs only) - Stage - Mitotic rate
Additional comments	Based on multidisciplinary board recommendations, following the first locoregional chemotherapy cycle, 28 patients received best supportive care for symptoms and 34 patients received treatments with curative intents, including surgery in 15 patients (6 of whom were submitted to ileo-inguinal lymph node dissections), surgery and diathermy-fulguration in six patients, ECT in one patient, locoregional chemotherapy procedures in 25 patients, systemic chemotherapy with temozolomide in one patient, immunotherapy with interleukin-2 in one patient and pembrolizumab in two patients. The two patients who received pembrolizumab were previously considered untreatable with this drug, due to prior absence of National Health System approval. At progression, all patients received

	best supportive care exclusively. Timing of locoregional chemotherapy repetitions (6/7-wk intervals) was based on previous studies, reporting disease-relapse in the presence of residual disease and initiation with progression by 8 week in aggressive disease states.15 Locoregional chemotherapy was not repeated, if: (1) locoregional metastases had progressed; (2) simultaneous distant relapses had occurred; (3) the general condition of the patient had worsened, or (4) if the patient refused treatment or withdrew consent. Bi-monthly surveillance included: clinical evaluation, photographic comparison, computed tomography (CT), magnetic resonance imaging (MRI) and/or positron emission tomography (PET)

1 **Participant characteristics**

	Study population (N = 62)
Female	67.7%
Median (IQR) age, years	68 (58-75)
Complete response (following 1 cycle)	24.2%
Partial response (following 1 cycle)	12.9%
ECOG ≥2	27.4%
High tumour burden (≥ 10 nodules; or one lesion > 3 cm)	46.8%
<1 mitosis per mm2	64.5%
Location	
Inferior limbs plus pelvis	
Inferior limbs	
Stage	
IIIB	75.8%

	Study population (N = 62)
IIIC	24.2%

Risk of bias (comparison of ILI vs ILP)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (participants were not randomised and selection of treatment was based on clinical characteristics)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High (participants underwent numerous additional therapies/surgeries and it is unclear how these different between treatment groups. Not adjusted for in multivariate analysis).
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High (Unclear follow-up schedule and length of follow-up for each treatment is not reported).
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (non-randomized, unclear follow-up and possibility for differences in subsequent therapies).
	Overall Directness	Directly applicable

1 **Risk of bias (prognostic)**

Section	Question	Answer
Selection of participants	Concerns for risk of bias for selection of participants domain	Low *(Study was not designed as a prognostic study. Risk factors are likely to be comorbid and patients with/without certain risk factors are likely to represent distinct groups)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Concerns for risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear protocol for follow-up during the study period. Unclear if follow-up differed significantly between treatment groups)*
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	High *(multivariate model was designed to account for probability of receiving a certain treatment but will not adequately account for possibility of risk factors being comorbid.).*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(potential for confounders which were not adequately adjusted for in a multivariate model. Unclear if follow-up differed significantly between treatment groups)*
	Concerns for applicability	Directly applicable

1 **Hughes (2016)**

Hughes, 2016

Bibliographic Reference	Hughes, Marybeth S; Zager, Jonathan; Faries, Mark; Alexander, H Richard; Royal, Richard E; Wood, Bradford; Choi, Junsung; McCluskey, Kevin; Whitman, Eric; Agarwala, Sanjiv; Siskin, Gary; Nutting, Charles; Toomey, Mary Ann; Webb, Carole; Beresnev, Tatiana; Pingpank, James F; Results of a Randomized Controlled Multicenter Phase III Trial of Percutaneous Hepatic Perfusion Compared with Best Available Care for Patients with Melanoma Liver Metastases.; Annals of surgical oncology; 2016; vol. 23 (no. 4); 1309-19

2 **Study details**

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Multicentre
Study dates	2006 - 2009

Sources of funding	Funded by the Intramural Program of the National Cancer Institute, National Institutes of Health. Additional funding was supplied via a Cooperative Research and Development Agreement (CRADA) between Delcath Systems, Inc., and the Surgery Branch of the National Cancer Institute.
Inclusion criteria	Melanoma biopsy proven, unresectable melanoma metastatic to the liver Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 Other inclusion criteria serum bilirubin <2.0 mg/dl, a platelet count >100,000, serum creatinine <1.5 mg/dl, and liver function tests <10 times the upper limit of normal
Exclusion criteria	Active brain metastases Other exclusion criteria conditions precluding anticoagulation, latex allergy, cirrhosis, or significant portal hypertension
Intervention(s)	Percutaneous hepatic perfusion is a percutaneous technique that allows delivery of high-dose melphalan directly to the liver via the hepatic artery over 30 min. A unique double balloon inferior vena cava catheter system (Delcath Systems, Inc., Queensbury, NY, USA) was used to catch the hepatic venous outflow and funnel the blood extracorporeally through melphalan-extracting charcoal filters, before returning the blood to the systemic vasculature via the internal jugular vein. All PHP-Mel procedures were carried out under general anesthesia and systemic anticoagulation with heparin. Melphalan was administered at a dose of 3 mg/kg based on ideal body weight. The melphalan dose on subsequent PHPs was reduced to 2.5 mg/kg if a dose-limiting toxicity (DLT) was encountered, defined as any of the following: grade 4 neutropenia >5 days in duration, with growth factor support or associated with neutropenic fever; grade 4 thrombocytopenia >5 days in duration or associated with bleeding requiring transfusion; grade 4 anemia >48 h in duration; grade 3 or 4 major non-hematologic organ toxicity not correctable within 24 h of the procedure (excluding fever, nausea, and weight gain). Subjects randomized to PHP-Mel received treatment approximately every 4–8 weeks when hematologic toxicity resolved to grade 2 or less. Up to six PHP procedures could be performed in any given patient in the absence of progressive disease.
Comparator	Primary BAC treatment strategies included systemic chemotherapy, embolization, and supportive care. Crossover to PHP-Mel was permitted at hepatic progression provided all entry and/or retreatment criteria were met.

Outcome measures	Progression free survival xPFS (defined as the time from the date of randomisation to the first observation of extrahepatic disease progression or death due to any cause) Overall survival
Number of participants	93
Duration of follow-up	1.5 years
Loss to follow-up	None
Additional comments	Patients with limited extrahepatic disease in the presence of clearly progressive advanced liver metastases that were the life-limiting component of their disease were deemed eligible.

1 **Study arms**

PHP-Mel (N = 44) Percutaneous hepatic perfusion with melphalan (PHP-Mel)
BAC (N = 49) Best alternative care (BAC)

2 **Arm-level characteristics**

	PHP-Mel (N = 44)	**BAC (N = 49)**
% Female		
Sample Size	n = 21 ; % = 47.7	n = 27 ; % = 55.1

	PHP-Mel (N = 44)	BAC (N = 49)
Mean age (SD)		
Custom value	Median 55.0 years (range 33 to 74)	Median 56.0 years (range 31 to 77)
Site of primary tumor		
Ocular		
Sample Size	n = 39 ; % = 88.6	n = 44 ; % = 89.8
Cutaneous		
Sample Size	n = 5 ; % = 11.4	n = 5 ; % = 10.2
Duration of hepatic metastasis in months		
Mean/SD	4.6 (7.7)	4.6 (5.5)
Percentage of hepatic tumor burden		
Custom value	Median 32.5 (range 5 to 85)	Median 25.0 (range 5 to 90)
Site of metastases		
Hepatic only		
Sample Size	n = 27 ; % = 61.4	n = 28 ; % = 57.1
Hepatic and extrahepatic		

	PHP-Mel (N = 44)	BAC (N = 49)
Sample Size	n = 17 ; % = 38.6	n = 21 ; % = 42.9
Previous treatment for liver metastases		
Chemotherapy/immunotherapy		
Sample Size	n = 8 ; % = 18.2	n = 10 ; % = 20.4
Regional therapy Included chemoembolization, radioembolization, or ablation		
Sample Size	n = 4 ; % = 9.1	n = 3 ; % = 6.1
Treatments administered to patients in the BAC arm		
Systemic chemotherapy		
Sample Size	n = 24 ; % = 49	n = NA
Chemoembolization		
Sample Size	n = 11 ; % = 22.4	n = NA
Radioembolization (with Yttrium Y-90 SirSpheres)		
Sample Size	n = 3 ; % = 6.1	n = NA
Combination systemic chemotherapy/ embolization		
Sample Size	n = 1 ; % = 2	n = NA

	PHP-Mel (N = 44)	BAC (N = 49)
Surgery		
Sample Size	n = 1 ; % = 2	n = NA
Supportive care		
Sample Size	n = 9 ; % = 18.4	n = NA

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	No information
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Some concerns *(There is no information about concealment of the allocation sequence)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes

Section	Question	Answer
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably no

Section	Question	Answer
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(There is no information about concealment of the allocation sequence)*
	Overall Directness	Indirectly applicable *(Intervention was percutaneous Hepatic Perfusion)*

1 **Katsarelias (2018)**

Katsarelias, 2018

Bibliographic Reference	Katsarelias, Dimitrios; Radbo, Erik; Ben-Shabat, Ilan; Mattsson, Jan; Olofsson Bagge, Roger; The Effect of Temperature and Perfusion Time on Response, Toxicity, and Survival in Patients with In-transit Melanoma Metastases Treated with Isolated Limb Perfusion.; Annals of surgical oncology; 2018; vol. 25 (no. 7); 1836-1842

1 **Study details**

Study type	Retrospective cohort study
Study location	Sweden
Study setting	Single centre
Study dates	1986 - 2017
Sources of funding	Not reported
Inclusion criteria	Melanoma in-transit metastases of malignant melanoma (stage III)
Predictors	Number of lesions (<10 versus >10) Gender (male versus female) Tumour size (bulky versus non-bulky) N-stage (N3 versus N2c) Vessel (external iliac vs femoral vs upper extremity)
Exclusion criteria	Receiving TNF-alpha due to bulky melanoma
Intervention(s)	**Isolated limb perfusion (ILP)** The patients underwent ILP via an axillary, brachial, or subclavian vascular approach for upper extremity (n = 34) and via the external iliac (n = 99) or femoral (n = 151) approach for the lower extremity. Limb isolation was achieved through clamping and cannulation of the major artery and vein for the extremity under treatment. The cannulas were connected to an oxygenated extracorporeal circuit. From October 2000, continuous leakage monitoring was performed using a precordial scintillation probe (Medic View, Sweden) to detect and

	measure leakage of technetium-99m labelled human serum albumin (Vasculosis, Cis-Bio International, Gif-sur-Yvette, France), which was injected into the perfusion circuit. The dose of melphalan was calculated as 13 mg/L perfused tissues for upper limb and 10 mg/L perfused tissues for lower limb. Between 1986 and 2002, the perfusion time and the highest tissue target temperature was 120 min and 41–41.5 °C respectively. In 2002, this was changed to 120 min at 39–40 °C, and this temperature was then used onward. In 2006, the total perfusion time was decreased to 90 min, and in 2012, the perfusion time was further decreased to 60 min. Before 2012, the melphalan was given as three bolus doses, with 50% of the total dose administered initially and the remaining 50% administered in two equivalent doses at 30-min intervals (total 60 min). In 2012, the administration of melphalan was changed into a 20-min infusion in the perfusate, followed by 40-min perfusion.
Comparator	There was no comparator
Outcome measures	Overall survival defined as the time from ILP to death or last follow-up
Number of participants	284
Duration of follow-up	10 years
Loss to follow-up	Not reported
Methods of analysis	Survival estimates were made according to the Kaplan-Meier method and prognostic factors for OS were analysed using Cox regression. Predictive factors for response and toxicity were analysed using logistic regression. A p value <0.05 was considered statistically significant.

1 **Study-level characteristics**

	Study (N = 284)
% Female	58.5%
Mean age (SD)	Median 70.5 years (range 23 to 95)

	Study (N = 284)
N-stage	
N2c	60.2%
N3	39.8%
Vessel	
Upper extremity	12%
Femoral	53.2%
External iliac	34.9%
Perfusion time/temp	
60 min/ 39–40 °C	32%
90 min/ 39–40 °C	30.3%
120 min/ 39–40 °C	6%
120 min/ 41–41.5 °C	31.7%
Number of metastases	
one	13.7%
2 to 3	24.3%
4 to 10	28.5%

	Study (N = 284)
>10	31%
Largest metastasis	
Nodular (<3 cm)	83.5%
Bulky (>3 cm)	12.7%
Missing	3.9%

1 **Risk of bias**

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Not applicable
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
	Risk of bias judgement for confounding	No information *(No information on whether confounding might be present.)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No information
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable

Section	Question	Answer
	Risk of bias judgement for selection of participants into the study	No information *(No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide.)*
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
	4.3. Were important co-interventions balanced across intervention groups?	No information
	4.4. Was the intervention implemented successfully for most participants?	Probably yes
	4.5. Did study participants adhere to the assigned intervention regimen?	Probably yes

Section	Question	Answer
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from intended interventions	No information *(No information on co-interventions.)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably yes
	5.2 Were participants excluded due to missing data on intervention status?	Probably no
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably yes
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Probably yes
	Risk of bias judgement for missing data	Low *(Missing data was low 14 patients (5%))*
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes

Section	Question	Answer
	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Not applicable, single arm study)*
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information *(Not applicable, single arm study)*
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(No information on whether confounding might be present. No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide. No information on co-interventions.)*
	Directness	Directly applicable

1

1 **Kenyon-Smith (2020)**

Kenyon-Smith, 2020	
Bibliographic Reference	Kenyon-Smith, T.J., Kroon, H.M., Miura, J.T. et al. (2020) Factors predicting toxicity and response following isolated limb infusion for melanoma: An international multi-centre study. European Journal of Surgical Oncology 46(11): 2140-2146

2 **Study details**

Study location	US and Australia
Study setting	9 centres
Inclusion criteria	AJCC 7th ed. IIIB/IIIC in-transit metastases confined to a limb undergone treatment for in-transit metastases (such as isolated limb perfusion (ILP), intra-lesional therapy, surgical excision or systemic therapy) prior to the first ILI.
Predictor variables	Gender Disease stage Burden of disease Low BOD: less than 10 distinct lesions, none greater than 2cm in maximal dimension High BOD: more than 10 distinct lesions, or any single lesion greater than 2cm in maximal dimension.
Study dates	1992 – 2018
Sources of funding	None
Intervention(s)	**Isolated limb infusion (ILI)** using a combination of melphalan (7.5 mg/L for lower extremities and 10 mg/L for upper extremities)

	and actinomycin-D (100 mg/L). Drug dosages were based on limbvolume measurements. For large limb volumes, the maximum melphalan dosage was restricted to 100 mg for lower limb ILI, and 50 mg for upper limb ILI. The melphalan dose was corrected for ideal body weight in the US centres. In patients with metastatic disease in their inguinal or axillary lymph nodes, a regional lymphadenectomy was undertaken following the ILI procedure under the same general anesthetic, after heparin reversal. Following the ILI procedure, patients were closely monitored with regular physical examination and measurement of serum creatine phosphokinase (CPK) levels daily. The Wieberdink scale was used to assess limb toxicity
Comparator	There was no comparator
Outcome measures	Limb toxicity
Number of participants	687
Duration of follow-up	Unclear.
Loss to follow-up	Not reported
Methods of analysis	Odd-ratios and 95% CIs are reported for the association of baseline factors with subsequent toxicity

Additional comments	Retrospective study design

1 **Participant characteristics**

	Study (N = 687)
% Female 56 patients with melanoma	
Sample Size	n = 412 ; % = 60
Disease stage	
IIIB	n = 383 ; % = 55.7
IIIC	n = 304 ; % = 44.3
Burden of disease	
Low	n = 371 ; % = 54.2
High	n = 313 ; % = 45.8
Mean Breslow thickness	
Mean (SD) mm	2.67 (2.5)

2 **Risk of bias**

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Probably yes *(Single arm study. Univariate analysis only with potential for confounders.)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	No information *(unclear length of follow-up for toxicity)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	No information *(No information about deviations, co-interventions or participant's adherence to intervention.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(potential for confounders. Univariate analysis only. Unclear follow-up*
	Directness	Directly applicable

1 **Lidsky (2013)**

Lidsky, 2013

Bibliographic Reference	Lidsky, M.E.; Turley, R.S.; Beasley, G.M.; Sharma, K.; Tyler, D.S.; Predicting disease progression after regional therapy for in-transit melanoma; JAMA Surgery; 2013; vol. 148 (no. 6); 493-498

2 **Study details**

Other publications associated with this study included in review	Sharma, Ketan, Beasley, Georgia, Turley, Ryan et al. (2012) Patterns of recurrence following complete response to regional chemotherapy for in-transit melanoma. Annals of surgical oncology 19(8): 2563-71
Trial registration number and/or trial name	
Study type	Retrospective cohort study Prospectively maintained regional therapy database, including records from 258 patients treated between 1995 and 2010, was reviewed
Study location	US
Study setting	Single centre
Study dates	1995 - 2010
Sources of funding	Not reported
Inclusion criteria	Melanoma Stage IIIB or IIIC and stage IV cancers based on the American Joint Committee on Cancer classification Patients undergoing first-time regional therapy
Intervention(s)	Isolated limb infusions, after placement of percutaneous catheters by interventional radiology into the contralateral limb such that the catheter tips terminate in the middle of the diseased extremity, chemotherapy (using melphalan with or without dactinomycin) was rapidly infused into the arterial portion of the circuit and circulated for 30 minutes after the extremity was warmed to 37.0°C. Melphalan was dosed at 7.5 mg/L for the lower extremity and at 10 mg/L for the upper extremity; dactinomycin was dosed at 75 and 100 µg/L for the lower and upper extremities, respectively. After the 30-minute circulation of chemotherapy, 0.5 to 1 L of isotonic crystalloid solution was flushed through the circuit for manual washout. Limb volume was calculated for both ILI and HILP by integrating the measured extremity circumference at 1.5-cm intervals up to the level of anticipated tourniquet placement, and chemotherapy dosing was typically corrected for ideal body weight (IBW) based on evidence that such modification reduces severe toxicity rates without altering response rates. Of the 134 patients undergoing ILI, 117 (87.3%) received melphalan dosing based on IBW.

Comparator	Hyperthermic isolated limb perfusions, the vessels to be cannulated were surgically isolated and then subsequently connected to a cardiopulmonary bypass circuit. A concurrent lymphadenectomy was often performed prior to vessel cannulation depending on the clinical scenario. Once extremity temperatures reached 38.5°C, chemotherapy was perfused through the circuit for 60 minutes, followed by a 15-minute washout with isotonic crystalloid solution. The HILP was performed using melphalan (10 mg/L for the lower extremity and 13 mg/L for the upper extremity). Of the 81 patients undergoing HILP, 22 (27.2%) received melphalan dosing based on IBW.
Outcome measures	Overall survival defined as the number of months from declaration of complete response at 12-weeks post-operatively to death from any cause
Number of participants	128
Duration of follow-up	After the first 3-month evaluation, patients were initially followed up every 3 months for 1 year and then every 6 months thereafter to determine progression-free survival.
Loss to follow-up	12%
Additional comments	

1 **Study arms**

ILI complete response (N = 40) Isolated limb infusion (ILI)
ILI progressive disease (N = 43)
HILP complete response (N = 36) Hyperthermic isolated limb perfusion (HILP)
HILP progressive disease (N = 9)

1 **Arm-level characteristics**

	ILI complete response (N = 40)	ILI progressive disease (N = 43)	HILP complete response (N = 36)	HILP progressive disease (N = 9)
% Female				
Sample Size	n = 23 ; % = 57.5	n = 24 ; % = 55.8	n = 22 ; % = 61.1	n = 6 ; % = 66.7
Mean age (SD)				
Custom value	Median 70 years (range 63 to 78)	Median 60 years (range 50 to 69)	Median 58 years (range 48 to 65)	Median 56 years (range 54 to 57)
Lower limb melanoma				
Sample Size	n = 36 ; % = 90	n = 36 ; % = 83.7	n = 6 ; % = 16.7	n = 8 ; % = 88.9
AJCC stage				
IIIB				
Sample Size	n = 22 ; % = 55	n = 19 ; % = 44.2	n = 13 ; % = 36.1	n = 3 ; % = 33.3
IIIC				
Sample Size	n = 15 ; % = 37.5	n = 22 ; % = 51.2	n = 19 ; % = 52.8	n = 6 ; % = 66.7
IV				
Sample Size	n = 3 ; % = 7.5	n = 2 ; % = 4.7	n = 4 ; % = 11.1	n = 0
Disease burden				

	ILI complete response (N = 40)	ILI progressive disease (N = 43)	HILP complete response (N = 36)	HILP progressive disease (N = 9)
Low				
Sample Size	n = 23 ; % = 57.5	n = 22 ; % = 51.2	n = 12 ; % = 33.3	n = 2 ; % = 22.2
High				
Sample Size	n = 15 ; % = 37.5	n = 21 ; % = 48.8	n = 5 ; % = 13.9	n = 3 ; % = 33.3
Unknown				
Sample Size	n = 2 ; % = 5	n = 0	n = 19 ; % = 52.8	n = 4 ; % = 44.4
Melphalan dose Median (range) mg/L				
Custom value	43.2 (33.6 to 54.6)	48.5 (41 to 63.5)	110 (100 to 130)	94.2 (72.1 to 115.0)
Toxicity Evaluated according to Common Terminology Criteria for Adverse Events version 3				
Sample Size	n = 5 ; % = 12.5	n = 11 ; % = 25.6	n = 9 ; % = 25	n = 5 ; % = 55.6

1 **Risk of bias**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Multivariate analysis was not performed to control for confounders.)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Serious *(Of the 134 patients undergoing ILI, 117 (87.3%) received melphalan dosing based on ideal body weight (IBW). Of the 81 patients undergoing HILP, 22 (27.2%) received melphalan dosing based on IBW.)*
5. Bias due to missing data	Risk of bias judgement for missing data	No information *(No information is reported about missing data or the potential for data to be missing.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(Multivariate analysis was not performed to control for confounders. Of the 134 patients undergoing ILI, 117 (87.3%) received melphalan dosing based on ideal body weight (IBW). Of the 81 patients undergoing HILP, 22 (27.2%) received melphalan dosing based on IBW. No information is reported about missing data or the potential for data to be missing.)*
	Directness	Directly applicable

1 **Muilenberg (2015)**

Muilenberg 2015

1

Bibliographic Reference	Muilenburg, Diego J, Beasley, Georgia M, Thompson, Zachary J et al. (2015) Burden of disease predicts response to isolated limb infusion with melphalan and actinomycin D in melanoma. Annals of surgical oncology 22(2): 482-8

2

3

4 **Study details**

Study location	US
Study setting	Two centres
Inclusion criteria	In-transit metastases (all patients were IIIB/IIIC) First time ILI-M for in transit extremity melanoma Measurable BOD noted and recorded pre-operatively 3-month follow-up data available.
Predictors	Burden of disease Low BOD: less than 10 distinct lesions, none greater than 2cm in maximal dimension High BOD: more than 10 distinct lesions, or any single lesion greater than 2cm in maximal dimension.
Study dates	December 2003 - February 2013,
Sources of funding	Not reported
Intervention(s)	**Isolated limb infusion (ILI)** each limb infusion involved percutaneous placement of arterial and venous catheters in the affected limb. Actinomycin-D (100 μg/L) and melphalan (7.5 mg/L for LE and 10 mg/L for UE) were dosed based on limb volume, and further corrected for patient ideal body weight. After the limb was warmed to ≥37 degrees Celsius, chemotherapy was circulated for 30 min and then the limb was washed out with

	saline before tourniquet release. Typically the ILI was performed within 2-3 weeks of the diagnosis or referral to our centers for in transit disease management. There was no difference in ILI technique or follow up for the patients at either center.
Comparator	There was no comparator
Outcome measures	Overall survival
Number of participants	160
Duration of follow-up	Up to 4 years
Loss to follow-up	Not reported
Methods of analysis	Risk ratios were calculated using event data reported in the trial
Additional comments	Retrospective cohort study

1 **Study-level characteristics**

	Study (N = 160)
% Female 56 patients with melanoma	57%
Mean (range) age	67 (29-89)

2 **Risk of bias**

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Probably yes *(Single arm study. Univariate analysis only with potential for confounders)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	No information *(No information about deviations, co-interventions or participant's adherence to intervention.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Probably yes *(multivariate analyses were conducted for some outcomes but not those relevant to this review)*
Overall bias	Risk of bias judgement	Serious *(potential for confounders. Univariate analysis only).*
	Directness	Directly applicable

1 **Olofsson (2013)**

Olofsson 2013

Bibliographic Reference	Olofsson, Roger; Mattsson, Jan; Lindner, Per (2013) Long-term follow-up of 163 consecutive patients treated with isolated limb perfusion for in-transit metastases of malignant melanoma. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 29(6): 551-7

1 **Study details**

Study location	Sweden
Study setting	Single centre taking all patients referred for ILP in Sweden
Study dates	January 1984 to December 2008
Inclusion criteria	In-transit metastases Treated using ILP for the first time No subsequent ILP
Predictor factors	- Number of lesions (<10 versus >10) - Gender (male versus female) - Tumour location (proximal versus distal) - Tumour size (bulky versus non-bulky) - N-stage (N3 versus N2c) - M-stage (M1 versus M0)
Sources of funding	Not reported
Intervention(s)	**Isolated limb perfusion (ILP)** The patients underwent ILP via the axillary (n=9), brachial (n=3), subclavian (n=2), iliac (n=92), or femoral (n=57) approach. The majority of the perfusions (91%) were M-ILPs. After 2002, 15 patients also received TM-ILP with the only indication being bulky disease. Limb isolation was achieved

	through clamping and cannulation of the major artery and vein. For femoral ILPs, the remaining collateral vessels were compressed using an inflatable tourniquet (Zimmer disposable tourniquet). With iliac and upper extremity ILPs, an Esmarch bandage secured around a Steinman pin (placed into either the anterior superior iliac spine or the humeral head) was used. The cannulas were connected to an oxygenated extracorporeal circuit. From October 2000, continuous leakage monitoring was carried out using a precordial scintillation probe (MedicView, Sweden) to detect and measure leakage of technetium-99 m-labelled human serum albumin (Vasculosis, Cis-Bio International, Gif-sur-Yvette, France) injected into the perfusion circuit. For M-ILP the dose of melphalan was 13 mg/L for upper limbs and 10 mg/L for lower limbs with 50% of the total dose administered initially. The remaining 50% was administered in two equivalent doses at 30-min intervals. Between 1984 and 2005 the perfusion time was 120 min. After 2005 the time was changed to 90 min. Between 1984 and 2003 the perfused tissue temperature was kept between 41–41.5 degrees C. In 2003 this was changed to 39–40 degrees C. At the end of the

	perfusion, the limb was irrigated with 1000mL of low molecular weight dextran (Rheomacrodex, Meda, Solna, Sweden). Thereafter, one unit of erythrocytes was transfused into the treated limb. For patients receiving TM-ILP, a bolus dose of TNF-alpha (Beromun, Boehringer, Ingelheim, Germany) was injected into the perfusion system (3 mg upper limb, 4mg lower limb), provided limb tissue temperature had reached 38 degrees C. After 30 min the temperature was increased to 39–40 degrees C and melphalan (13 mg/L upper limb, 10 mg/L lower limb) was administered during a 20-min infusion. The total perfusion time was 90 min. After perfusion the limb was irrigated with at least 1000–2000mL (upper limb) and 3000–4000mL (lower limb) of Ringer's solution (Ringer Acetat, Baxter Medical, Kista, Sweden). Thereafter, one unit of erythrocytes was transfused into the treated extremity.
Comparator	There was no comparator
Outcome measures	Overall survival Severe toxicity (Wieberdink grade ≥3)
Number of participants	155

Duration of follow-up	Median follow-up of 27 months (3–222 months).
Loss to follow-up	Not reported
Methods of analysis	Multivariate/univariate analyses taken directly from study.
Additional comments	Retrospective cohort study

1 **Participant characteristics**

	Study (N = 155)
% Female	
%	64%
Age	
Median (range) years	70 (23–94)
Age ≤65 years	
Sample Size	n = 30 ; % = 53.6
Breslow thickness	
Mean (range)	6.0mm (0.8–137 mm)
Bulky tumour	
%	18%
Type of chemotherapy	

	Study (N = 155)
% Melphalan + TNF-alpha	9%
% Melphalan	91%
Time from primary tumour to first in-transit	
Mena (range)	25 months (0–220 months)
Time from first in-transit to ILP	
Mean (range)	13 months (0–157 months)

1 **Risk of bias**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Probably yes *(Single arm study with potential for confounders.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Yes *(patients who underwent a subsequent ILP due to progression or recurrence were not included in analysis)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	No information *(No information about deviations, co-interventions or participant's adherence to intervention.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High *(multivariate analyses only conducted on univariate analyses significant to level of p <0.01)*
Overall bias	Risk of bias judgement	Serious *(Potential for confounders. Multivariate analysis not adequately conducted and patients who received subsequent ILP after progression were excluded).*
	Directness	Directly applicable

1 **Kroon (2008 and 2009)**

Kroon 2009	
Bibliographic Reference	Kroon, H. M., Moncrieff, M., Kam, P. C., & Thompson, J. F. (2009). Factors predictive of acute regional toxicity after isolated limb infusion with melphalan and actinomycin D in melanoma patients. *Annals of surgical oncology*, *16*(5), 1184-1192.

2 **Study details**

Study location	Australia
Study setting	Single centre
Study dates	1992 - 2007
Inclusion criteria	Advanced metastatic melanoma of the limb
Predictor factors	Gender (male vs female)

	Final melphalan concentration Tourniquet time Disease stage (entered as continuous variable, according to modified MD Anderson staging) Breslow thickness (entered as continuous variable) Complete response to IPI (Yes vs no)
Sources of funding	Not reported
Intervention(s)	**Isolated limb infusion (ILI)** Briefly, the technical details were as follows: Preoperatively limb volume measurements were made using a water-displacement method, as described by Wieberdink et al. and markings were made on the limb at multiple levels to indicate tissue volumes.13 Radiological catheters with additional side-holes near their tips were inserted percutaneously into the axial artery and vein of the disease-bearing limb via the contralateral groin, and their tips were positioned at the level of the knee or elbow joint. Tissues more proximally located in the limb, but distal to the level of the tourniquet, were perfused in a retrograde fashion via collateral vascular channels. The patient was then given a general anesthetic and heparin (3 mg/kg) was infused to achieve full systemic heparinization. From 1994

	onwards a single 5 mg IV dose of tropisetron, a 5HT3 antagonist, was administered as prophylaxis against postoperative nausea and vomiting. A pneumatic tourniquet was inflated around the root of the limb to be treated at the appropriate level and the cytotoxic agents were infused into the isolated circuit via the arterial catheter. The drugs that were used in all cases were melphalan 7.5 mg/L of tissue and actinomycin D 75 lg/L of tissue in 400 ml warmed, heparinized normal saline. For the duration of the ILI procedure (approximately 20 min for 66 patients and approximately 30 min for 119 patients), the infusate was continually circulated by repeated aspiration from the venous catheter and reinjection into the arterial catheter using a syringe attached to a threeway tap in the external circuit. The limb temperature was increased by incorporating a blood-warming coil in the extracorporeal circuit, by surrounding the limb with a hotair blanket, and by placing a radiant heater over it. On completion of the planned drug exposure period, the limb was flushed with 1 L Hartmann's solution via the arterial catheter, and the venous effluent was discarded. The limb

	tourniquet was then deflated to restore normal limb circulation, and the catheters were removed. Subcutaneous and intramuscular limb temperatures were monitored continuously during the ILI procedure, and blood samples were taken at regular intervals to measure the melphalan concentrations and blood gases. The drug leakage rate from the isolated limb into the systemic circulation was assessed retrospectively in all patients, on the basis of systemic melphalan concentrations that were measured from blood samples taken every 5 min for the duration of the procedure. Intraoperative systemic leakage monitoring was not performed, after early studies determined that systemic leakage was invariably very low. In seven patients with metastatic disease in their groin lymph nodes as well as in-transit metastases in their lower limb, radical lymph node dissection of the groin was performed after the ILI procedure had been completed, the catheters withdrawn, and the systemic heparin reversed. Postoperatively, as prophylaxis against venous and arterial thrombosis, patients were administered 5,000 units calcium heparin subcutaneously 8-hourly and a daily dose

	of 300 mg aspirin for the duration of their hospital admission. Aspirin was continued for 3 months after leaving the hospital.
Comparator	There was no comparator
Outcome measures	Severe toxicity (Wieberdink grade ≥3)
Number of participants	185
Duration of follow-up	Unclear
Loss to follow-up	Not reported
Methods of analysis	Event data taken directly from study. Multivariate hazard ratio taken directly from study.
Additional comments	Retrospective cohort study

1 **Participant characteristics**

	Study (N = 185)
% Female	
%	62%
Age	
Median (range) years	74 (29–93)
Number of ILIs	

	Study (N = 185)
1	59.9%
2	34.1%
3	4.3%
4	1.7%
Modified MD Anderson stage	
I Primary melanoma	3%
II Local recurrence / satellite lesions	8%
IIIa In-transit metastases	40%
IIIab In-transit metastases with nodal involvement	32%
IV Distant metastases	16%

Risk of bias

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Probably yes *(Single arm study with potential for confounders.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	No information *(Unclear follow-up time in which toxicity could occur. No information about deviations, co-interventions or participant's adherence to intervention.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High *(multivariate analysis was not pre-specified in protocol. It was decided based on output of univariate analysis that all intraoperative factors would be input into the model)*
Overall bias	Risk of bias judgement	Serious *(potential for not likely to have been adequately controlled for. Unclear protocol for follow-u and co-interventions)).*
	Directness	Directly applicable

1 **Beasley (2009)**

Beasley 2009

Bibliographic Reference	Beasley, G. M., Caudle, A., Petersen, R. P., McMahon, N. S., Padussis, J., Mosca, P. J., ... & Tyler, D. S. (2009). A multi-institutional experience of isolated limb infusion: defining response and toxicity in the US. *Journal of the American College of Surgeons*, *208*(5), 706-715.

Study details

Study location	USA
Study setting	8 centres
Study dates	2001 - 2008
Inclusion criteria	Stage IIIB – IV melanoma
Predictor factors	mean melphalan dose (mg; continuous variable) Length of hospital stage (days; continuous variable) Peak Creatine Kinase (U/L; continuous variable)
Sources of funding	Not reported
Intervention(s)	**Isolated limb infusion (ILI)** On the day of ILI, high-flow (usually 6F) arterial and venous catheters were inserted into an uninvolved extremity and positioned in the involved extremity using the Seldinger technique and fluoroscopic guidance. Some sites placed a shorter venous catheter below the tourniquet on the ipsilateral side to improve blood flow and total volume of blood circulated. Tips of catheters were positioned in the artery and vein of the involved limb near the knee or elbow joint. One skin and one muscle temperature probe were then placed. A warming blanket using circulated heated water was then wrapped around the extremity and kept in place for the duration of the procedure. The patient was fully heparinized before the arterial and venous catheters were connected to the infusion circuit. Circulation was begun through the circuit using a syringe (usually 20 mL) connected to the venous catheter, when blood was aspirated from the venous side of the extremity, pushed toward the heat exchanger, and then back into the limb on the arterial side. Once circulation of

	blood through the catheters was adequate, a pneumatic or Esmarch tourniquet was positioned and inflated or tightened around the proximal portion of the extremity. After the extremity was warmed to at least 37.0°C, chemotherapy was rapidly infused (2 to 5 minutes) in the arterial line. Once the rapid infusion was complete, a circulation (usually 30 minutes) of chemotherapy through the circuit was started. Circuit blood gases at most institutions were taken at 25 and 30 minutes after initial infusion of chemotherapy to document the degree of hypoxia and acidosis. After 30 minutes of circulation of chemotherapy through the circuit, the limb was flushed through the arterial catheter with 500 to 1,000 mL isotonic crystalloid solution at room temperature using a manually pressurized circuit. Flush/effluent was manually extracted from the venous catheter and discarded using the syringe. When the effluent was clearing and 50% to 80% of the flush had been extracted, the tourniquet was deflated and arterial and venous catheters were removed. Protamine was generally administered to all patients to reverse heparinization. In addition to close monitoring by physical examination, serial CK levels were checked postoperatively. **Chemotherapy** The combination of melphalan plus dactinomycin was initially described for use in ILI. Although melphalan has historically been the drug of choice for HILP, dactinomycin was added after data from SMU demonstrated that the melphalan plus dactinomycin produced exceptionally good response rates (CR = 73%) when administered by conventional HILP in a small number of patients without any apparent increase in toxicity.20 In this study, all procedures were performed using melphalan (7.5 mg/L lower extremity, 10 mg/L upper extremity) SD dactinomycin (75 Ug/L lower extremity, 100 Ug/L upper extremity). The volume of the extremity was measured at most centers by measuring the patient's leg or arm circumference at 1.5-cm intervals up to the level of the tourniquet, encompassing the entire area to be infused. Alternatively, some centers used a water displacement method to measure limb volume. Additionally, some centers correct the chemotherapy doses for ideal body weight (IBW) based on preliminary evidence that this dosing modification is associated with lower toxicity without altering response.
Comparator	There was no comparator
Outcome measures	Severe toxicity (Wieberdink grade ≥3)
Number of participants	128
Duration of follow-up	3 months

Loss to follow-up	12
Methods of analysis	Mean (SD) taken directly from study.
Additional comments	Retrospective cohort study

1 **Study-level characteristics**

		Study (N = 155)
Female		55%
Melphalan + dactinomycin		93%
Papaverine use		60%
Correction for ideal body weight		42%
Age		67 (19-90)
Location		
	Upper extremity	14%
	Lower extremity	86%
30 min infusion		96%
Time from first in-transit to ILI		13 months (0–157 months)

2 **Risk of bias**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Probably yes *(Single arm study with potential for confounders.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	High *(m*ean results with standard deviations are selectively reported*)*
Overall bias	Risk of bias judgement	Serious *(potential for confounders without multivariate analyses. Selective reporting).*
	Directness	Directly applicable

1 **OPTiM**

OPTiM trial

2

Bibliographic Reference	Andtbacka, RHI; Collichio, F; Harrington, KJ; Middleton, MR; Downey, G; Öhrling, K; Kaufman, HL; Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III-IV melanoma; Journal for immunotherapy of cancer; 2019; vol. 7 (no. 1); 145

1 **Study details**

Other publications associated with this study included in review	Andtbacka, RH, Ross, M, Puzanov, I et al. (2016) Patterns of Clinical Response with Talimogene Laherparepvec (T-VEC) in Patients with Melanoma Treated in the OPTiM Phase III Clinical Trial. Annals of surgical oncology 23(13): 4169-4177 Andtbacka, Robert H I, Agarwala, Sanjiv S, Ollila, David W et al. (2016) Cutaneous head and neck melanoma in OPTiM, a randomized phase 3 trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor for the treatment of unresected stage IIIB/IIIC/IV melanoma. Head & neck 38(12): 1752-1758 Andtbacka, Robert H I, Kaufman, Howard L, Collichio, Frances et al. (2015) Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(25): 2780-8 Harrington, K.J., Andtbacka, R.H.I., Collichio, F. et al. (2016) Efficacy and safety of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in patients with stage IIIB/C and IVMIa melanoma: Subanalysis of the phase III OPTiM trial. OncoTargets and Therapy 9: 7081-7093
Trial registration number and/or trial name	OPTiM trial NCT00769704
Study type	Randomised controlled trial (RCT)
Study location	Canada, South Africa, UK, US
Study setting	Multicentre
Study dates	2009 - 2014
Sources of funding	This trial was initially funded by BioVex, who were subsequently acquired by Amgen Inc. during the OPTiM trial.
Inclusion criteria	Age

	≥ 18 years Melanoma histologically confirmed, unresectable, bidimensionally measurable stage IIIB/C/IV melanoma according to the 7th edition AJCC staging system Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1 Adequate organ function Other inclusion criteria serum lactate dehydrogenase ≤1.5 × upper limit of normal; ≤3 visceral lesions (excluding lung or nodal lesions associated with visceral organs) with none > 3 cm ≥1 cutaneous, subcutaneous or nodal lesions that was suitable for direct or ultrasound-guided injection
Exclusion criteria	Patients with a primary ocular melanoma Mucosal melanoma Other exclusion criteria • Patients requiring intermittent or chronic treatment with an antiviral agent (eg, acyclovir) or high-dose steroids. • >3 visceral metastases (except lung or nodal metastases associated with visceral organs), or any visceral metastasis >3 cm; liver metastases had to be stable for ≥ 1 month before random assignment. • Use of high-dose steroids Clinically active cerebral metastases
Intervention(s)	Talimogene laherparepvec
Comparator	Granulocyte-macrophage colony-stimulating factor
Outcome measures	Overall survival defined as the time from random assignment to death from any cause Serious adverse events

Subgroup analysis	Melanoma stage
Number of participants	436
Duration of follow-up	Median follow-up was 49 months
Loss to follow-up	Not reported

1 **Study arms**

Talimogene laherparepvec (N = 295)
The first dose of talimogene laherparepvec was given at a dose of 10^6 pfu/mL to seroconvert herpes simplex virus (HSV)-1-seronegative patients. The second dose of 10^8 pfu/mL was given 3 weeks later and repeated every 2 weeks thereafter. A maximum total volume of 4.0 mL could be injected at each treatment visit, with per lesion volumes ranging from 0.1 mL for lesions ≤0.5 cm to 4.0 mL for lesions >5 cm in diameter.

GM-CSF (N = 141)
Granulocyte-macrophage colony-stimulating factor (GM-CSF) was given once daily at a dose of 125 µg/m2 for 14 days in 28-day cycles.

2 **Participant characteristics**

	Talimogene laherparepvec (N = 295)	**GM-CSF (N = 141)**
% Female	41%	45%
Mean age (SD)	Median 63 years (range 22 to 94)	Median 64 years (range 26 to 91)
Disease substage		
IIIB	8%	9%

	Talimogene laherparepvec (N = 295)	GM-CSF (N = 141)
IIIC	22%	22%
IVM1a	24%	30%
IVM1b	22%	18%
IVM1c	23%	21%
Unknown	1%	0%
Line of therapy		
First	47%	46%
Second or later	53%	54%
BRAF status		
Mutation	16%	16%
Wild-type	15%	16%
Unknown or missing	69%	67%

1 **Risk of bias (intervention)**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

Section	Question	Answer
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable

Section	Question	Answer
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no

Section	Question	Answer
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Partially Applicable *(Comparator was not listed in the protocol (intralesional Rose Bengal [PV-10]))*

1

2 **Steinman (2014)**

Steinman, 2014

3

Bibliographic Reference	Steinman, Jonathan; Ariyan, Charlotte; Rafferty, Brian; Brady, Mary S; Factors associated with response, survival, and limb salvage in patients undergoing isolated limb infusion.; Journal of surgical oncology; 2014; vol. 109 (no. 5); 405-9

4 **Study details**

Study location	US
Study setting	Single centre
Study dates	1999 - 2011
Predictors	Burden of disease (high versus low) High: >10 lesions or any single lesion >3cm in maximal dimension Low: <10 lesions, none > 3cm in maximal dimension

	Gender (male versus female) Tumour stage (IIIB versus IIIC)
Sources of funding	Not reported
Intervention(s)	**Isolated limb infusion (ILI)** After disease confirmation by biopsy, the surgeon identifies measurable lesions (index lesions) pre-infusion, and the size and location of these are recorded. Pre-infusion photographs are used to facilitate documentation of disease burden and index lesion size and location. Patients with deep lesions difficult to assess by surface inspection are measured and documented using CT or magnetic resonance imaging. On the day of ILI, large-bore, multi side hole angiographic catheters are placed in the involved limb from a remote site (usually contralateral groin). The catheters are positioned in the popliteal or brachial artery and vein of the involved limb. The patient is given systemic heparin at the start of catheter placement and this is maintained throughout the procedure until the catheters are removed. In the operating room or angiography suite the patient is placed on a warming blanket and general anesthesia is performed. A proximal tourniquet is placed on the involved extremity, and skin and muscle temperature probes are placed on the limb. The warming blanket is set to 42°C and the limb is heated to 37°C. Serotonin receptor antagonist and dexamethasone are administered as antinausea prophylaxis. When the skin temperature of the limb reaches 37°C, 60 mg of papaverine is injected into the arterial catheter and the tourniquet is inflated to 350 mmHg. Melphalan and dactinomycin are rapidly infused into the arterial catheter with doses determined by limb volume, more recently adjusted for ideal body weight. Melphalan is used at a dose of 5–10 mg/L limb volume, and dactinomycin at a dose of 50–100 mg/L limb volume. The most common melphalan dose used was 7.5 mg/L limb volume and that of dactinomycin, 75 mg/L limb volume (maximum 500 mg). Once the chemotherapy is administered via the arterial catheter, the circuit is established and the infusion begins. Sixty milliliter are extracted from the venous catheter and re-injected into the arterial catheter via the blood warmer and bubble excluder. The chemotherapy is circulated for 25 min (20 min in the initial experience). The length of infusion was increased to 25 min. After completion of the chemotherapy infusion, crystalloid (approximately 800 ml to 1 L) is used to flush the limb and an equal volume of venous effluent is extracted and discarded. Total infusate volume is recorded. The tourniquet is deflated, the angiographic catheters are removed, and protamine is administered. Manual compression is applied to the puncture sites at the root of the limb.
Comparator	There was no comparator

Outcome measures	Overall survival
Number of participants	62 patients: • melanoma (n=58) • Merkel cell carcinoma (n=2) • oft tissue sarcoma (n=2)
Duration of follow-up	The median follow up of melanoma patients was 22 months.
Loss to follow-up	Not reported
Methods of analysis	Kaplan Meyer survival curves and log rank analysis were used to compare subgroups
Additional comments	Prospectively collected data was reviewed and updated follow up on patients accrued to a phase II clinical trial evaluating the safety and efficacy of ILI in patients with extremity melanoma and soft tissue sarcoma (n=37). In addition, electronic medical record (EMR) was retrospectively reviewed to include patients in the subsequent experience once the trial closed, and included an additional 25 patients. Inclusion/exclusion criteria were not reported.

1 **Study-level characteristics**

	Study (N = 56)
% Female 56 patients with melanoma	62.5%
Age ≤65 years	46.4%
Age ≤65 years	53.6%
Stage	
IIIB	59%

	Study (N = 56)
IIIC	36%
IV	5%
Tumour burden	
High	57%
Low	41%
Not available	2%

1 **Risk of bias**

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No information
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No

Section	Question	Answer
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably no
	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
	Risk of bias judgement for confounding	No information *(No information on whether confounding might be present)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No information
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
	Risk of bias judgement for selection of participants into the study	No information *(No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide.)*
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
	4.3. Were important co-interventions balanced across intervention groups?	No information
	4.4. Was the intervention implemented successfully for most participants?	Probably yes
	4.5. Did study participants adhere to the assigned intervention regimen?	No information
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
	Risk of bias judgement for deviations from intended interventions	No information *(No information about deviations, co-interventions or participant's adherence to intervention.)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably yes
	5.2 Were participants excluded due to missing data on intervention status?	No information
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable

Section	Question	Answer
	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably no
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(No information on whether confounding might be present. No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide. No information about deviations, co-interventions or participant's adherence to intervention.)*
	Directness	Partially Applicable *(There was no comparator)*

Read (2019)

Read, 2019	
Bibliographic Reference	Read, Tavis; Fayers, Warren; Thomas, Janine; Wagels, Michael; Barbour, Andrew; Mark Smithers, B; Patients with in-transit melanoma metastases have comparable survival outcomes following isolated limb infusion or intralesional PV-10-A propensity score matched, single center study.; Journal of surgical oncology; 2019; vol. 119 (no. 6); 717-727

Study details

Trial registration number and/or trial name	Not reported
Study type	Retrospective cohort study Patients were screened for inclusion using the data retrieved from a prospectively maintained database
Study location	Australia

Study setting	Single centre
Study dates	1997 - 2017
Sources of funding	Health Innovation, Investment and Research Office, Department of Health, Queensland Government
Inclusion criteria	Age over the age of 18 years histopathologically or cytologically confirmed metastases and measurable lesions >2mm in diameter
Intervention(s)	**ILI treatment protocol** All in-transit melanoma metastases were included within the ILI. In summary, the technical specifications were as follows: limb volume was determined through water displacement and melphalan alone was selected as the cytotoxic agent (7.5 mg/L of soft tissue, dispersed in 400 mL of warmed 0.9% saline infusate). Patients were admitted preoperatively and two large bore radiological catheters were percutaneously inserted into the axial vessels of the disease-containing extremity. In the operating theater, general anesthesia was administered and the limb heated to achieve mild hyperthermia (42°C circulating hot air). A pneumatic tourniquet was inflated at the proximal extent of the limb and an Esmarch compressive bandage used to exclude the distal limb (hand or foot) if these regions were macroscopically uninvolved with the disease. The prepared infusate was introduced via the arterial catheter into the isolated limb circuit and continually circulated by manual aspiration for 15 minutes. After this, the limb was flushed with a standard volume of Hartmann's solution via the arterial catheter and a corresponding volume of venous effluent removed. After sufficient drainage time (>15 minutes) the tourniquet was deflated to restore open limb circulation and the catheters removed. The cutaneous, subcutaneous, and intramuscular temperatures were recorded throughout. Unfractionated heparin anticoagulation was administered before the procedure and was reversed afterward with protamine sulfate. If the patient required a regional lymph node dissection this was subsequently undertaken during the same general anesthetic.
Comparator	**PV-10 treatment protocol** PV-10 was dispensed as a sterile, nonpyrogenic solution of 10% concentration Rose Bengal (4,5,6,7-tetrachloro-2,4,5,7-tetraiodofluorescein disodium). After the injection of local anesthetic, PV-10 was administered using a fanning technique with multiple passes to uniformly infiltrate lesions. All clinically evident lesions were injected with PV-10 except for in two patients who were included in a PV-10phase II study and thereby restricted to have 20 designated “study lesions” treated according to the trial criteria. The total dosage was calculated using a standardized volumetric algorithm developed by Provectus Biopharmaceuticals (Knoxville, TN) and limited to 1500 mg (ie, 15 mL of PV-10).

Outcome measures	Overall survival Melanoma-specific survival
Number of participants	72
Duration of follow-up	120 months
Loss to follow-up	Not reported
Methods of analysis	**Propensity score matching** Patients were screened for inclusion using the data retrieved from a prospectively maintained database. Those who received both therapies or with incomplete records were excluded from the matching procedure. Matching was performed using a 1:1 ratio based on the covariates: age, gender, primary site, and Breslow thickness within a multiple logistic regression model using STATA (v14.0) statistical software. Due to the limited availability of data including the size and number of melanoma metastases for the ILI subgroup, tumor volume was not included. A total of 46 potential PV-10 patients and 86 corresponding ILI patients were identified as eligible. Patients were anonymized and matching was completed blinded to the primary outcome. Final propensity score modeling yielded a total of 36 patients matched in each treatment arm.
Additional comments	Patients with both (AJCC 7th Edition) stage III and IV disease were treated provided they had previously undergone or were inappropriate for complete surgical excision of all evident intransit disease and not better suited to systemic treatments as determined through discussion at a multidisciplinary meeting.

1 **Study arms**

ILI (N = 36) Isolated limb infusion (ILI)
PV-10 (N = 36) Intralesional Rose Bengal (PV-10)

1 **Participant characteristics**

		ILI (N = 36)	PV-10 (N = 36)
% Female		44.4%	44.%
Mean age (SD)		76.5 (69 to 83)	74.5 (65.5 to 81)
In-transit melanoma anatomical location			
	head and neck	0%	5.6%
	Trunk	0%	2.8%
	Upper limb	11.1%	8.3%
	Lower limb	88.9%	83.3%
AJCC 7th Edition stage at treatment			
	IIIB	44.4%	25%
	IIIC	55.6%	63.9%
	IV	0%	11.1%
Sample Size		n = 0	n = 4 ; % = 11.1
BRAF mutation status			
	Positive (mutant)	0%	5.6%
	Negative (wild-type)	5.6%	50%

		ILI (N = 36)	PV-10 (N = 36)
Breslow thickness (mm)		2.8 (1.7 to 4.9)	2.6 (1.6 to 4.4)
Clark level			
	Levels I and II	2.8%	5.6%
	Level III	2.8%	11.1%
	Level IV	75%	63.9%
	Level V	19.4%	19.4%
Ulceration		38.9%	44.4%
Tumor stage			
	≤T2a	36.1%	33.3%
	T2b-T3a	16.7%	19.5%
	T3b-T4a	25%	30.5%
	T4b	22.2%	16.7%

1 **Risk of bias**

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes

Section	Question	Answer
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Yes
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
	Risk of bias judgement for confounding	Moderate *(Confounding expected controlled using propensity score matching. Given the matching procedure was based on estimated propensity scores, performing a*

Section	Question	Answer
		regression analysis effectively created a two-part model that did not account for the standard errors of the first stage.)
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
	4.3. Were important co-interventions balanced across intervention groups?	No information
	4.4. Was the intervention implemented successfully for most participants?	Probably yes
	4.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
	Risk of bias judgement for deviations from intended interventions	No information *(No information is reported on whether there is deviation from the intended intervention.)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably yes
	5.2 Were participants excluded due to missing data on intervention status?	No information
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
	Risk of bias judgement for missing data	No information *(No information is reported about missing data or the potential for data to be missing.)*
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	No information
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes

Section	Question	Answer
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably no
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(Given the matching procedure was based on estimated propensity scores, performing a regression analysis effectively created a two-part model that did not account for the standard errors of the first stage. No information is reported on whether there is deviation from the intended intervention. No information is reported about missing data or the potential for data to be missing.)*
	Directness	Partially Applicable *(Comparator was not listed in the protocol (intralesional Rose Bengal [PV-10]))*

1 **Ressler (2020)**

Ressler, 2020

2

Bibliographic Reference	Ressler, J. M., Karasek, M., Koch, L., Silmbrod, R., Mangana, J., Latifyan, S., ... & Hoeller, C. (2021). Real-life use of talimogene laherparepvec (T-VEC) in melanoma patients in centers in Austria, Switzerland and Germany. *Journal for Immunotherapy of Cancer*, *9*(2).

3 **Study details**

Trial registration number and/or trial name	Not reported
Study type	Retrospective cohort study Patients were screened for inclusion using the data retrieved from a prospectively maintained database
Study location	Austria, Switzerland and Germany
Study setting	10 melanoma centres
Study dates	May 2016 – January 2020
Sources of funding	The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.
Inclusion criteria	• Treated with T-VEC • Stage IIIB-IVM1d
Intervention(s)	**TVEC** - Unclear treatment protocol
Comparator	**None**

Outcome measures	Overall survival Recurrence-free survival
Number of participants	88
Duration of follow-up	Median follow-up period was 542 days (range: 14–1463 days)
Predictors	Whether T-VEC treatment was first or second line
Multivariate analyses	none

1 **Participant characteristics**

	Study population (N = 88)
Female	50%
Complete response	43.2%
Partial response	20.5%
Stable disease	9.1%
Progressive disease	27.3%
ECOG ≥1	22.7%
BRAF +	35.2%
Location	
Head	13.6%

	Study population (N = 88)
Trunk	9.1%
Extremities	73.9%

1 **Risk of bias**

Section	Question	Answer
Selection of participants	Concerns for risk of bias for selection of participants domain	Low *(Study was not designed as a prognostic study. Risk factors are likely to be comorbid and patients with/without certain risk factors are likely to represent distinct groups)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Concerns for risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear protocol for follow-up during the study period)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no multivariate model).*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(potential for confounders which were not adjusted for in a multivariate model)*

Section	Question	Answer
	Concerns for applicability	Directly applicable

Schellerer (2021)

Schellerer, 2021

Bibliographic Reference	Schellerer, V. S., Frenger, J., Merkel, S., Goehl, J., Kersting, S., Gruetzmann, R., ... & Foertsch, T. (2021). Results of isolated limb perfusion for metastasized malignant melanoma. *Surgical Oncology*, *38*, 101603

Study details

Study type	Retrospective cohort study
Study location	Germany
Study setting	Singe centre
Study dates	January 2007 – December 2016
Sources of funding	Not reported
Inclusion criteria	- Underwent Hyperthermic isolated limb perfusion (HILP). Indications for Hyperthermic isolated limb perfusion include: (i) In patients with locoregional disease but without distant metastases for curative intention (n = 45) (ii) In patients with bulky disease and without the possibility of local tumor control, which would otherwise require limb amputation. This group of patients included those with proven distant metastases

Intervention(s)	**Hyperthermic isolated limb perfusion** For limb perfusion, the limb is temporarily isolated from the systemic circulation utilizing a heart-lung machine (HLM). This independent circuit is used to apply cytostatic drugs in much higher concentrations than the patient's system would be able to tolerate under normal circumstances. The additional hyperthermia also increases the toxic effect of the cytostatic drugs. The HILP procedure can be divided into four steps: (i) The creation of conditions for an autonomous circulation: The vessels supplying the affected limb are surgically exposed and visualized. In the case of the upper extremity, these are the axillary or brachial artery and vein; in the lower extremity, the external iliac artery and vein or the femoral artery and vein, depending on the most proximal metastatic lesion. **(ii)** After cannulation of the exposed vessels, the limb is perfused by the HLM. A heat exchange process warms up the perfusate. In the circuit an oxygenator supplies the extremity with oxygen. In the case of perfusions with Tumor necrosis factor–alpha (TNF-alpha), leakage control is essential. Leakage control is performed using a gamma camera and radionuclide labeled erythrocytes. TNF-alpha is added to the perfusate if the leakage rate is below 1% at the beginning of the HILP. Leakage control is furthermore performed continuously during the operation to immediately detect any leakage and to stop perfusion when the leakage rate increases above 5%. This is done in order to avoid systemic side effects caused by TNF-alpha, especially septic organ failure. **(iii)** Application of cytostatic drugs and maintenance of circulation for 90 min under hyperthermia and continuous monitoring: The cytostatic drugs are administered into the arterial line during a time frame of 20 min, once the limb tissue temperature reaches 38 ◦C. Furthermore, this temperature is increased to 40.5 ◦C and perfusion is performed for 90 min. The perfusate's and the extremity's temperatures are measured continuously by subcutaneously applied temperature probes inserted proximally and distally on the extremity. Laboratory parameters such as 02 saturation, hematocrit, and pH value are continually monitored. **(iv)** After 90 min perfusion time, the solution is washed out of the extremity with albumin or hydroxyethyl starch. After decannulation, the vessels are sutured and the wound is closed, and normal perfusion of the extremity is checked. Postoperatively, a regular check of blood circulation, motoric function, and sensitivity must be performed. In case of lymph node metastases suspected clinically or by computer-tomography (CT), a lymph node dissection is performed.
Exclusion criteria	receiving re-perfusion
Comparator	none
Outcome measures	Overall survival and severe (grade 3-5) toxicity.

Number of participants	80
Duration of follow-up	The mean follow-up time was 38 months (median 28 months; range 13 days to 11 years).
Predictors	- Gender - Location of perfused limb
Multivariate analyses	none

1 **Participant characteristics**

		Study population (N = 80)
Female		37%
Median (range) age, years		66 (16-87)
Treatment for palliative intent		44%
Initial tumour thickness >4mm		25%
BMI <30 kg/m^2		68%
Disease stage		
	IIIA	0%
	IIIB	30%

	Study population (N = 80)
IIIC	25%
IIID	1%
IV	44%
Location	
Upper extremity	9%
Lower extremity	91%

1 **Risk of bias**

Section	Question	Answer
Selection of participants	Concerns for risk of bias for selection of participants domain	Low *(Study was not designed as a prognostic study. Risk factors are likely to be comorbid and patients with/without certain risk factors are likely to represent distinct groups)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Concerns for risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear protocol for follow-up during the study period)*

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no multivariate model).*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(potential for confounders which were not adjusted for in a multivariate model. However, all participants received similar treatment.)*
	Concerns for applicability	Directly applicable

1

Appendix E - Forest plots

Figure 3: Grade 3-5 adverse events in CHECKMATE-067 and -069

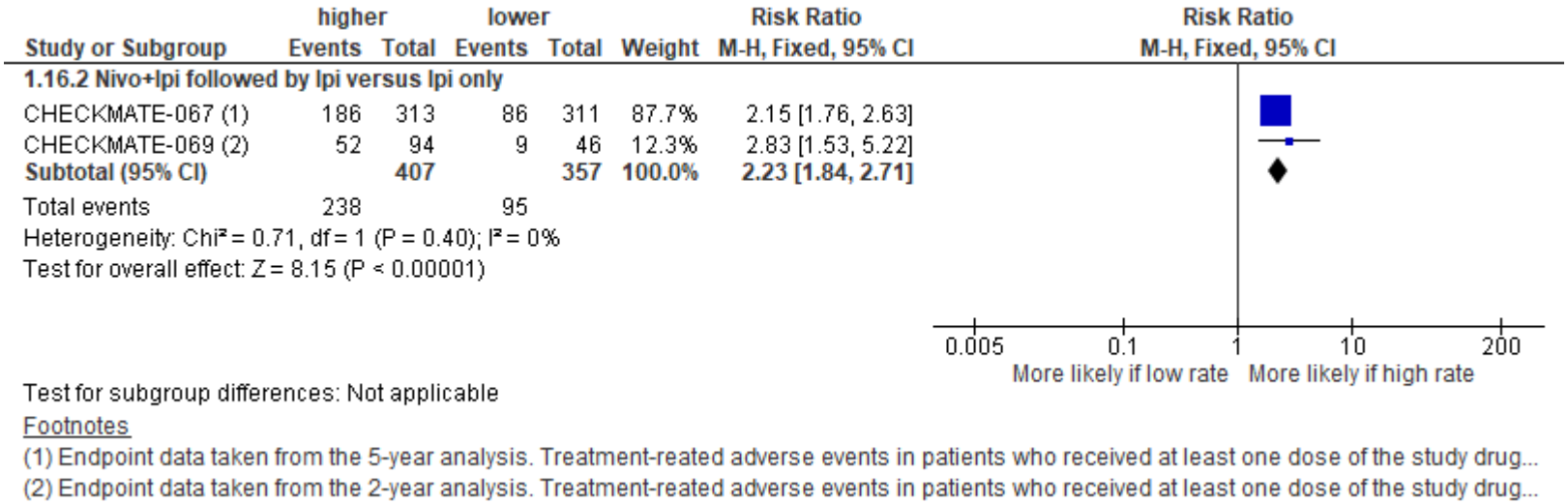


Figure 4: Adverse events leading to discontinuation of study drug(s) in CHECKMATE-067 and -069

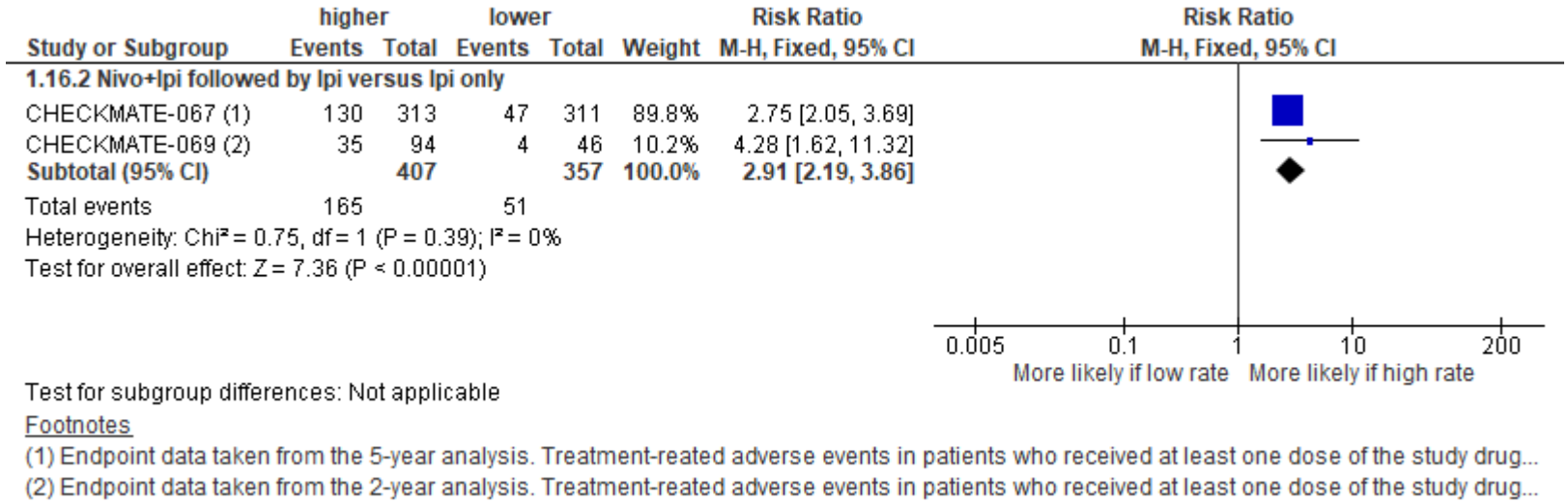


Figure 5: Any grade vitiligo in CHECKMATE-067 and -069

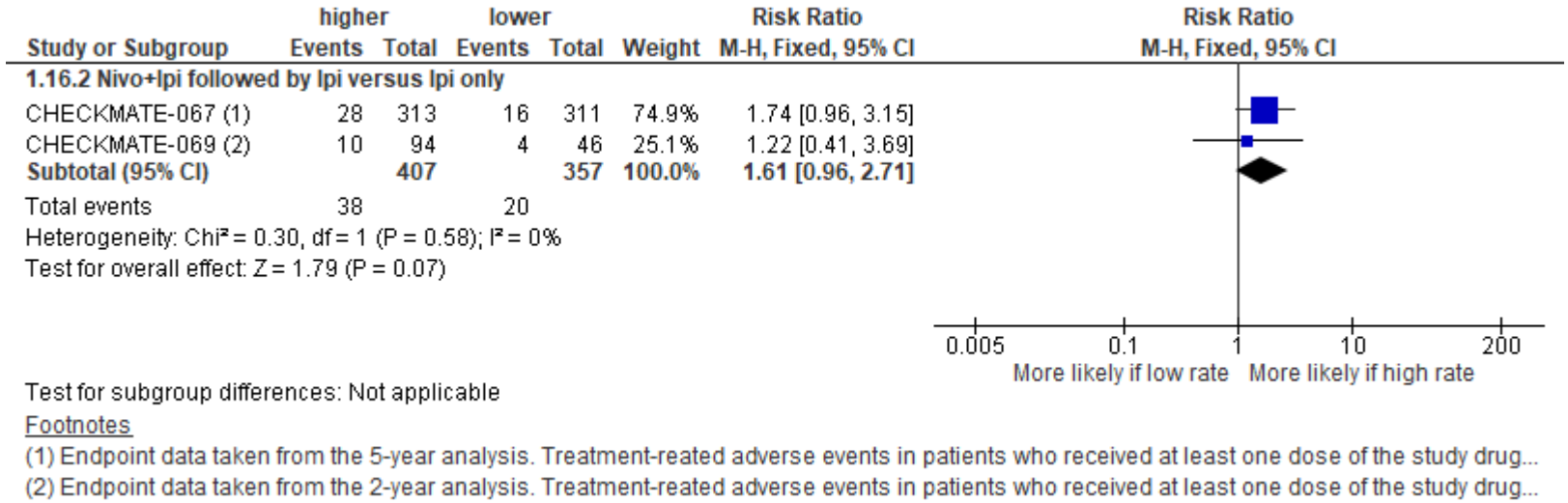
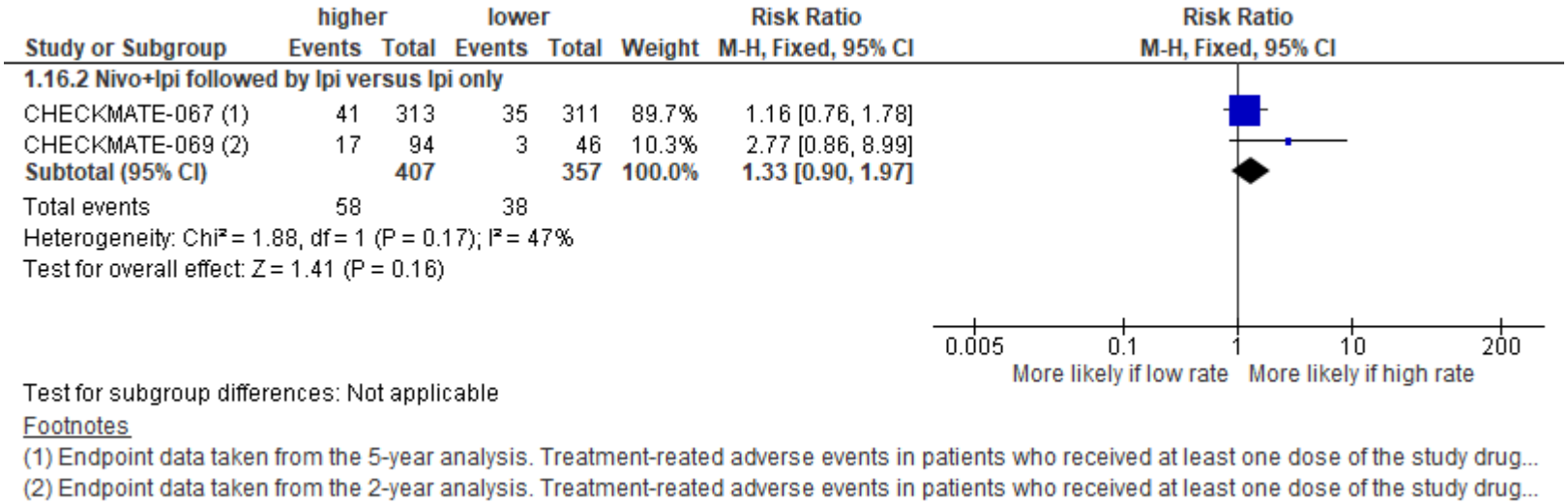


Figure 6: Any grade colitis in CHECKMATE-067 and -069



Appendix F – GRADE tables for pairwise data

F.1 Immunological and targeted therapies

Overall survival

Table 10 Overall survival

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. investigator's choice of chemotherapy – Overall survival at 2 years (HR <1 favour nivolumab)								
CHECKMATE 037	257	Aged <65 years	HR 1.17 (0.84, 1.63)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
	148	Aged ≥65 years	HR 0.62 (0.41, 0.94)	Very serious[1]	Not serious	N/A	Not serious	Low
	246	ECOG PF 0	HR 0.95 (0.67, 1.34)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
	158	ECOG PF 1	HR 0.89 (0.60, 1.31)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
	211	LDH ≤ULN	HR 0.84 (0.57, 1.23)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
	191	LDH >ULN	HR 0.78 (0.55, 1.11)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
	68	LDH > 2x ULN	HR 0.67 (0.38 ,1.18)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
	73	History of brain metastases	HR 1.42 (0.73, 2.46)	Very serious[1]	Not serious	N/A	Serious[3]	Very low
Dabrafenib + Trametinib (150/2 dose) vs. dabrafenib alone– Overall survival at 5 years								
BRF113220	61	LDH ≤ULN	RR 0.76 (0.52, 1.11)	Not serious	Not serious	N/A	Serious[4]	Moderate
	47	LDH >ULN	RR 1.12 (0.93, 1.34)	Not serious	Not serious	N/A	Serious[4]	Moderate
Pembrolizumab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumab – Overall survival up to 5 years								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
KEYNOTE-006	364	Only patients receiving first line therapy	Pembro (10mg/2W) vs IPI: HR 0.74 (0.56, 0.97)	Not serious	Not serious	N/A	Not serious	High
	366		Pembro (10mg/3W) vs IPI: HR 0.72 (0.55, 0.95)	Not serious	Not serious	N/A	Not serious	High
	290	Second line therapy	HR 0.75 (0.55, 1.03)	Serious[2]	Not serious	N/A	Serious[3]	Low
	544	BRAF wild-type	HR 0.73 (0.58, 0.93)	Serious[2]	Not serious	N/A	Not serious	Moderate
	290	BRAF mutated	HR (0.71 (0.48, 1.08)	Serious[2]	Not serious	N/A	Serious[3]	Low
	167	BRAF mutated and BRAF/MEK inhibitor naïve (also normal LDH as per protocol)	HR 0.70 (0.44, 1.11)	Serious[2]	Not serious	N/A	Serious[3]	Low
	147	BRAF mutated and received prior BRAF/MEK inhibitor therapy	HR 0.71 (0.46, 1.08)	Serious[2]	Not serious	N/A	Serious[3]	Low
Vemurafenib vs. dacarbazine – overall survival up to 5 years (effect sizes <1 favour vemurafenib)								
BRIM-3	514	Aged <65 years	RR 0.97 (0.91, 1.03)	Not serious	Not serious	N/A	Not serious	High
	161	Aged ≥65 years	RR 0.92 (0.84, 1.01)	Not serious	Not serious	N/A	Not serious	High
	459	ECOG PF 0	HR 0.86 (0.70–1.07)	Not serious	Not serious	N/A	Serious[3]	Moderate
	216	ECOG PF 1	HR 0.68 (0.52-0.91)	Not serious	Not serious	N/A	Not serious	High
	284	LDH ≤ULN	HR 0.88 (0.70–1.11)	Not serious	Not serious	N/A	Serious[3]	Moderate

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	391	LDH >ULN	HR 0.66 (0.52–0.85)	Not serious	Not serious	N/A	Not serious	High
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – Overall survival up to 2 years (effect sizes <1 favour nivolumab followed by ipilimumab)								
CHECKMATE 064	138	Overall adjusting for ECOG, history of brain metastases, and baseline PD-L1 expression	HR 0·57 (0·33–0·99)	Very serious[1]	Not serious	N/A	Not serious	Low
	82	Aged <65 years	HR 0.54 (0.29, 1.01)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
	56	Aged ≥65 years	HR 0.40 (0.16, 0.97)	Very serious[1]	Not serious	N/A	Not serious	Low
	84	ECOG PF 0	HR 0.51 (0.25, 1.06)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
	54	ECOG PF 1	HR 0.55 (0.27, 1.13)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
	86	LDH ≤ULN	HR 0.71 (0.33, 1.53)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
	52	LDH >ULN	HR 0.32 (0.16, 0.64)	Very serious[1]	Not serious	N/A	Not serious	Low
	117	LDH ≤ 2x ULN	HR 0.55 (0.31, 0.98)	Very serious[1]	Not serious	N/A	Not serious	Low
	21	LDH > 2x ULN	HR 0.31 (0.11, 0.90)	Very serious[1]	Not serious	N/A	Not serious	Low
Nivolumab only versus ipilimumab only – overall survival up to 5 years (effect sizes <1 favour nivolumab only)								
CHECKMATE 067	380	Aged <65 years	HR 0.60 (0.47, 0.78)	Not serious	Not serious	N/A	Not serious	High
	252	Aged ≥65 years	HR 0.69 (0.51, 0.93)	Not serious	Not serious	N/A	Not serious	High
	461	ECOG PF 0	HR 0.61 (0.48, 0.78)	Not serious	Not serious	N/A	Not serious	High
	170	ECOG PF 1+	HR 0.74 (0.52, 1.04)	Not serious	Not serious	N/A	Serious[4]	Moderate
	391	LDH ≤ULN	HR 0.58 (0.44, 0.76)	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	227	LDH >ULN	HR 0.71 (0.53, 0.96)	Not serious	Not serious	N/A	Not serious	High
	67	LDH >2x ULN	HR 0.68 (0.41, 1.15)	Not serious	Not serious	N/A	Serious[4]	Moderate
	433	BRAF WT	HR 0.64 (0.50, 0.81)	Not serious	Not serious	N/A	Not serious	High
	198	BRAF mutated	HR 0.63 (0.44, 0.90)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only – overall survival up to 5 years (effect sizes <1 favour combo)								
CHECKMATE 067	367	Aged <65 years	HR 0.48 (0.37, 0.63)	Not serious	Not serious	N/A	Not serious	High
	262	Aged ≥65 years	HR 0.59 (0.43, 0.81)	Not serious	Not serious	N/A	Not serious	High
	454	ECOG PF 0	HR 0.50 (0.39, 0.64)	Not serious	Not serious	N/A	Not serious	High
	174	ECOG PF 1	HR 0.59 (0.42, 0.85)	Not serious	Not serious	N/A	Not serious	High
	393	LDH ≤ULN	HR 0.48 (0.37, 0.64)	Not serious	Not serious	N/A	Not serious	High
	229	LDH >ULN	HR 0.58 (0.43, 0.79)	Not serious	Not serious	N/A	Not serious	High
	67	LDH >2x ULN	HR 0.50 (0.29, 0.86)	Not serious	Not serious	N/A	Not serious	High
	426	BRAF WT	HR 0.57 (0.45, 0.73)	Not serious	Not serious	N/A	Not serious	High
	203	BRAF mutated	HR 0.44 (0.30, 0.64)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – overall survival up to 5 years (effect sizes <1 favour combo)								
CHECKMATE 067	383	Aged <65 years	HR 0.80 (0.60, 1.06)	Not serious	Not serious	N/A	Serious[4]	Moderate
	247	Aged ≥65 years	HR 0.86 (0.62, 1.20)	Not serious	Not serious	N/A	Serious[4]	Moderate
	467	ECOG PF 0	HR 0.82 (0.63, 1.06)	Not serious	Not serious	N/A	Serious[4]	Moderate
	162	ECOG PF 1	HR 0.81 (0.55, 1.18)	Not serious	Not serious	N/A	Serious[4]	Moderate
	396	LDH ≤ULN	HR 0.83 (0.62, 1.12)	Not serious	Not serious	N/A	Serious[4]	Moderate
	226	LDH >ULN	HR 0.82 (0.59, 1.13)	Not serious	Not serious	N/A	Serious[4]	Moderate

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	74	LDH >2x ULN	HR 0.73 (0.43, 1.24)	Not serious	Not serious	N/A	Serious[4]	Moderate
	429	BRAF WT	HR 0.89 (0.69, 1.15)	Not serious	Not serious	N/A	Serious[4]	Moderate
	201	BRAF mutated	HR 0.70 (0.46, 1.05)	Not serious	Not serious	N/A	Serious[4]	Moderate
Nivolumab + ipilimumab followed by ipilimumab only vs. ipilimumab only – overall survival up to 2 years (effect sizes <1 favour combo)								
CHECKMATE 069	68	Aged <65 years	HR 0.52 (0.24, 1.12)	Not serious	Not serious	N/A	Serious[4]	Moderate
	74	Aged ≥65 years	HR 0.95 (0.45, 2.02)	Not serious	Not serious	N/A	Serious[4]	Moderate
	116	ECOG PF 0	HR0.79 (0.42, 1.48)	Not serious	Not serious	N/A	Serious[4]	Moderate
	24	ECOG PF 1	HR 0.56 (0.19, 1.67)	Not serious	Not serious	N/A	Serious[4]	Moderate
	106	LDH ≤ULN	HR 0.72 (0.37, 1.43)	Not serious	Not serious	N/A	Serious[4]	Moderate
	35	LDH >ULN	HR 0.67 (0.28, 1.60)	Not serious	Not serious	N/A	Serious[4]	Moderate
	110	BRAF wild-type	0.60 (0.32, 1.11)	Not serious	Not serious	N/A	Serious[4]	Moderate
	32	BRAF mutated	HR 1.35 (0.43, 4.26)	Not serious	Not serious	N/A	Serious[4]	Moderate
Encorafenib plus Binimetinib versus vemurafenib – overall survival up to 5 years (effect sizes <1 favour combo)								
COLUMBUS	272	Aged <65 years	HR 0.65 (0.49, 0.88)	Not serious	Not serious	N/A	Not serious	High
	111	Aged ≥65 years	HR 0.64 (0.41, 1.01)	Not serious	Not serious	N/A	Serious[4]	Moderate
	279	ECOG PF 0	HR 0.66 (0.49, 0.89)	Not serious	Not serious	N/A	Not serious	High
	104	ECOG PF 1	HR 0.57 (0.36, 0.89)	Not serious	Not serious	N/A	Not serious	High
	276	LDH ≤ULN	HR 0.53 (0.38, 0.73)	Not serious	Not serious	N/A	Not serious	High
	107	LDH >ULN	HR 0.93 (0.62, 1.39)	Not serious	Not serious	N/A	Serious[4]	Moderate

1. Study was at high risk of bias
2. Study was at low risk of bias but was marked down for this analysis as only pooled data (combining both pembrolizumab arms) was presented.
3. 95% CIs cross one the line of no effect (1.00)

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4. 95% CIs cross one line of the MID (0.8, 1.25)								

Progression-free survival

Table 11 Progression-free survival

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Debrafenib + Trametinib (150/2 dose) vs. dabrafenib alone– Overall survival at 5 years								
BRF113220	61	LDH ≤ULN	RR 0.84 (0.68, 1.04)	Not serious	Not serious	N/A	Serious[4]	Moderate
Pembrolizumbab (2mg) vs. ICC – up to 2 years (effect sizes <1 favour pembro 2mg)								
KEYNOTE-002	370	Aged <65 years	HR 0.47 (0.34, 0.66)	Serious[4]	Not serious	N/A	Not serious	Moderate
		Aged ≥65 years	HR 0.70 (0.48, 1.01)	Serious[4]	Not serious	N/A	Serious[3]	Low
		ECOG PF 0	HR 0.55 (0.40, 0.76)	Serious[4]	Not serious	N/A	Not serious	Moderate
		ECOG PF 1	HR 0.62 (0.43, 0.89)	Serious[4]	Not serious	N/A	Not serious	Moderate
		LDH ≤ULN	HR 0.50 (0.36, 0.70)	Serious[4]	Not serious	N/A	Not serious	Moderate
		LDH >ULN	HR 0.65 (0.46, 0.93)	Serious[4]	Not serious	N/A	Not serious	Moderate
		BRAF WT	HR 0.51 (0.39, 0.67)	Serious[4]	Not serious	N/A	Not serious	Moderate
		BRAF M	HR 0.74 (0.46, 1.18)	Serious[4]	Not serious	N/A	Serious[3]	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Pembrolizumab (10mg) vs. ICC – up to 2 years (effect sizes <1 favour pembro 2mg)								
KEYNOTE-002	370	Aged <65 years	HR 0.42 (0.30, 0.59)	Serious[4]	Not serious	N/A	Not serious	Moderate
		Aged ≥65 years	HR 0.60 (0.41, 0.88)	Serious[4]	Not serious	N/A	Not serious	Moderate
		ECOG PF 0	HR 0.50 (0.35, 0.70)	Serious[4]	Not serious	N/A	Not serious	Moderate
		ECOG PF 1	HR 0.54 (0.38, 0.77)	Serious[4]	Not serious	N/A	Not serious	Moderate
		LDH ≤ULN	HR 0.43 (0.31, 0.61)	Serious[4]	Not serious	N/A	Not serious	Moderate
		LDH >ULN	HR 0.62 (0.43, 0.89)	Serious[4]	Not serious	N/A	Not serious	Moderate
		BRAF WT	HR 0.53 (0.40, 0.69)	Serious[4]	Not serious	N/A	Not serious	Moderate
		BRAF M	HR 0.44 (0.26, 0.74)	Serious[4]	Not serious	N/A	Not serious	Moderate
Pembrolizumbab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumab – Overall survival up to 4 years								
KEYNOTE-006	364	Only patients receiving first line therapy	Pembro (10mg/2W) vs IPI: HR 0.54 (0.42, 0.69)	Not serious	Not serious	N/A	Not serious	High
	366		Pembro (10mg/3W) vs IPI: HR 0.54 (0.42, 0.69)	Not serious	Not serious	N/A	Not serious	High
Nivolumab only versus ipilimumab only – overall survival up to 5 years (effect sizes <1 favour nivolumab only)								
CHECKMATE 067	380	Aged <65 years	HR 0.56 (0.44, 0.71)	Not serious	Not serious	N/A	Not serious	High
	252	Aged ≥65 years	HR 0.49 (0.37, 0.66)	Not serious	Not serious	N/A	Not serious	High
	461	ECOG PF 0	HR 0.51 (0.41, 0.63)	Not serious	Not serious	N/A	Not serious	High
	170	ECOG PF 1+	HR 0.63 (0.44, 0.89)	Not serious	Not serious	N/A	Not serious	High
	391	LDH ≤ULN	HR 0.50 (0.39, 0.63)	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	227	LDH >ULN	HR 0.50 (0.44, 0.80)	Not serious	Not serious	N/A	Not serious	High
	67	LDH >2x ULN	HR 0.57 (0.33, 1.00)	Not serious	Not serious	N/A	Not serious	High
	433	BRAF WT	HR 0.46 (0.37, 0.58)	Not serious	Not serious	N/A	Not serious	High
	198	BRAF mutated	HR 0.73 (0.53, 1.01)	Not serious	Not serious	N/A	Serious[4]	Moderate
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only – overall survival up to 5 years (effect sizes <1 favour combo)								
CHECKMATE 067	367	Aged <65 years	HR 0.41 (0.31, 0.52)	Not serious	Not serious	N/A	Not serious	High
	262	Aged ≥65 years	HR 0.44 (0.33, 0.59)	Not serious	Not serious	N/A	Not serious	High
	454	ECOG PF 0	HR 0.41 (0.33, 0.51)	Not serious	Not serious	N/A	Not serious	High
	174	ECOG PF 1	HR 0.47 (0.32, 0.67)	Not serious	Not serious	N/A	Not serious	High
	393	LDH ≤ULN	HR 0.38 (0.30, 0.49)	Not serious	Not serious	N/A	Not serious	High
	229	LDH >ULN	HR 0.46 (0.34, 0.62)	Not serious	Not serious	N/A	Not serious	High
	67	LDH >2x ULN	HR 0.40 (0.23, 0.70)	Not serious	Not serious	N/A	Not serious	High
	426	BRAF WT	HR 0.41 (0.33, 0.52)	Not serious	Not serious	N/A	Not serious	High
	203	BRAF mutated	HR 0.44 (0.31, 0.62)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – overall survival up to 5 years (effect sizes <1 favour combo)								
CHECKMATE 067	383	Aged <65 years	HR 0.73 (0.56, 0.94)	Not serious	Not serious	N/A	Not serious	High
	247	Aged ≥65 years	HR 0.89 (0.65, 1.23)	Not serious	Not serious	N/A	Serious[4]	Moderate
	467	ECOG PF 0	HR 0.80 (0.63, 1.01)	Not serious	Not serious	N/A	Serious[4]	Moderate
	162	ECOG PF 1	HR 0.74 (0.51, 1.10)	Not serious	Not serious	N/A	Serious[4]	Moderate
	396	LDH ≤ULN	HR 0.76 (0.59, 0.99)	Not serious	Not serious	N/A	Not serious	High
	226	LDH >ULN	HR 0.77 (0.56, 1.05)	Not serious	Not serious	N/A	Serious[4]	Moderate

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	74	LDH >2x ULN	HR 0.70 (0.41, 1.17)	Not serious	Not serious	N/A	Serious[4]	Moderate
	429	BRAF WT	HR 0.89 (0.70, 1.13)	Not serious	Not serious	N/A	Serious[4]	Moderate
	201	BRAF mutated	HR 0.60 (0.43, 0.86)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by ipilimumab only vs. ipilimumab only – overall survival up to 2 years (effect sizes <1 favour combo)								
CHECKMATE 069	68	Aged <65 years	HR 0.29 (0.14, 0.60)	Not serious	Not serious	N/A	Not serious	High
	74	Aged ≥65 years	HR 0.43 (0.24, 0.79)	Not serious	Not serious	N/A	Not serious	High
	116	ECOG PF 0	HR 0.34 (0.20, 0.56)	Not serious	Not serious	N/A	Not serious	High
	24	ECOG PF 1	HR 0.44 (0.15, 1.34)	Not serious	Not serious	N/A	Serious[4]	Moderate
	106	LDH ≤ULN	HR 0.35 (0.21, 0.60)	Not serious	Not serious	N/A	Not serious	High
	35	LDH >ULN	HR 0.42 (0.16, 1.05)	Not serious	Not serious	N/A	Serious[4]	Moderate
	110	BRAF wild-type	HR 0.36 (0.21, 0.60)	Not serious	Not serious	N/A	Not serious	High
	32	BRAF mutated	HR 0.36 (0.14, 0.97)	Not serious	Not serious	N/A	Not serious	High

1. Study was at high risk of bias
2. Study was at low risk of bias but was marked down for this analysis as only pooled data (combining both pembrolizumab arms) was presented.
3. 95% CIs cross one the line of no effect (1.00)
4. 95% CIs cross one line of the MID (0.8, 1.25)
5. Study was at moderate risk of bias

Grade ≥3 adverse events

Table 12 Grade 3-5 adverse events

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. investigator's choice of chemotherapy – Treatment-related events occurring on or up to 30 days after treatment (per protocol)										
CHECKMATE 037	370	Nivolumab (3 mg/kg every 2 weeks) 126/268 (47.0%)	ICC (dacarbazine or carboplatin) 46/102 (45.1%)	N/A	RR 1.04 (0.81, 1.34)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
Nivolumab vs. dacarbazine – Treatment-related events (in those who received at least one dose of study drug)										
CHECKMATE 066	411	nivolumab (3 mg/kg every 2 weeks) 33/206	dacarbazine (1,000 mg/m2 every 3 weeks) 36/205	N/A	RR 0.91 (0.59, 1.40)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Debrafenib + Trametinib (low dose) vs. Debrafenib + Trametinib (high dose) vs. dabrafenib alone– Treatment-related events										
BRF113220	109	dabrafenib (150mg 2xdaily) plus trametinib (1mg 1x daily)	dabrafenib (150mg 2xdaily) plus trametinib (2mg 1x daily)	Dabrafenib alone (150mg 2xdaily)	Combo (low dose) vs. mono: RR 1.14 (0.78, 1.66)	Serious[2]	Not serious	N/A	Very serious[5]	Very low

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		29/54	37/55	25/53	Combo (high dose) vs mono: RR 1.43 (1.02, 2.00)	Serious[2]	Not serious	N/A	Serious[4]	Low
					Combo (low dose) vs high dose: RR 0.80 (0.59, 1.09)	Serious[2]	Not serious	N/A	Serious[4]	Low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC - Treatment-related events occurring on or up to 30 days after treatment (per protocol)										
KEYNOTE-002	528	Pembrolizumab (2mg every 3 months) 24/178	Pembrolizumab (10mg every 3 months) 29/179	ICC 45/171	2mg vs 10mg: RR 0.83 (0.51, 1.37)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
					2mg vs. ICC: RR0.51 (0.33, 0.80)	Serious[2]	Not serious	N/A	Not serious	Moderate
					10mg vs ICC: RR 0.62 (0.41, 0.93)	Serious[2]	Not serious	N/A	Serious[4]	Low
Pembrolizumab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumamb - Treatment-related events occurring until 30 days (90 days for serious adverse events) after the last dose of study drug or before the initiation of a new anticancer treatment										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
KEYNOTE-006 2 years	811	Pembrolizumab (10mg every 2 week) 47/278	Pembrolizumab (10mg every 3 weeks) 46/277	ipilimumab 3 mg/kg every 3 weeks 50/256	Pembro 2 week vs 3 week: RR 1.02 (0.70, 1.48)	Not serious	Not serious	N/A	Very serious[5]	Low
					Pembro 2 week vs ipi: RR 0.87 (0.60, 1.24)	Not serious	Not serious	N/A	Serious[4]	Moderate
					Pembro 3 week vs. ipi RR 0.85 (0.59, 1.22)	Not serious	Not serious	N/A	Serious[4]	Moderate
Pembrolizumbab (low dose) vs. Pembrolizumab (high dose) vs. ICC - Treatment-related events occurring until 30 days (90 days for serious adverse events) after the last dose of study drug or before the initiation of a new anticancer treatment										
KEYNOTE-006	811	Pembrolizumab (10mg every 2/3 months) 102/555	ipilimumab 3 mg/kg every 3 weeks 54/256	NA	RR 0.87 (0.65, 1.17)	Serious[3]	Not serious	N/A	Serious[4]	Low
Ipilimumab + nivolumab vs. nivolumab – treatment-related adverse events (each patient entered once)										
ABC trial	60	ipilimumab (3 mg/kg every 3 weeks for four doses), then nivolumab	nivolumab 3 mg/kg every 2 weeks. 4/25	N/A	RR 3.93 (1.54, 9.99)	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		(3 mg/kg every 2 weeks) 22/35								
Vemurafenib vs. dacarbazine - treatment-related adverse events (each patient entered once)										
BRIM 3	623	vemurafenib (960mg twice daily) 252/336	dacarbazine (1000 mg/m2 every 3 weeks) 123/287	N/A	RR 1.75 (1.51, 2.03)	Not serious	Not serious	N/A	Not serious	High
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – treatment-related adverse events in patients who received at least one study dose until up to 30 days after last dose.										
CHECKMATE 064	138	Nivolumab (3 mg/kg every 2 weeks for up to six doses during weeks 1 to 13), followed by ipilimumab (3 mg/kg every 3 weeks for up to four doses during weeks 13–25) 43/68	Ipilimumab followed by nivolumab (reverse of arm 1) 35/70	N/A	RR 1.26 (0.94, 1.70)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – treatment-related adverse events in patients who received at least one dose of study drug, up to 100 days after last dose										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 067 **5-year data*	626	Nivolumab + ipilimumab followed by nivolumab 186/313	Nivolumab only 73/313	N/A	RR 2.55 (2.04, 3.18)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only - – treatment-related adverse events in patients who received at least one dose of study drug, up to 30 (CHECKMATE-069) or 100 days (CHECKMATE-067) after last dose										
CHECKAMTE 067 *(*5-year)* and CHECKMATE 069 (**2 year)*	764	Nivolumab + ipilimumab followed by nivolumab 238/407	Ipilimumab only 95/357	N/A	RR 2.20 (1.82, 2.66)	Not serious	Not serious	Not serious	Not serious	High
Debrafenib + Trametinib versus dabrafenib alone – treatment-related adverse events up to 30 days after last dose										
COMBI-D	420	Dabrafenib + trametinib 66/209	Dabrafenib alone 63/211	N/A	RR 1.06 (0.79, 1.41)	Not serious	Not serious	N/A	Very serious[5]	Low
Debrafenib + Trametinib versus Vemurafenib – treatment-related adverse events up to 30 days after last dose										
COMBI-V	699	Dabrafenib + trametinib 167/350	Vemurafenib 198/349	N/A	RR 0.84 (0.73, 0.97)	Very serious[1]	Not serious	N/A	Serious[4]	Very low
Encorafenib Plus Binimetinib vs. vemurafenib vs. encorafenib alone – treatment-related adverse events in patients who received at least one dose of study drug										
COLUMBUS	570	Encorafenib Plus Binimetinib	Vemurafenib	Encorafenib	Combo vs Veru: RR 1.04	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		131/192	122/186	130/192	(0.90, 1.20)					
					Combo vs Enco RR 1.01 (0.88, 1.16)	Not serious	Not serious	N/A	Not serious	High
					Veru vs. enco: RR 0.97 (0.84, 1.12)	Not serious	Not serious	N/A	Not serious	High

6. Study was at high risk of bias
7. Study was at moderate risk of bias
8. Study was at low risk of bias but was marked down for this analysis as only pooled data (combining both pembrolizumab arms) was presented.
9. 95% CIs cross one line of the MID (0.8, 1.25)
10. 95% CIs cross both lines of the MID (0.8, 1.25)

Adverse events leading to discontinuation of study drug

Table 13 Adverse events leading to discontinuation of study drug

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. investigator's choice of chemotherapy – Treatment-related events occurring on or up to 30 days after treatment (per protocol)										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 037	370	Nivolumab (3 mg/kg every 2 weeks) 39/268	ICC (dacarbazine or carboplatin) 16/102	N/A	RR 0.93 (0.54, 1.58)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low
Nivolumab vs. dacarbazine – Treatment-related events (in those who received at least one dose of study drug)										
CHECKMATE 066	411	nivolumab (3 mg/kg every 2 weeks) 19/206	dacarbazine (1,000 mg/m2 every 3 weeks) 8/205	N/A	RR 2.36 (1.06, 5.28)	Serious[2]	Not serious	N/A	Serious[4]	Low
Pembrolizumbab (low dose) vs. Pembrolizumab (high dose) vs. ICC - Treatment-related events occurring on or up to 30 days after treatment (per protocol)										
KEYNOTE-002	528	Pembrolizumab (2mg every 3 months) 8/178	Pembrolizumab (10mg every 3 months) 15/179	ICC 9/171	2mg vs 10mg: RR 0.54 (0.23, 1.23)	Serious[2]	Not serious	N/A	Serious[4]	Low
					2mg vs ICC: RR 0.85 (0.34, 2.16)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
					10mg vs ICC: RR 1.59 (0.72, 3.54)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Pembrolizumbab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumamb - Treatment-related events occurring until 30 days (90 days for serious adverse events) after the last dose of study drug or before the initiation of a new anticancer treatment										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
KEYNOTE-006 2 years	811	Pembrolizumab (10mg every 2 weeks) 29/278	Pembrolizumab (10mg every 3 weeks) 45/277	ipilimumab 3 mg/kg every 3 weeks 35/256	Pembro 2 week vs. penbro 3 weeks: RR 0.64 (0.42, 0.99)	Not serious	Not serious	N/A	Serious[4]	Moderate
					Pembro 2 week vs. ipi: RR 0.76 (0.48, 1.21)	Not serious	Not serious	N/A	Serious[4]	Moderate
					Pembro 3 week vs. ipi: RR 1.19 (0.79, 1.79)	Not serious	Not serious	N/A	Very serious[5]	Low
Pembrolizumbab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumamb - Treatment-related events occurring until 30 days (90 days for serious adverse events) after the last dose of study drug or before the initiation of a new anticancer treatment										
KEYNOTE-006 5 years[3]	811	Pembrolizumab (10mg every 2/3 weeks) 55/555	ipilimumab 3 mg/kg every 3 weeks 23/256	NA	RR 1.10 (0.69, 1.75)	Serious[3]	Not serious	N/A	Very serious[5]	Very low
Ipilimumab + nivolumab vs. nivolumab – treatment-related adverse events (each patient entered once)										
ABC trial	60	ipilimumab (3 mg/kg every 3 weeks for four doses), then nivolumab	nivolumab 3 mg/kg every 2 weeks. 1/25	N/A	RR 6.43 (0.87, 47.56)	Not serious	Not serious	N/A	Serious[4]	Moderate

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		(3 mg/kg every 2 weeks) 9/35								
Vemurafenib vs. dacarbazine - treatment-related adverse events (each patient entered once)										
BRIM 3	623	vemurafenib (960mg twice daily) 25/336	dacarbazine (1000 mg/m2 every 3 weeks) 5/287	N/A	RR 4.27 (1.66, 11.01)	Not serious	Not serious	N/A	Not serious	High
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – treatment-related adverse events in patients who received at least one study dose until up to 30 days after last dose.										
CHECKMATE 064	138	Nivolumab (3 mg/kg every 2 weeks for up to six doses during weeks 1 to 13), followed by ipilimumab (3 mg/kg every 3 weeks for up to four doses during weeks 13–25) 25/68	Ipilimumab followed by nivolumab (reverse of arm 1) 23/70	N/A	RR 1.12 (0.71, 1.77)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – treatment-related adverse events in patients who received at least one dose of study drug, up to 100 days after last dose										
CHECKMATE 067 **5-year data*	626	Nivolumab + ipilimumab followed by nivolumab 130/313	Nivolumab only 40/313	N/A	RR 3.25 (2.37, 4.47)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only - – treatment-related adverse events in patients who received at least one dose of study drug, up to 30 (CHECKMATE-069) or 100 days (CHECKMATE-067) after last dose										
CHECKAMTE 067 *(*5-year)* and CHECKMATE 069 (**2 year)*	764	Nivolumab + ipilimumab followed by nivolumab 165/407	Ipilimumab only 51/357	N/A	RR 2.84 (2.14, 3.75)	Not serious	Not serious	N/A	Not serious	High
Debrafenib + Trametinib versus dabrafenib alone – treatment-related adverse events up to 30 days after last dose										
COMBI-D	420	Dabrafenib + trametinib 24/209	Dabrafenib alone 14/211	N/A	RR 1.73 (0.92, 3.25)	Not serious	Not serious	N/A	Serious[4]	Moderate
Debrafenib + Trametinib versus Vemurafenib – treatment-related adverse events up to 30 days after last dose										

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
COMBI-V	699	Dabrafenib + trametinib 46/350	Vemurafenib 42/349	N/A	RR 1.09 (0.74, 1.61)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low
Encorafenib Plus Binimetinib vs. vemurafenib vs. encorafenib alone – treatment-related adverse events in patients who received at least one dose of study drug										
COLUMBUS	570	Encorafenib Plus Binimetinib 20/192	Vemurafenib 26/186	Encorafenib 24/192	Combo vs vemu: RR 0.75 (0.43, 1.29)	Not serious	Not serious	N/A	Very serious[5]	Low
					Combo vs enco: 0.83 (0.48, 1.46)	Not serious	Not serious	N/A	Very serious[5]	Low
					Vemu vs enco: RR 1.12 (0.67, 1.88)	Not serious	Not serious	N/A	Very serious[5]	Low
Debrafenib vs. dacarbazine – treatment-related adverse events										
BREAK-3	250	Dabrafenib 5/187	Dacarbazine 2/63	N/A	RR 0.84 (0.17, 4.23)	Not serious	Not serious	N/A	Very serious[5]	Low

1. Study was at high risk of bias
2. Study was at moderate risk of bias
3. Study was at low risk of bias overall but was marked down for this analysis as only pooled data (combining both pembrolizumab arms) was presented.
4. 95% CIs cross one line of the MID (0.8, 1.25)
5. 95% CIs cross both lines of the MID (0.8, 1.25)

Vitiligo (any grade)

Table 14 Any grade adverse events: Vitiligo

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. investigator's choice of chemotherapy – Treatment-related events occurring on or up to 30 days after treatment (per protocol)										
CHECKMATE 037	370	Nivolumab (3 mg/kg every 2 weeks) 29/268	ICC (dacarbazine or carboplatin) 0/102	N/A	RR 22.59 (1.39, 366.32)	Very serious[1]	Not serious	N/A	Not serious	Low
Nivolumab vs. dacarbazine – Treatment-related events (in those who received at least one dose of study drug)										
CHECKMATE 066	411	nivolumab (3 mg/kg every 2 weeks) 34/206	dacarbazine (1,000 mg/m2 every 3 weeks) 1/205	N/A	RR 33.83 (4.68, 244.85)	Serious[2]	Not serious	N/A	Not serious	Moderate
Pembrolizumbab (low dose) vs. Pembrolizumab (high dose) vs. ICC - Treatment-related events occurring on or up to 30 days after treatment (per protocol)										
KEYNOTE-002	528	Pembrolizumab (2mg every 3 months) 13/178	Pembrolizumab (10mg every 3 months) 14/179	ICC 2/171	2mg vs 10mg: RR 0.93 (0.45, 1.93)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
					2mg vs ICC: RR 6.24 (1.43, 27.26)	Serious[2]	Not serious	N/A	Not serious	Moderate

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
					10mg vs ICC: RR 6.69 (1.54, 28.99)	Serious[2]	Not serious	N/A	Not serious	Moderate
Pembrolizumbab (10mg every 2 weeks) vs. Pembrolizumab (10mg every 3 weeks) vs. Ipilimumamb - Treatment-related events occurring until 30 days (90 days for serious adverse events) after the last dose of study drug or before the initiation of a new anticancer treatment										
KEYNOTE-006	811	Pembrolizumab (10mg every 2/3 weeks) 71/555	ipilimumab 3 mg/kg every 3 weeks 4/256	NA	RR 8.19 (3.02, 22.17)	Serious[3]	Not serious	N/A	Not serious	Moderate
Ipilimumab + nivolumab vs. nivolumab – treatment-related adverse events (each patient entered once)										
ABC trial	60	ipilimumab (3 mg/kg every 3 weeks for four doses), then nivolumab (3 mg/kg every 2 weeks) 4/35	nivolumab 3 mg/kg every 2 weeks. 2/25	N/A	RR 1.43 (0.28, 7.20)	Not serious	Not serious	N/A	Very serious[5]	Low
Vemurafenib vs. dacarbazine - treatment-related adverse events (each patient entered once)										
BRIM 3	623	vemurafenib (960mg twice daily)	dacarbazine (1000 mg/m2 every 3 weeks)	N/A	RR 4.27 (0.21, 88.64)	Not serious	Not serious	N/A	Very serious[5]	Low

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		2/336	0/287							
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – treatment-related adverse events in patients who received at least one study dose until up to 30 days after last dose.										
CHECKMATE 064	138	Nivolumab (3 mg/kg every 2 weeks for up to six doses during weeks 1 to 13), followed by ipilimumab (3 mg/kg every 3 weeks for up to four doses during weeks 13–25) 8/68	Ipilimumab followed by nivolumab (reverse of arm 1) 10/70	N/A	RR 0.82 (0.35, 1.96)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – treatment-related adverse events in patients who received at least one dose of study drug, up to 100 days after last dose										
CHECKMATE 067 **5-year data*	626	Nivolumab + ipilimumab followed by nivolumab 28/313	Nivolumab only 33/313	N/A	RR 0.85 (0.53, 1.37)	Not serious	Not serious	N/A	Very serious[5]	Low

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only - – treatment-related adverse events in patients who received at least one dose of study drug, up to 30 (CHECKMATE-069) or 100 days (CHECKMATE-067) after last dose										
CHECKAMTE 067 *(*5-year)* and CHECKMATE 069 (*1-year)*	764	Nivolumab + ipilimumab followed by nivolumab 38/407	Ipilimumab only 20/357	N/A	RR 1.61 (0.96, 2.71)	Not serious	Not serious	N/A	Serious[4]	Moderate

1. Study was at high risk of bias
2. Study was at moderate risk of bias
3. Study was at low risk of bias but was marked down for this analysis as only pooled data (combining both pembrolizumab arms) was presented.
4. 95% CIs cross one line of the MID (0.8, 1.25)
5. 95% CIs cross both lines of the MID (0.8, 1.25)

Colitis (any grade)

Table 15 Any grade adverse events: Colitis

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. investigator's choice of chemotherapy – Treatment-related events occurring on or up to 30 days after treatment (per protocol)										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 037	370	Nivolumab (3 mg/kg every 2 weeks) 4/268	ICC (dacarbazine or carboplatin) 0/102 (45.1%)	N/A	RR 3.45 (0.19, 63.44)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low
Nivolumab vs. dacarbazine – Treatment-related events (in those who received at least one dose of study drug)										
CHECKMATE 066	411	nivolumab (3 mg/kg every 2 weeks) 2/206	dacarbazine (1,000 mg/m2 every 3 weeks) 0/205	N/A	RR 4.98 (0.24, 103.01)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Ipilimumab + nivolumab vs. nivolumab – treatment-related adverse events (each patient entered once)										
ABC trial	60	ipilimumab (3 mg/kg every 3 weeks for four doses), then nivolumab (3 mg/kg every 2 weeks) 22/35	nivolumab 3 mg/kg every 2 weeks. 5/25	N/A	RR 3.14 (1.38, 7.17)	Not serious	Very serious[3]	N/A	Not serious	Low
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – treatment-related adverse events in patients who received at least one study dose until up to 30 days after last dose.										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 064	138	Nivolumab (3 mg/kg every 2 weeks for up to six doses during weeks 1 to 13), followed by ipilimumab (3 mg/kg every 3 weeks for up to four doses during weeks 13–25) 11/68	Ipilimumab followed by nivolumab (reverse of arm 1) 18/70	N/A	RR 0.63 (0.32, 1.23)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – treatment-related adverse events in patients who received at least one dose of study drug, up to 100 days after last dose										
CHECKMATE 067 **5-year data*	626	Nivolumab + ipilimumab followed by nivolumab 41/313	Nivolumab only 8/313	N/A	RR 5.13 (2.44, 10.75)	Not serious	Not serious	N/A	Not serious	High
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only - – treatment-related adverse events in patients who received at least one dose of study drug, up to 30 (CHECKMATE-069) or 100 days (CHECKMATE-067) after last dose										
CHECKAMTE 067 *(*5-year)* and CHECKMATE 069 (**2 year)*	764	Nivolumab + ipilimumab followed by nivolumab	Ipilimumab only 38/357	N/A	RR 1.33 (0.90, 1.97)	Not serious	Not serious	Serious[6]	Serious[4]	Low

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		58/407								
Encorafenib Plus Binimetinib vs. vemurafenib vs. encorafenib alone – treatment-related adverse events in patients who received at least one dose of study drug										
COLUMBUS	570	Encorafenib Plus Binimetinib 2/192	Vemurafenib 1/186	Encorafenib 1/192	Combo vs vemu: RR 1.94 (0.18, 21.19)	Not serious	Not serious	N/A	Very serious[5]	Low
					Combo vs enco: RR 2.00 (0.18, 21.87)	Not serious	Not serious	N/A	Very serious[5]	Low
					Vemu vs enco: RR 1.03 (0.07, 16.38)	Not serious	Not serious	N/A	Very serious[5]	Low

1. Study was at high risk of bias
2. Study was at moderate risk of bias
3. Study was only indirectly applicable to the review question for this outcome: Outcome was combination of colitis or diarrhoea
4. 95% CIs cross one line of the MID (0.8, 1.25)
5. 95% CIs cross both lines of the MID (0.8, 1.25)
6. I^2 >33.3%

Hepatic adverse events (grade ≥3 only)

Table 16 Grade 3-5 hepatic adverse events (increased aspartate aminotransferase [AST], increased alanine aminotransferase [ALT], hepatitis, increased blood alkaline phosphate)

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. investigator's choice of chemotherapy –increased AST, ALT or increased blood alkaline phosphatase on or up to 30 days after treatment (per protocol)										
CHECKMATE 037	370	Nivolumab (3 mg/kg every 2 weeks) 7/268	ICC (dacarbazine or carboplatin) 0/102	N/A	RR 5.74 (0.33, 99.66)	Very serious[1]	Not serious	N/A	Very serious[5]	Very low
Debrafenib + Trametinib (low dose) vs. Debrafenib + Trametinib (high dose) vs. dabrafenib alone– Increased ALT										
BRF113220	109	dabrafenib (150mg 2xdaily) plus trametinib (1mg 1x daily) 2/54	dabrafenib (150mg 2xdaily) plus trametinib (2mg 1x daily) 2/55	Dabrafenib alone (150mg 2xdaily) 0/53	Low vs high dose combo: RR 1.02 (0.15, 6.97)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
					Low dose combo vs mono: RR 4.91 (0.24, 99.90)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
					High dose combo vs mono: RR 4.82 (0.24, 98.13)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Ipilimumab + nivolumab vs. nivolumab – increased ALT, increased AST and hepatitis										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
ABC trial	60	ipilimumab (3 mg/kg every 3 weeks for four doses), then nivolumab (3 mg/kg every 2 weeks) 9/35	nivolumab 3 mg/kg every 2 weeks. 2/25	N/A	RR 3.21 (0.76, 13.62)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Vemurafenib vs. dacarbazine - any hepatobiliary adverse event										
BRIM 3	623	vemurafenib (960mg twice daily) 8/336	dacarbazine (1000 mg/m2 every 3 weeks) 2/287	N/A	RR 3.42 (0.73, 15.96)	Serious[3]	Not serious	N/A	Very serious[5]	Very low
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab – increased ALT and increased ALT in patients who received at least one study dose until up to 30 days after last dose										
CHECKMATE 064	138	Nivolumab (3 mg/kg every 2 weeks for up to six doses during weeks 1 to 13), followed by ipilimumab (3 mg/kg every 3 weeks for up to four doses during weeks 13–25)	Ipilimumab followed by nivolumab (reverse of arm 1) 3/70	N/A	RR 4.12 (1.22, 13.95)	Very serious[1]	Not serious	N/A	Serious[4]	Very low

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		12/68								
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only – increased ALT and increased ALT in patients who received at least one dose of study drug, up to 100 days after last dose										
CHECKMATE 067	626	Nivolumab + ipilimumab followed by nivolumab 46/313	Nivolumab only 7/313	Ipilimumab only 7/311	Combo vs nivo: RR 6.57 (3.01, 14.33)	Serious[2]	Not serious	N/A	Not serious	Moderate
					Combo vs ipi: RR 6.53 (2.99, 14.24)	Serious[2]	Not serious	N/A	Not serious	Moderate
					Nivo vs ipi: RR 1.64 (0.77, 3.50)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only - – increased ALT and increased ALT in patients who received at least one dose of study drug, up to 30 (CHECKMATE-069) or 100 days (CHECKMATE-067) after last dose										

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 069	764	Nivolumab + ipilimumab followed by nivolumab 17/94	Ipilimumab only 0/46	N/A	RR 17.32 (1.06, 281.72)	Serious[2]	Not serious	N/A	Serious[4]	Low
Debrafenib + Trametinib versus dabrafenib alone – increased ALT and increased ALT up to 30 days after last dose										
COMBI-D	420	Dabrafenib + trametinib 66/209	Dabrafenib alone 63/211	N/A	RR 1.06 (0.79, 1.41)	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Encorafenib Plus Binimetinib vs. vemurafenib vs. encorafenib alone – increased ALT and increased ALT in patients who received at least one dose of study drug										
COLUMBUS	570	Encorafenib Plus Binimetinib 14/192	Vemurafenib 6/186	Encorafenib 3/192	Combo vs vemu: RR 2.46 (1.18, 5.13)	Serious[2]	Not serious	N/A	Serious[4]	Low
					Combo vs enco: RR 4.67 (1.36, 15.98)	Serious[2]	Not serious	N/A	Not serious	Moderate
					Vemu vs enco: RR 2.06 (0.52, 8.13)	Serious[2]	Not serious	N/A	Very serious[5]	Very low

1. Study was at high risk of bias

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2. Study was at low risk of bias overall but was marked down for this outcome as the number of events was a composite of different hepatic events and it is unclear whether double counting of participants occurred (where one participant had multiple hepatic events and was counted several times) 3. Study was at low risk of bias overall but was marked down for this outcome as it is unclear whether those participants with multiple events were counted just once. 4. 95% CIs cross one line of the MID (0.8, 1.25) 5. 95% CIs cross both lines of the MID (0.8, 1.25)										

1 Receiving subsequent treatment after study drug(s)

2 **Table 17 Number of patients who went on to receive subsequent anti-cancer treatment after study drug(s)**

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. dacarbazine										
CHECKMATE 066	411	nivolumab (3 mg/kg every 2 weeks) 124/210	dacarbazine (1,000 mg/m2 every 3 weeks) 153/208	N/A	RR 0.80 (0.70, 0.92)	Serious[2]	Not serious	N/A	Serious[4]	Low
Nivolumab followed by ipilimumab vs. ipilimumab followed by nivolumab										
CHECKMATE 064	138	Nivolumab (3 mg/kg every 2 weeks for up to six doses during	Ipilimumab followed by nivolumab	N/A	RR 1.84 (1.05, 3.23)	Very serious[1]	Not serious	N/A	Serious[4]	Very low

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
		weeks 1 to 13), followed by ipilimumab (3 mg/kg every 3 weeks for up to four doses during weeks 13–25) 25/68	(reverse of arm 1) 14/70							
Vemurafenib vs. dacarbazine										
BRIM 3	623	vemurafenib (960mg twice daily) 175/337	dacarbazine (1000 mg/m2 every 3 weeks) 173/338	N/A	RR 1.01 (0.88, 1.17)	Serious[3]	Not serious	N/A	Not serious	Moderate
Debrafenib + Trametinib (low dose) vs. Debrafenib + Trametinib (high dose) vs. dabrafenib alone										
BRF113220	109	dabrafenib (150mg 2xdaily) plus trametinib (1mg 1x daily) 27/54	dabrafenib (150mg 2xdaily) plus trametinib (2mg 1x daily) 29/55	Dabrafenib alone (150mg 2xdaily) 50/54	Low vs high dose combo: RR 0.95 (0.66, 1.37)	Serious[2]	Not serious	N/A	Very serious[3]	Very low
					Low dose combo vs mono: RR 0.54 (0.41, 0.71)	Serious[2]	Not serious	N/A	Not serious	Moderate

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
					High dose combo vs mono: RR 0.57 (0.44, 0.74)	Serious[2]	Not serious	N/A	Not serious	Moderate
Nivolumab + ipilimumab followed by nivolumab only versus Nivolumab only										
CHECKMATE 067	626	Nivolumab + ipilimumab followed by nivolumab 143/314	Nivolumab only 185/316	Ipilimumab only 237/315	Combo vs nivo: RR 0.78 (0.67, 0.91)	Serious[2]	Not serious	N/A	Serious[4]	Low
					Combo vs ipi: RR 0.61 (0.53, 0.69)	Serious[2]	Not serious	N/A	Not serious	Moderate
					Nivo vs ipi: RR 0.78 (0.70, 0.87)	Serious[2]	Not serious	N/A	Serious[4]	Low
Nivolumab + ipilimumab followed by nivolumab only versus ipilimumab only										

Study	Sample size	# adverse events (%) Arm 1	Arm 2	Arm 3	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
CHECKMATE 069	764	Nivolumab + ipilimumab followed by nivolumab 33/95	Ipilimumab only 33/47	N/A	RR 0.49 (0.35, 0.69)	Serious[2]	Not serious	N/A	Not serious	Moderate
Debrafenib + Trametinib versus dabrafenib alone										
COMBI-D	420	Dabrafenib + trametinib 70/209	Dabrafenib alone 108/211	N/A	RR 0.65 (0.52, 0.83)	Serious[2]	Not serious	N/A	Serious[4]	Low
Debrafenib + Trametinib versus Vemurafenib										
COMBI-V	699	Dabrafenib + trametinib 70/350	Vemurafenib 150/349	N/A	RR 0.47 (0.37, 0.59)	Very serious[1]	Not serious	N/A	Not serious	Low
Encorafenib Plus Binimetinib vs. vemurafenib vs. encorafenib alone – increased ALT and increased ALT in patients who received at least one dose of study drug										
COLUMBUS	570	Encorafenib Plus Binimetinib 82/156	Vemurafenib 122/177	Encorafenib 107/172	Combo vs vemu: RR 0.76 (0.64, 0.91)	Serious[2]	Not serious	N/A	Serious[4]	Low
					Combo vs enco: RR 0.84 (0.70, 1.02)	Serious[2]	Not serious	N/A	Serious[4]	Low

Study	Sample size	# adverse events (%)			Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
					Vemu vs enco: RR 1.11 (0.95, 1.29)	Serious[2]	Not serious	N/A	Serious[4]	Low

1. Study was at high risk of bias
2. Study was at low risk of bias overall but was marked down for this outcome as the number of events was a composite of different hepatic events and it is unclear whether double counting of participants occurred (where one participant had multiple hepatic events and was counted several times)
3. 95% CIs cross both lines of the MID (0.8, 1.25)
4. 95% CIs cross one line of the MID (0.8, 1.25)

1 **EORTC QLQ-C30 – Global health status**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	259	Nivolumab (3 mg/kg every 2 weeks) 1.8 (-0.76, 5.36)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 0.9 (-5.83, 7.63)[1]	N/A	MD 0.9 (-6.0, 7.8)	Very serious[2]	Not serious	N/A	No serious	Low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12										
	520		Pembrolizumab	ICC	MD 6.50	Serious[4]	Not serious	N/A	Serious[5]	Low

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
KEYNOTE-002		Pembrolizumab (2mg every 3 months) -2.6 (-6.2, 1.0)	(10mg every 3 months) -2.6 (-6.0, 0.9)	-9.1 (-12.9, - 5.4)	(1.37, 11.63)[3]					
					MD 6.50 (1.44, 11.56)[6]	Serious[4]	Not serious	N/A	Serious[5]	Low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12 (least squares means)										
KEYNOTE-006	459	Pembrolizumab (10mg every 2 months) -1.9 (-4.86, 1.01)	Pembrolizumab (10mg every 3 months) -2.5 (-5.32, 0.37)	Ipilimumab 3 mg/kg every 3 weeks -10.0 (-13.16, - 6.85)	MD 8.1 (3.89, 12.27)[7]	Serious[8]	Not serious	N/A	Serious[5]	Low
					MD 7.5 (3.40, 11.66)[9]	Serious[8]	Not serious	N/A	Serious[5]	Low
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	505	Nivolumab + ipilimumab -5.8 (-7.77, -3.83)[1]	Nivolumab + placebo -3.6 (-5.37, -1.83)[1]	N/A	MD -2.2 (-4.84, 0.44)[10]	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	492	Nivolumab + ipilimumab -5.8 (-7.77, -3.83)[1]	Ipilimumab + placebo -5.9 (-7.87, - 3.93)[1]	N/A	MD 0.1 (-2.5, 2.7)	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 067	519	Nivolumab + placebo -3.6 (-5.37, -1.83)[1]	Ipilimumab + placebo -7.1 (-9.07, - 5.13)[1]	N/A	MD 3.6 (1.2, 6.0)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	234	Dabrafenib + trametinib 3.0 (NR)	Vemurafenib -4.57 (NR)	NA	MD 7.56 (3·56, 11·57)	Very serious [11]	Not serious	N/A	Serious[5]	Very low
Dabrafenib vs. Dacarbazine – at week 12 (mixed-model repeated measures)										
BREAK-3	151	Dabrafenib (150 mg twice daily) 2.47 (-0.38, 5.32)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 0.55 (-7.31, 8.41)[1]	N/A	MD 1.92 (-5.99, 9.38)	Serious [12]	Not serious	N/A	Not serious	Moderate

5. 95% CI calculated from SE
6. This study was moderate risk overall but marked down for this outcome because 259 of 418 randomised participants completed questionnaires throughout treatment
7. Pembrolizumab (2mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
8. Study at moderate risk of bias
9. 95% confidence interval crosses one end of a defined MID interval (-10, +10)
10. Pembrolizumab (10mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
11. Pembrolizumab (10mg every 2 months) vs ipilimumab

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						

12. This study was low risk overall but marked down for this outcome because 459 of 844 randomised participants had baseline and week 12 observations
13. Pembrolizumab (10mg every 3 months) vs ipilimumab
14. MD calculated with Review Manager 5.3
15. Study at high risk of bias
16. This study was low risk overall but marked down for this outcome because 151 of 250 randomised participants completed questionnaires at week 12

1 **EORTC QLQ-C30 – Physical functioning**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	259	Nivolumab (3 mg/kg every 2 weeks) -4.4 (-7.56, -1.24)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) -2.7 (-7.85, 2.45)[1]	N/A	MD -1.7 (-7.1, 3.8)	Very serious[2]	Not serious	N/A	Serious[3]	Very low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12										
KEYNOTE-002	520	Pembrolizumab (2mg every 3 months) -4.2 (-7.5, -1.0)	Pembrolizumab (10mg every 3 months) -2.8 (-5.9, 0.4)	ICC -5.2	MD 1.00 (-3.70, 5.70)[4]	Serious[5]	Not serious	N/A	Not serious	Moderate
					MD 2.40	Serious[5]	Not serious	N/A	Serious[3]	Low

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
				(-8.6, - 1.8)	(-2.17, 6.97)[6]					
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	505	Nivolumab + ipilimumab -6.2 (-8.17, -4.23)[1]	Nivolumab + placebo -4.5 (-6.47, -2.53)[1]	N/A	MD - 1.70 (-4.47, 1.07)[7]	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	492	Nivolumab + ipilimumab -6.2 (-8.17, -4.23)[1]	Ipilimumab + placebo -6.7 (-8.67, -4.73)[1]	N/A	MD 0.5 (-1.8, 2.9)	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	519	Nivolumab + placebo -4.5 (-6.47, -2.53)[1]	Ipilimumab + placebo -8.2 (-10.17, -6.23)[1]	N/A	MD 3.7 (1.4, 6.0)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	236	Dabrafenib + trametinib 1.75 (NR)	Vemurafenib -6.99 (NR)	NA	MD 8.74 (5.15, 12.32)	Very serious[8]	Not serious	N/A	Serious[3]	Very low
Dabrafenib + trametinib vs. Dabrafenib + placebo – at week 40										

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
COMBI-D	143	Dabrafenib + trametinib NR	Dabrafenib + placebo NR	N/A	MD 4.93 (0.70, 9.17)	Serious[9]	Not serious	N/A	Serious[3]	Low
Dabrafenib vs. Dacarbazine – at week 12 (mixed-model repeated measures)										
BREAK-3	152	Dabrafenib (150 mg twice daily) -2.41 (-5.09, 0.27)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) -5.75 (-12.84, 1.34)[1]	N/A	MD 3.33 (-3.84, 10.51)	Serious [10]	Not serious	N/A	Serious[3]	Low

1. 95% CI calculated from SE
2. This study was moderate risk overall but marked down for this outcome because 259 of 418 randomised participants completed questionnaires throughout treatment
3. 95% confidence interval crosses one end of a defined MID interval (-7, +6)
4. Pembrolizumab (2mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
5. Study at moderate risk of bias
6. Pembrolizumab (10mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
7. MD calculated with Review Manager 5.3
8. Study at high risk of bias
9. This study was low risk overall but marked down for this outcome because 143 of 423 randomised participants completed questionnaires at week 40
10. This study was low risk overall but marked down for this outcome because 152 of 250 randomised participants completed questionnaires at week 12

1 **EORTC QLQ-C30 – Role functioning**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	259	Nivolumab (3 mg/kg every 2 weeks) -1.2 (-5.75, 3.35)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 3.6 (-4.12, 11.32)[1]	N/A	MD - 4.8 (-12.9, 3.2)	Very serious[2]	Not serious	N/A	Serious[3]	Very low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12										
KEYNOTE-002	520	Pembrolizumab (2mg every 3 months) -4.7 (-9.3, -0.2)	Pembrolizumab (10mg every 3 months) -5.8 (-10.2, -1.3)	ICC -9.3 (-14.1, - 4.5)	MD 4.60 (-2.00, 11.20)[4]	Serious[5]	Not serious	N/A	Serious[3]	Low
					MD 3.50 (-2.40, 9.40)[6]	Serious[5]	Not serious	N/A	Not serious	Moderate
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	505	Nivolumab + ipilimumab -9.8 (-12.56, -7.04)[1]	Nivolumab + placebo -5.9 (-8.46, -3.34)[1]	N/A	MD - 3.90 (-7.64, - 0.16)[7]	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 067	492	Nivolumab + ipilimumab -9.8 (-12.56, -7.04)[1]	Ipilimumab + placebo -6.9 (-9.66, -4.14)[1]	N/A	MD - 2.8 (- 6.2, 0.6)	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	519	Nivolumab + placebo -5.9 (-8.46, -3.34)[1]	Ipilimumab + placebo -8.7 (-11.26, -6.14)[1]	N/A	MD 2.8 (-0.5, 6.1)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	236	Dabrafenib + trametinib 2.04 (NR)	Vemurafenib -12.64 (NR)	NA	MD 14.68 (9.35, 20.01)	Very serious[8]	Not serious	N/A	Serious[3]	Very low
Dabrafenib + trametinib vs. Dabrafenib + placebo – at week 40										
COMBI-D	143	Dabrafenib + trametinib NR	Dabrafenib + placebo NR	N/A	MD 5.26 (-1.67, 12.19)	Serious[9]	Not serious	N/A	Serious[3]	Low
Dabrafenib vs. Dacarbazine – at week 12 (mixed-model repeated measures)										

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
BREAK-3	150	Dabrafenib (150 mg twice daily) -0.65 (-4.23, 2.93)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 1.70 (-8.20, 11.60)[1]	N/A	MD - 2.35 (-12.29, 7.57)	Serious [10]	Not serious	N/A	Serious[3]	Low

1. 95% CI calculated from SE
2. This study was moderate risk overall but marked down for this outcome because 259 of 418 randomised participants completed questionnaires throughout treatment
3. 95% confidence interval crosses one end of a defined MID interval (-11, +11)
4. Pembrolizumab (2mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
5. Study at moderate risk of bias
6. Pembrolizumab (10mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
7. MD calculated with Review Manager 5.3
8. Study at high risk of bias
9. This study was low risk overall but marked down for this outcome because 143 of 423 randomised participants completed questionnaires at week 40
10. This study was low risk overall but marked down for this outcome because 150 of 250 randomised participants completed questionnaires at week 12

1 **EORTC QLQ-C30 – Emotional functioning**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 066	259	Nivolumab (3 mg/kg every 2 weeks) 6.3 (3.14, 9.46)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 5.3 (-0.04, 10.64)[1]	N/A	MD 1.0 (-4.5, 6.5)	Very serious[2]	Not serious	N/A	Serious[3]	Very low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12										
KEYNOTE-002	520	Pembrolizumab (2mg every 3 months) 0.2 (-2.9, 3.3)	Pembrolizumab (10mg every 3 months) 0.60 (-2.4, 3.6)	ICC -1.1 (-4.4, 2.2)	MD 1.30 (-3.20, 5.80)[4]	Serious[5]	Not serious	N/A	Not serious	Moderate
					MD 1.70 (-2.73, 6.13)[6]	Serious[5]	Not serious	N/A	Serious[3]	Low
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	505	Nivolumab + ipilimumab 2.8 (1.03, 4.57)[1]	Nivolumab + placebo 4.3 (2.72, 5.88)[1]	N/A	MD -1.50 (-3.86, 0.86)[7]	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	492	Nivolumab + ipilimumab 2.8 (1.03, 4.57)[1]	Ipilimumab + placebo 3.2 (1.43, 4.97)[1]	N/A	MD -0.4 (-2.6, 1.8)	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 067	519	Nivolumab + placebo 4.3 (2.72, 5.88)[1]	Ipilimumab + placebo 2.1 (0.53, 3.67)[1]	N/A	MD 2.1 (0.1, 4.2)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	236	Dabrafenib + trametinib 7.93 (NR)	Vemurafenib 1.60 (NR)	NA	MD 6.33 (2.46, 10.21)	Very serious[8]	Not serious	N/A	Serious[3]	Very low
Dabrafenib + trametinib vs. Dabrafenib + placebo – at week 40										
COMBI-D	143	Dabrafenib + trametinib NR	Dabrafenib + placebo NR	N/A	MD 4.23 (-1.34, 9.79)	Serious[9]	Not serious	N/A	Serious[3]	Low
Dabrafenib vs. Dacarbazine – at week 12 (mixed-model repeated measures)										
BREAK-3	146	Dabrafenib (150 mg twice daily) 8.32 (5.48, 11.16)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) -0.33 (-8.44, 7.78)[1]	N/A	MD 8.64 (0.57, 16.71)	Serious [10]	Not serious	N/A	Serious[3]	Low

1. 95% CI calculated from SE

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						

2. This study was moderate risk overall but marked down for this outcome because 259 of 418 randomised participants completed questionnaires throughout treatment
3. 95% confidence interval crosses one end of a defined MID interval (-6, +6)
4. Pembrolizumab (2mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
5. Study at moderate risk of bias
6. Pembrolizumab (10mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
7. MD calculated with Review Manager 5.3
8. Study at high risk of bias
9. This study was low risk overall but marked down for this outcome because 143 of 423 randomised participants completed questionnaires at week 40
10. This study was low risk overall but marked down for this outcome because 152 of 250 randomised participants completed questionnaires at week 12

1 **EORTC QLQ-C30 – Cognitive functioning**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	259	Nivolumab (3 mg/kg every 2 weeks) 0.4 (-2.96, 3.76)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 1.0 (-5.33, 7.33)[1]	N/A	MD - 0.7 (-7.2, 5.9)	Very serious[2]	Not serious	N/A	Serious[3]	Very low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12										

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
KEYNOTE-002	520	Pembrolizumab (2mg every 3 months) -2.1 (-5.1, 0.8)	Pembrolizumab (10mg every 3 months) -1.4 (-4.2, 1.5)	ICC -3.5 (-6.6, - 0.4)	MD 1.40 (-2.88, 5.68)[4]	Serious[5]	Not serious	N/A	Not serious	Moderate
					MD 2.10 (-2.05, 6.25)[6]	Serious[5]	Not serious	N/A	Serious[3]	Low
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	505	Nivolumab + ipilimumab -3.4 (-4.98, -1.82)[1]	Nivolumab + placebo -2.5 (-3.88, -1.12)[1]	N/A	MD - 0.90 (-2.98, 1.18)[7]	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	492	Nivolumab + ipilimumab -3.4 (-4.98, -1.82)[1]	Ipilimumab + placebo -3.6 (-5.17, -2.03)[1]	N/A	MD 0.2 (-1.9, 2.3)	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	519	Nivolumab + placebo -2.5 (-3.88, -1.12)[1]	Ipilimumab + placebo -4.0 (-5.57, -2.43)[1]	N/A	MD 1.5 (-0.4, 3.4)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
COMBI-V	236	Dabrafenib + trametinib -2.00 (NR)	Vemurafenib -5.22 (NR)	NA	MD 3.22 (-0.47, 6.91)	Very serious[8]	Not serious	N/A	Serious[3]	Very low
Dabrafenib + trametinib vs. Dabrafenib + placebo – at week 40										
COMBI-D	143	Dabrafenib + trametinib NR	Dabrafenib + placebo NR	N/A	MD 5.68 (1.12, 10.23)	Serious[9]	Not serious	N/A	Serious[3]	Low
Dabrafenib vs. Dacarbazine – at week 12 (mixed-model repeated measures)										
BREAK-3	149	Dabrafenib (150 mg twice daily) -0.97 (-3.38, 1.44)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) -4.00 (-10.72, 2.72)[1]	N/A	MD 3.03 (-3.70, 9.77)	Serious [10]	Not serious	N/A	Very serious[11]	Very low

1. 95% CI calculated from SE
2. This study was moderate risk overall but marked down for this outcome because 259 of 418 randomised participants completed questionnaires throughout treatment
3. 95% confidence interval crosses one end of a defined MID interval (-3, +6)
4. Pembrolizumab (2mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
5. Study at moderate risk of bias
6. Pembrolizumab (10mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
7. MD calculated with Review Manager 5.3

Study	Sample size	Mean change from baseline (95% CI) Arm 1	Arm 2	Arm 3	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
8. Study at high risk of bias 9. This study was low risk overall but marked down for this outcome because 143 of 423 randomised participants completed questionnaires at week 40 10. This study was low risk overall but marked down for this outcome because 149 of 250 randomised participants completed questionnaires at week 12 11. 95% confidence interval crosses both ends of a defined MID interval (-3, +6)										

1 **EORTC QLQ-C30 – Social functioning**

Study	Sample size	Mean change from baseline (95% CI) Arm 1	Arm 2	Arm 3	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	259	Nivolumab (3 mg/kg every 2 weeks) -0.8 (-4.75, 3.15)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 0.3 (-7.02, 7.62)[1]	N/A	MD - 1.1 (-8.6, 6.3)	Very serious[2]	Not serious	N/A	Not serious	Low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12										
KEYNOTE-002	520	Pembrolizumab (2mg every 3 months) -2.7 (-6.7, 1.3)	Pembrolizumab (10mg every 3 months) -2.4 (-6.3, 1.5)	ICC -4.7	MD 2.00 (-3.76, 7.76)[3] MD 2.30	Serious[4] Serious[4]	Not serious Not serious	N/A N/A	Not serious Not serious	Moderate Moderate

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
				(-8.9, - 0.5)	(-3.39, 7.99)[5]					
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	505	Nivolumab + ipilimumab -4.3 (-6.66, -1.94)[1]	Nivolumab + placebo -2.2 (-4.37, -0.03)[1]	N/A	MD - 2.10 (-5.29, 1.09)[6]	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	492	Nivolumab + ipilimumab -4.3 (-6.66, -1.94)[1]	Ipilimumab + placebo -2.8 (-4.97, -0.63)[1]	N/A	MD - 1.5 (-4.4, 1.3)	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	519	Nivolumab + placebo -2.2 (-4.37, -0.03)[1]	Ipilimumab + placebo -4.8 (-7.16, -2.44)[1]	N/A	MD 2.6 (-0.3, 5.4)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	236	Dabrafenib + trametinib 3.75 (NR)	Vemurafenib -5.98 (NR)	NA	MD 9.73 (5.20, 14.26)	Very serious[7]	Not serious	N/A	Serious[8]	Very low

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Dabrafenib + trametinib vs. Dabrafenib + placebo – at week 40										
COMBI-D	143	Dabrafenib + trametinib NR	Dabrafenib + placebo NR	N/A	MD 6.20 (0.07, 12.32)	Serious[9]	Not serious	N/A	Serious[8]	Low
Dabrafenib vs. Dacarbazine – at week 12 (mixed-model repeated measures)										
BREAK-3	149	Dabrafenib (150 mg twice daily) 3.58 (-0.01, 7.17)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) -3.00 (-12.55, 6.55)[1]	N/A	MD 6.57 (-3.09, 16.23)	Serious [10]	Not serious	N/A	Serious[8]	Low

1. 95% CI calculated from SE
2. This study was moderate risk overall but marked down for this outcome because 259 of 418 randomised participants completed questionnaires throughout treatment
3. Pembrolizumab (2mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
4. Study at moderate risk of bias
5. Pembrolizumab (10mg every 3 months) vs ICC; MD calculated with Review Manager 5.3
6. MD calculated with Review Manager 5.3
7. Study at high risk of bias
8. 95% confidence interval crosses one end of a defined MID interval (-9, +8)
9. This study was low risk overall but marked down for this outcome because 143 of 423 randomised participants completed questionnaires at week 40
10. This study was low risk overall but marked down for this outcome because 149 of 250 randomised participants completed questionnaires at week 12

1 **EQ-5D utility index score**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	257	Nivolumab (3 mg/kg every 2 weeks) 0.04 (0.00, 0.08)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 0.02 (-0.06, 0.10)[1]	N/A	MD 0.01 (-0.06, 0.09)	Very serious[2]	Not serious	N/A	Serious[3]	Very low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12 (least squares means)										
KEYNOTE-006	459	Pembrolizumab (10mg every 2 months) NR	Pembrolizumab (10mg every 3 months) NR	Ipilimumab 3 mg/kg every 3 weeks NR	MD 0.08 (0.04, 0.12)[4]	Serious[5]	Not serious	N/A	Serious[3]	Low
					MD 0.08 (0.04, 0.12)[6]	Serious[5]	Not serious	N/A	Serious[3]	Low
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	503	Nivolumab + ipilimumab -0.019 (-0.04, 0.00)[1]	Nivolumab + placebo 0.001 (-0.02, 0.02)[1]	N/A	MD - 0.02 (-0.05, 0.01)[7]	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 067	490	Nivolumab + ipilimumab -0.019 (-0.04, 0.00)[1]	Ipilimumab + placebo -0.024 (-0.05, 0.00)[1]	N/A	MD 0.006 (-0.02, 0.03)	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	515	Nivolumab + placebo 0.001 (-0.02, 0.02)[1]	Ipilimumab + placebo -0.033 (-0.05, -0.01)[1]	N/A	MD 0.03 (0.007, 0.060)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	224	Dabrafenib + trametinib 0.07 (NR)	Vemurafenib -0.04 (NR)	NA	MD 0.11 (0.06, 0.15)	Very serious[8]	Not serious	N/A	Serious[3]	Very low

1. 95% CI calculated from SE
2. This study was moderate risk overall but marked down for this outcome because 257 of 418 randomised participants completed questionnaires throughout treatment
3. 95% confidence interval crosses one end of a defined MID (≥0.08)
4. Pembrolizumab (10mg every 2 months) vs ipilimumab
5. This study was low risk overall but marked down for this outcome because 459 of 844 randomised participants had baseline and week 12 observations
6. Pembrolizumab (10mg every 3 months) vs ipilimumab
7. MD calculated with Review Manager 5.3
8. Study at high risk of bias

1 **EQ-5D VAS score**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Nivolumab vs. dacarbazine – across 61 weeks (mixed-effects model for repeated measures)										
CHECKMATE 066	257	Nivolumab (3 mg/kg every 2 weeks) 2.2 (-1.36, 5.76)[1]	Dacarbazine (1,000 mg/m^2 every 3 weeks) 1.8 (-4.93, 8.53)[1]	N/A	MD 0.4 (-6.6, 7.4)	Very serious[2]	Not serious	N/A	Serious[3]	Very low
Pembrolizumab (low dose) vs. Pembrolizumab (high dose) vs. ICC – at week 12 (least squares means)										
KEYNOTE-006	459	Pembrolizumab (10mg every 2 months) NR	Pembrolizumab (10mg every 3 months) NR	Ipilimumab 3 mg/kg every 3 weeks NR	MD 5.33 (1.70, 8.97)[4]	Serious[5]	Not serious	N/A	Serious[3]	Low
					MD 3.39 (0.20, 6.98)[6]	Serious[5]	Not serious	N/A	Not serious	Moderate
Nivolumab + ipilimumab followed by nivolumab only vs. Nivolumab + placebo vs. Ipilimumab + placebo – across 55 weeks (mixed-effects model for repeated measures, least squares means)										
CHECKMATE 067	503	Nivolumab + ipilimumab -3.4 (-5.37, -1.43)[1]	Nivolumab + placebo -1.7 (-3.47, 0.07)[1]	N/A	MD - 1.70 (-4.34, 0.94)[7]	Not serious	Not serious	N/A	Not serious	High

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
CHECKMATE 067	490	Nivolumab + ipilimumab -3.4 (-5.37, -1.43)[1]	Ipilimumab + placebo -4.4 (-6.37, -2.43)[1]	N/A	MD 1.0 (-1.4, 3.5)	Not serious	Not serious	N/A	Not serious	High
CHECKMATE 067	515	Nivolumab + placebo -1.7 (-3.47, 0.07)[1]	Ipilimumab + placebo -5.3 (-7.07, 3.53)[1]	N/A	MD 3.6 (1.3, 5.9)	Not serious	Not serious	N/A	Not serious	High
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	228	Dabrafenib + trametinib 6.39 (NR)	Vemurafenib -2.69 (NR)	NA	MD 9.08 (4.96, 13.20)	Very serious[8]	Not serious	N/A	Serious[3]	Very low

1. 95% CI calculated from SE
2. This study was moderate risk overall but marked down for this outcome because 257 of 418 randomised participants completed questionnaires throughout treatment
3. 95% confidence interval crosses one end of a defined MID (≥7)
4. Pembrolizumab (10mg every 2 months) vs ipilimumab
5. This study was low risk overall but marked down for this outcome because 459 of 844 randomised participants had baseline and week 12 observations
6. Pembrolizumab (10mg every 3 months) vs ipilimumab
7. MD calculated with Review Manager 5.3
8. Study at high risk of bias

1 **Functional Assessment of Cancer Therapy—Melanoma (FACT-M) Melanoma Subscale score**

Study	Sample size	Mean change from baseline (95% CI)			Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2	Arm 3						
Dabrafenib + trametinib vs. Vemurafenib – at week 48										
COMBI-V	224	Dabrafenib + trametinib 1.98 (NR)	Vemurafenib -1.02 (NR)	NA	MD 3.00 (1.52, 4.48)	Very serious[1]	Not serious	N/A	Very serious[2]	Very low

1. Study at high risk of bias
2. 95% confidence interval crosses both ends of a defined MID interval (2 to 4)

F.12 Localised therapies

3 **Randomised and non-randomised controlled trials**

4 **T-VEC + ipi vs ipi alone**

5 **Table 18 T-VEC + ipilimumab versus ipilimumab alone**

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2						
Overall survival up to 3 years									

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2						
Chesney 2018 (RCT)	190	N/A	N/A	HR 0.80 (0.44, 1.46)	Not serious	Not serious	N/A	Very serious[1]	Low
Progression-free survival up to 3 years									
Chesney 2018 (RCT)	190	N/A	N/A	HR 0.83 (0.56, 1.23)	Not serious	Not serious	N/A	Serious[2]	Moderate
Adverse events leading to discontinuation of study drug(s): treatment-emergent adverse events in patients who received at least one dose of the study drug									
Chesney 2018 (RCT)	190	14/95	17/95	RR 0.82 (0.43, 1.57)	Not serious	Not serious	N/A	Very serious[1]	Low
Grade 3-5 adverse events: treatment-emergent adverse events in patients who received at least one dose of the study drug									
Chesney 2018 (RCT)	190	43/95	33/95	RR 1.30 (0.92, 1.86)	Not serious	Not serious	N/A	Serious[2]	Moderate
Mortality due to adverse event(s): treatment-emergent adverse events in patients who received at least one dose of the study drug (deemed to not be treatment-rela investigator)									
Chesney 2018 (RCT)	180	3/95	0/95	7.00 (0.37, 133.70)	Not serious	Not serious	N/A	Very serious[1]	Low

1. 95% CIs cross both lines of the MID (0.8, 1.25)
2. 95% CIs cross one line of the MID (0.8, 1.25)

1 **Percutaneous hepatic perfusion vs. best available care**

2 **Table 19 Percutaneous hepatic perfusion vs. best available care**

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2						
Overall survival – up to 20 months									
Hughes 2016 (RCT)	93	N/A	N/A	HR 0.92 (0.52, 1.62)	Serious[1]	Not serious	N/A	Very serious[5]	Very low
Progression-free survival – up to 20 months									
Hughes 2016 (RCT)	93	N/A	N/A	HR 0.40 (0.25, 0.65)	Serious[1]	Not serious	N/A	Not serious	Moderate
Hepatic progression-free survival – up to 20 months									
Hughes 2016 (RCT)	93	N/A	N/A	HR 0.30 (0.18, 0.50)	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias
2. 95% CIs cross both lines of the MID (0.8, 1.25)
3. 95% CIs cross one line of the MID (0.8, 1.25)

1 **T-VEC vs GM-CSF**

2 **Table 20 T-VEC versus GM-CSF for the treatment of unresectable stage IIIB-IV melanoma**

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2						
Overall survival – up to 5 years									
OPTim trial *Overall*	436	N/A	N/A	HR: 0.73 (0.59, 0.92)[1]	Not serious	Not serious	N/A	Not serious	High
Stage IIIB-C	127	N/A	N/A	HR 0.48 (0.29, 0.80)	Not serious	Not serious	N/A	Not serious	High
Stage IIIB-IVM1a	249	N/A	N/A	HR 0.56 (0.40, 0.79)	Not serious	Not serious	N/A	Not serious	High
Stage IVM1b	90	N/A	N/A	HR 1.06 (0.62, 1.78)	Not serious	Not serious	N/A	Serious[2]	Moderate
Stage IVM1c	96	N/A	N/A	HR 1.08 (0.68, 1.74)	Not serious	Not serious	N/A	Serious[2]	Moderate
First-line therapy	203	N/A	N/A	HR 0.50 (0.35, 0.72) Could not differentiate in second-line subgroup (95%CIs reported incorrectly)	Not serious	Not serious	N/A	Not serious	High
ECOG-0	306	N/A	N/A	HR 0.85 (0.63, 1.14)	Not serious	Not serious	N/A	Serious[2]	Moderate
ECOG-1	114	N/A	N/A	HR 0.57 (0.36, 0.89)	Not serious	Not serious	N/A	Not serious	High
Head and neck cancer only (taken from Andtbacka, 2016)	87	N/A	N/A	HR 0.38 (0.20, 0.72)[4]	Serious[4]	Not serious	N/A	Not serious	Moderate
Time to treatment failure – up to 5 years									

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		Arm 1	Arm 2						
OPTim trial (taken from Andtbacka, 2016)	87	N/A	N/A	HR: 0.32 (0.17, 0.61)	Very serious[5]	Not serious	N/A	Not serious	Low
Grade 3-5 adverse events – up to 5 years									
OPTim trial	419	33/292	6/127	HR 2.39 (1.03, 5.57)	Serious[4]	Not serious	N/A	Not serious	Moderate
Any grade vitiligo – up to 5 years									
OPTim trial	419	18/292	1/127	HR 7.83 (1.06, 58.02)	Serious[4]	Not serious	N/A	Not serious	Moderate
Adverse events leading to discontinuation of study drug – up to 5 years									
OPTim trial	419	31/292	8/127	HR 1.69 (0.80, 3.56)	Serious[4]	Not serious	N/A	Serious[2]	Low

1. Adjusted for accounting for subsequent systemic anti-cancer treatment (including ipilimumab, vemurafenib, dabrafenib, trametinib or an anti-PD-1). Unadjusted HR= 0.7 1.00).
2. 95% CIs cross the line of no effect (1.00).
3. Adjusted for potential clinically meaningful imbalances in prognostic factors of sex, disease stage, and ECOG. Unadjusted HR = 0.57 (0.32–1.03).
4. Study was at low risk of bias overall but was marked down once for risk of bias for this outcome as data were taken from a post-hoc analysis and therefore original coho not balanced specifically for patients with head and neck cancer.
5. See footnote 4. This outcome was marked down an additional level as the analysis did not adjust for baseline confounders.

ILI vs intralesional PV-10 therapy

Table 21 ILI vs intralesional PV-10 therapy

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		ILI	PV-10						
Melanoma-specific survival									
Read 2019 *1 year*	72	5/36	6/36	RR 0.83 (0.28, 2.49)	Serious[1]	Serious[2]	N/A	Very serious[3]	Very low
3 year		14/36	17/36	RR 0.82 (0.48, 1.41)	Serious[1]	Serious[2]	N/A	Very serious[3]	Very low
5 year		14/36	23/36	RR 0.61 (0.38, 0.98)	Serious[1]	Serious[2]	N/A	serious[4]	Very low
Grade 3-5 toxicity									
Read 2019	72	5/36	1/36	RR 5.00 (0.61, 40.70)	Serious[1]	Serious[2]	N/A	Very serious[3]	Very low

1. Study was at moderate risk of bias.
2. Study was only partially applicable to the review question.
3. 95% CIs cross both lines of the MID (0.8, 1.25).
4. 95% CIs cross one line of the MID (0.8, 1.25).

ILI vs hyperthermic ILP

Table 22 ILI vs. hyperthermic ILP

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		ILI	HILP						
Progression-free survival									

Study	Sample size	# events (%)		Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
		ILI	HILP						
Lidsky 2013 (prospective cohort study – 3 months)	215	43/134	9/81	RR 2.89 (1.49, 5.61)	Serious[1]	Serious[2]	N/A	Not serious	Low
Guadagni 2021	62	N/A	N/A	HR 3.57 (1.64, 7.69)	Very serious[4]	Not serious	N/A	Not serious	Low
Overall survival									
Guadagni 2021	62	N/A	N/A	HR 4.28 (1.94, 9.45)	Very serious[4]	Not serious	N/A	Not serious	Low
Overall survival –at 3 years after treatment: only in patients who achieved complete response after treatment with ILI/HILP									
Sharma 2012 (prospective cohort study)	73	17/37	8/36	RR 2.07 (1.02, 4.18)	Serious[1]	Serious[2]	N/A	Serious[3]	Very low
Recurrence – at 3 years after treatment: only in patients who achieved complete response after treatment with ILI/HILP									
Sharma 2012 (prospective cohort study)	73	31/37	23/36	RR 1.31 (0.99, 1.74)	Serious[1]	Serious[2]	N/A	Serious[3]	Very low

1. Study was at moderate risk of bias
2. Study was only partially applicable to the review question
3. 95% CIs cross one line of the MID (0.8, 1.25)
4. Study was at high risk of bias

Predictors of overall survival following T-VEC

Table 23 Factors predictive of progressive disease following T-VEC

Study	Sample size	Effect size	No. with progressive disease		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			First-line TVEC	Second-line TVEC					
First vs second line treatment: Effect sizes <1									
Ressler 2020	88	RR 0.57 (0.28, 1.17)	9/45	15/43	Serious[1]	Not serious	N/A	Serious[2]	Low

1. Study at moderate risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25).

Predictors of overall survival following ILP

Table 24 Factors predictive of overall survival following ILP

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Number of lesions (>10 vs ≤10): effect sizes <1 = lower risk of mortality if >10 lesions									
Katsarelias 2018[6]	137	OR 1.55 (0.87, 2.59)[1]	Not reported	Not reported	Serious[7]	Not serious	N/A	Serious[9]	Low
Olofsson 2013[2]	163	OR 1.81 (1.18, 2.76)[3]	Not reported	Not reported	Serious[7]	Not serious	N/A	Serious[9]	Low
Gender (male vs female): effect sizes <1 = lower risk of mortality if male									
Katsarelias 2018	284	OR 1.12 (0.79, 1.71)[1]	Not reported	Not reported	Serious[7]	Not serious	N/A	Very serious[10]	Very low
Olofsson 2013[2]	163	OR 1.58 (1.07, 2.33)[3]	Not reported	Not reported	Serious[7]	Not serious	N/A	Serious[9]	Low
Schellerer 2021	80	RR 1.18 (0.92, 1.51)	24/29	35/50	Serious[7]	Not serious	N/A	Serious[9]	Low

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
5 years									
Tumour location (proximal vs distal): effect sizes <1 = lower risk of mortality if proximal									
Olofsson 2013[2]	158	OR 1.34 (0.71, 2.52)[3]	Not reported	Not reported	Serious[7]	Not serious	N/A	Very serious[10]	Very low
Tumour size (bulky vs. non-bulky): effect sizes <1 = lower risk of mortality is bulky melanoma									
Katsarelias 2018	273	OR 2.56 (1.59, 4.10)[1]	Not reported	Not reported	Serious[7]	Not serious	N/A	Not serious	Moderate
Olofsson 2013[2,5]	163	OR 1.84 (1.09, 3.11)[4]	Not reported	Not reported	Serious[7]	Not serious	N/A	Serious[9]	Low
N-stage (N3 vs N2c): effect sizes <1 = lower risk of mortality if N3									
Katsarelias 2018	284	OR 1.99 (1.41, 2.61)[1]	Not reported	Not reported	Serious[7]	Not serious	N/A	Not serious	Moderate
Olofsson 2013[2]	163	OR 2.08 (1.38, 3.15)[4]	Not reported	Not reported	Serious[7]	Not serious	N/A	Not serious	Moderate
M-stage (M1 vs M0): effect sizes <1 = lower risk of mortality if M1									
Olofsson 2013[2]	160	OR 3.67 (1.76, 7.61)[3]	Not reported	Not reported	Serious[7]	Not serious	N/A	Not serious	Moderate
Vessel (external iliac vs. femoral): effect sizes <1 = lower risk of mortality is administered via external iliac vessel									
Katsarelias 2018	250	OR 1.24 (0.83, 1.82)[1]	Not reported	Not reported	Serious[7]	Not serious	N/A	Very serious[10]	Very low
Vessel (upper extremity vs. femoral): effect sizes <1 = lower risk of mortality if administered via upper extremity vessel									
Katsarelias 2018	185	OR 1.78 (1.01, 2.89)[1]	Not reported	Not reported	Serious[7]	Not serious	N/A	Serious[9]	Low

1. Adjusted OR taken directly from study. Adjusted for age, gender, N-stage, size, vessel, perfusion time/temp, response, local toxicity.
2. Cancer-specific survival
3. Unadjusted OR taken directly from study.
4. Adjusted OR taken directly from study. Adjusted for complete response, N-stage and bulky disease.

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					

5. Bulky disease defined as >4cm
6. Compared those with >10 lesions specifically to reference category of 1 lesion
7. Study was at moderate risk of bias
8. Study was only partially applicable to the review question
9. 95% CIs cross one line of the MID (0.8, 1.25)
10. 95% CIs cross both lines of the MID (0.8, 1.25)

1 Predictors of severe toxicity following ILP

2 **Table 25 Factors predictive of severe toxicity following ILP**

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Number of lesions (>10 vs 1): effect sizes <1 = lower risk of severe toxicity if >10 lesions									
Katsarelias 2018[3]	137	OR 0.85 (0.21, 3.49[1]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low
Gender (male vs. female): effect sizes <1 = lower risk of severe toxicity if male									
Katsarelias 2018[3]	284	OR 0.95 (0.36, 2.52)[1]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low
Olofsson 2013[4]	163	OR 0.99 (0.50, 1.99)[2]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low
Schellerer 2021 *5 years*	80	RR 0.15 (0.02, 1.12)	1/30	11/50	Serious[7]	Not serious	N/A	Serious[9]	Low
Tumour size (bulky vs. non-bulky): effect sizes <1 = lower risk of severe toxicity if bulky lesion(s)									
Katsarelias 2018[3]	273	OR 0.96 (0.23, 4.06)[1]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
N-stage (N3 vs N2c): effect sizes <1 = lower risk of severe toxicity if N3									
Katsarelias 2018[3]	284	OR 0.53 (0.19, 1.47)[1]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low
Vessel (external iliac vs. femoral): effect sizes <1 = lower risk of severe toxicity if administered via external iliac vessel									
Katsarelias 2018[3]	250	OR 0.25 (0.07, 0.87)[1]	Not reported	Not reported	Serious[5]	Not serious	N/A	Serious[7]	Very low
Vessel (upper extremity vs. femoral): effect sizes <1 = lower risk of severe toxicity if administered via upper extremity vessel									
Katsarelias 2018[3]	185	OR 0.51 (0.10, 2.73)[1]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low
Location of limb perfusion (upper vs lower extremity): effect sizes <1 = lower risk of severe toxicity if lower extremity									
Schellerer 2021 *5 years*	80	RR 0.95 (0.14, 6.30)	1/7	11/73	Serious[7]	Not serious	N/A	Very serious[8]	Very low
Type of perfusion (TNF-alpha and melphalan ILP vs melphalan ILP): effect sizes <1 = lower risk of severe toxicity if TN-ILP									
Olofsson 2013[4]	163	OR 0.81 (0.25, 2.60)[2]	Not reported	Not reported	Serious[5]	Not serious	N/A	Very serious[8]	Very low

1. Adjusted OR taken directly from study. Adjusted for age, gender, N-stage, size, vessel, perfusion time/temp, response, local toxicity.
2. Unadjusted OR taken directly from study.
3. Severe toxicity defined as Wieberdink IV-V
4. Severe toxicity defined as Wieberdink III-V
5. Study was at moderate risk of bias
6. Study was only partially applicable to the review question

Predictors of overall survival following ILI

Table 26 Factors predictive of overall survival following ILP

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Burden of disease (high [>10 lesions or any single lesion >2cm in maximal dimension] vs low [<10 lesions, none > 2cm in maximal dimension]): effect sizes <1 = lower risk of mortality if high BOD									
Muilenberg 2015 *Up to 4 years*	160	RR 0.96 (0.60, 1.53)	High BOD: 19/60	Low BOD; 33/100	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Steinman 2014[1] *Up to 5 years*	55	RR 2.36 (1.23, 4.55)	High BOD: 23/32	Low BOD: 7/23	Serious[2]	Not serious	N/A	Serious[4]	Low
Gender (male vs female): effect sizes <1 = lower risk of mortality if male									
Steinman 2014[1] *Up to 5 years*	68	RR 1.55 (1.00, 2.39)	Male: 22/32	Female: 16/36	Serious[2]	Not serious	N/A	Serious[4]	Low
Tumour stage (IIIC vs IIIB): effect sizes <1 = lower risk of mortality if IIIC									
Steinman 2014[1] *Up to 5 years*	55	RR 0.77 (0.46, 1.27)	IIIC: 11/23	IIIB: 20/32	Serious[2]	Not serious	N/A	Very serious[5]	Very low
Disease stage: effect sizes >1 = Greater risk of mortality in higher stages									
Kroon 2009	185	HR 2.07 (1.46, 3.09)[5]	Not reported	Not reported	Serious[1]	Not serious	N/A	Not serious	Moderate
Melanoma Breslow thickness: effect sizes >1 = Greater risk of mortality in larger melanomas									
Kroon 2009	185	HR 1.75 (1.34, 2.37)[5]	Not reported	Not reported	Serious[1]	Not serious	N/A	Not serious	Moderate

Study	Sample size	Effect size	No. of death		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Complete response to ILI: effect sizes >1 = Greater risk of mortality if patient achieved complete response									
Kroon 2009	185	HR 1.25 (1.03, 1.53)[5]	Not reported	Not reported	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Used 3cm as cut-off for maximal dimension.
2. Study was at moderate risk of bias
3. Study was only partially applicable to the review question
4. 95% CIs cross one line of the MID (0.8, 1.25)
5. 95% CIs cross both lines of the MID (0.8, 1.25)
6. Adjusted for disease stage, whether patient achieved a complete response to IPI and thickness of primary melanoma

1 Predictors of severe toxicity following ILI

2 Table 27 Factors predictive of severe limb toxicity (grade 3-4) following ILI

Study	Sample size	Effect size	No. with severe toxicity		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Burden of disease (high [>10 lesions or any single lesion >2cm in maximal dimension] vs low [<10 lesions, none > 2cm in maximal dimension]): effect sizes <1 = lower risk of severe toxicity if high BOD									
Kenyon-Smith (2020)	687	RR 0.92 (0.73, 1.18)	High BOD: 84/314	Low BOD: 108/373	Serious[1]	Not serious	N/A	Serious[3]	Low
Gender (male vs. female): effect sizes <1 = lower risk of severe toxicity if male									
Kenyon-Smith (2020)	687	RR 0.66 (0.51, 0.87)	Male: 59/275	Female: 133/412	Serious[1]	Not serious	N/A	Serious[3]	Low
Disease stage (IIIC vs IIIB): effect sizes <1 = lower risk of severe toxicity if IIIC									

Study	Sample size	Effect size	No. with severe toxicity		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Kenyon-Smith (2020)	687	RR 1.18 (0.93, 1.50)	IIIC: 93/304	IIIB: 99/383	Serious[1]	Not serious	N/A	Serious[3]	Low
Final melphalan concentration (IM): HR >1 and positive mean differences = risk of severe toxicity increases alongside concentration									
Kroon 2009	273	HR 1.33 (1.19, 1.58)[4]	Not reported	Not reported	Serious[1]	Not serious	N/A	Not serious	Moderate
Beasley 2009	113	Mean difference: + 7.00 (1.73, 12.27)	Mean (SD) melphalan dose in grade I-II toxicity: 44.8 (17.2) mg	Mean (SD) melphalan dose in grade III-IV toxicity: 51.8 (14.7) mg	Very serious[5]	Not serious	N/A	Serious[6]	Very low
Peak creatine kinase: HR >1 and positive mean differences = risk of severe toxicity increases alongside concentration									
Kroon 2009	273	HR 1.33 (1.19, 1.58)[4]	Not reported	Not reported	Serious[1]	Not serious	N/A	Not serious	Moderate
Beasley 2009	158	Mean difference: + 1653.00 (695.10, 2610.90)	Mean (SD) Peak CK in grade I-II toxicity: 1,483 (2,562) U/L	Mean (SD) Peak CK in grade III-IV toxicity: 3,136 (3,578) U/L	Serious[1]	Not serious	N/A	Serious[7]	Low
Tourniquet time: effect sizes <1 = risk of severe toxicity decreases alongside time									
Kroon 2009	273	HR 0.91 (0.81, 0.97)[4]	Not reported	Not reported	Serious[1]	Not serious	N/A	Not serious	Moderate
Length of hospital stay: Positive mean differences = longer stay in people with severe toxicity									

Study	Sample size	Effect size	No. with severe toxicity		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Arm 1	Arm 2					
Beasley 2009	158	Mean difference: + 1.80 (0.67, 2.93)	Mean (SD) stay in grade I-II toxicity: 6.8 (2.7) days	Mean (SD) stay in grade III-IV toxicity: 8.6 (4.6) days	Serious[1]	Not serious	N/A	Serious[8]	Low
Melphalan dose corrected for ideal body weight (yes vs. no): effect sizes <1 = lower risk of severe toxicity if dose was adjusted for IBW									
Beasley 2009	158	RR: 0.44 (0.26, 0.74)	Corrected: 14/68	Not corrected: 44/94	Serious[1]	Not serious	N/A	Serious[8]	Low

1. Study was at moderate risk of bias
2. Study was only partially applicable to the review question.
3. 95% CIs cross one line of the MID (0.8, 1.25)
4. Adjusted for Esmarch, drug exposure time, tourniquet time, melphalan concentration (Infused, peak and final), circulating volume, Infused actinomycin D (lg/l), differences in temperature (subcutaneous and intramuscular) between start and finish of procedure, peak temperature (subcutaneous and intramuscular) and differences between start and finish of procedure in: pCO2 (mmHg), pO2 (mmHg), pH, base excess (mmol/l), saturation
5. Study was at moderate risk of bias but was marked down an additional time for this outcome as 49 patients had missing data for this outcome however a full sample size had to be assumed to calculate mean difference effect size.
6. 95% CIs cross one line of the MID (8.6)
7. 95% CIs cross one line of the MID (1,281.00)
8. 95% CIs cross one line of the MID (1.35)

1
2

1

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Change in HbA1c (%)								
28 studies	RCT	9119	See appendix K	Serious[1]	No serious[2]	No serious[3]	Serious[4]	Low
All hypoglycaemia								
27 studies	RCT	10,251	See appendix K	Serious[1]	No serious[2]	No serious[3]	Very serious[5]	Very low
Severe/ major hypoglycaemia								
27 studies	RCT	10,584	See appendix K	Serious[1]	No serious[2]	No serious[3]	Very serious[6]	Very low
Nocturnal hypoglycaemia								
22 studies	RCT	8092	See appendix K	Serious[1]	No serious[2]	No serious[3]	Serious[7]	Low

[1] *Greater than 33.3% of studies in the NMA were at moderate or high risk of bias. Downgrade 1 level for serious risk of bias.*

[2] *Fewer than 33.3% studies in the NMA were partially indirect. The overall network was not downgraded.*

[3] *The DIC of the inconsistency model was not 3 points lower than the DIC of the consistency model. See Appendix K for DIC.*

[4] *The evidence did not identify any meaningful differences between the long-acting insulins, but the evidence did aid the committee to draw the conclusion that there was complete equivalence. Downgrade 1 level for serious imprecision.*

[5] *The evidence did not identify any meaningful differences and did not demonstrate equivalence. Downgrade 2 levels for very serious imprecision.*

[6] *Some significant evidence was identified which supported the use of detemir twice daily compared to NPH once/twice daily and detemir once/twice daily when compared to NPH once/twice daily. However, 95% confidence intervals were wide demonstrating uncertainty in the evidence. Downgrade 2 levels for very serious imprecision.*

[7] *Committee were able to draw some conclusions from the evidence particularly for insulins such as detemir twice daily and degludec U100 once daily. However, there was uncertainty in the evidence for all other long-acting insulins. Downgrade 1 level for serious risk of bias.*

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Change in HbA1c (%)								
28 studies	RCT	9119	See appendix K	Serious[1]	No serious[2]	No serious[3]	Serious[4]	Low
All hypoglycaemia								
27 studies	RCT	10,251	See appendix K	Serious[1]	No serious[2]	No serious[3]	Very serious[5]	Very low
Severe/ major hypoglycaemia								
27 studies	RCT	10,584	See appendix K	Serious[1]	No serious[2]	No serious[3]	Very serious[6]	Very low
Nocturnal hypoglycaemia								
22 studies	RCT	8092	See appendix K	Serious[1]	No serious[2]	No serious[3]	Serious[7]	Low

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

[1] *Greater than 33.3% of studies in the NMA were at moderate or high risk of bias. Downgrade 1 level for serious risk of bias.*

[2] *Fewer than 33.3% studies in the NMA were partially indirect. The overall network was not downgraded.*

[3] *The DIC of the inconsistency model was not 3 points lower than the DIC of the consistency model. See Appendix K for DIC.*

[4] *The evidence did not identify any meaningful differences between the long-acting insulins, but the evidence did aid the committee to draw the conclusion that there was complete equivalence. Downgrade 1 level for serious imprecision.*

[5] *The evidence did not identify any meaningful differences and did not demonstrate equivalence. Downgrade 2 levels for very serious imprecision.*

[6] *Some significant evidence was identified which supported the use of detemir twice daily compared to NPH once/twice daily and detemir once/twice daily when compared to NPH once/twice daily. However, 95% confidence intervals were wide demonstrating uncertainty in the evidence. Downgrade 2 levels for very serious imprecision.*

[7] *Committee were able to draw some conclusions from the evidence particularly for insulins such as detemir twice daily and degludec U100 once daily. However, there was uncertainty in the evidence for all other long-acting insulins. Downgrade 1 level for serious risk of bias.*

Appendix G – GRADE tables for NMA

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall survival								
10 studies	RCT	4,603	See write up	No serious[1]	No serious[2]	No serious[3]	Serious[4]	Moderate
Progression-free survival								
10 studies	RCT	4,603	See write up	No serious[1]	No serious[2]	No serious[3]	Serious[4]	Moderate

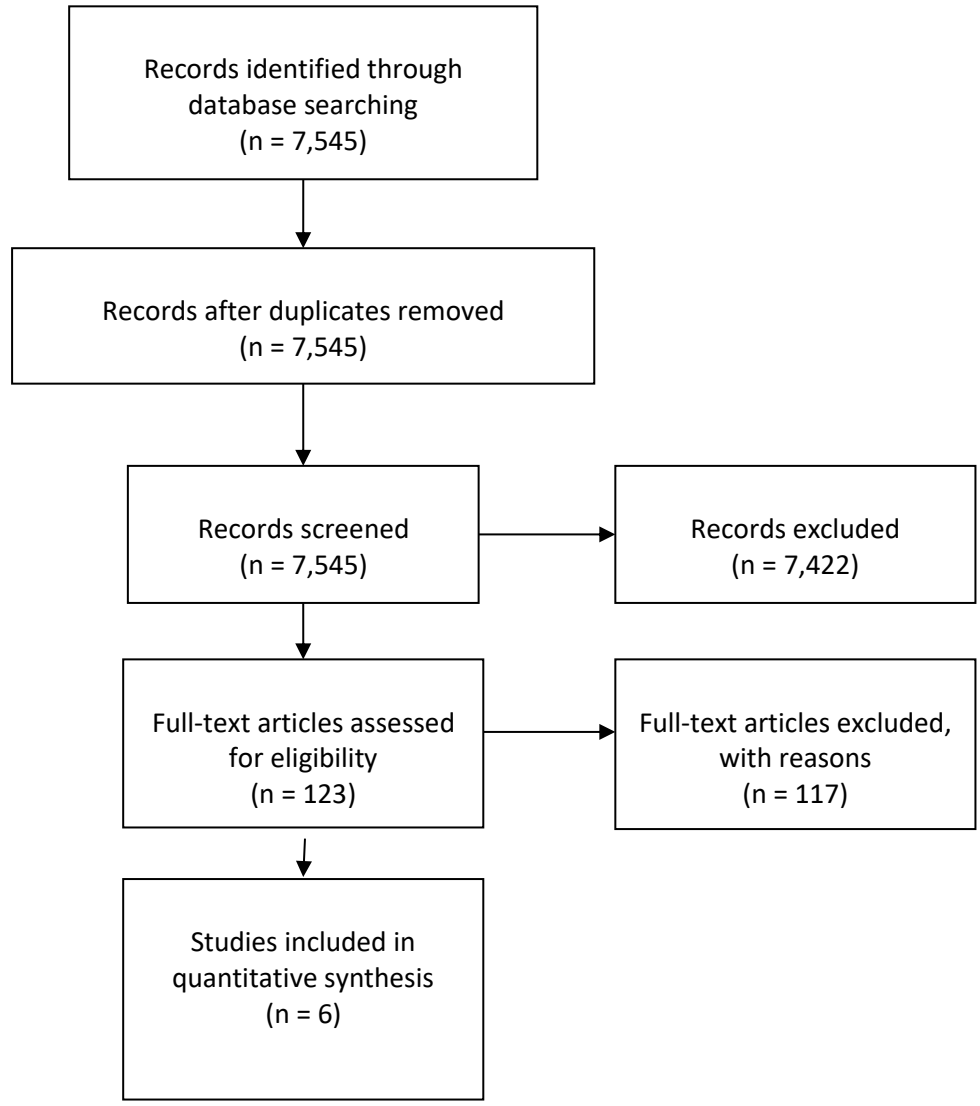
[1] *Fewer than 33.3% of studies in the NMA were at moderate or high risk of bias. The overall network was not downgraded.*

[2] *Fewer than 33.3% studies in the NMA were partially indirect. The overall network was not downgraded.*

[3] *The DIC of the inconsistency model was 3 points lower than the DIC of the consistency model. See the NMA report for DIC. However, the comparisons that related to treatments in this guideline were not affected by the inconsistency in the network. The overall network was not downgraded.*

[4] *Some significant evidence was identified which supported the use of nivolumab+ipilimumab as the most effective treatment. The evidence did not identify any meaningful differences between nivolumab and pembrolizumab. However, there was uncertainty in the evidence for the targeted therapies. 95% confidence intervals were wide demonstrating uncertainty in the evidence. Downgrade 1 level for serious imprecision.*

Appendix H – Economic evidence study selection



Appendix I – Economic evidence tables

Study	Fleeman et al. (2017) Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Three state partitioned survival model **Approach to analysis:** Health states were non-progressive disease, progressive disease, and death. PFS and OS for T-VEC were based on OPTiM trial data, and for ipilimumab, were derived from the Korn methods, based on the meta-analysis in metastatic melanoma by Korn (2008). The modified Korn method was previously developed and used for the STA of ipilimumab in advanced melanoma, and the two-step Korn method was developed for this STA. Data for ipilimumab patients was taken from two RCTs. Parametric curves were applied to extrapolate the PFS and OS curves past the trial period. **Perspective:** UK NICE perspective **Time horizon:** Lifetime (30 years) **Discounting:** 3.5% for costs and outcomes	**Population:** People with previously untreated advanced melanoma **Intervention:** Talimogene laherparepvec **Comparator:** (1) ipilimumab, (2) dacarbazine, (3) BSC	**Cost difference:** Not reported for any comparison. T-VEC had lower total costs than ipilimumab. **Currency and cost year:** 2014 GBP **Costs included:** Treatment costs, disease progression costs, AE costs.	**QALY difference:** (1) 1.34 (modified Korn), 0.35 (two-step Korn) (2, 3) Not reported	**Incremental analysis:** The study only modelled pairwise comparisons and presented the following ICERs relative to T-VEC: (1) T-VEC was dominant: -£16,367 (modified Korn), -£60,271 (two-step Korn) (2) £23,900 (company estimate[1]), £29,303 (ERG estimate[1]) (3) £24,100 (company estimate [1]), £30,427 (ERG estimate[1]) **Analysis of uncertainty:** A range of one-way deterministic sensitivity analyses were conducted which showed that the most influential parameters were the duration of treatment and the drug prices. The probabilistic sensitivity analysis showed that using the modified Korn method the probability of T-VEC being cost-effective compared with ipilimumab was 98.4% and 99.7%, at thresholds of £20,000 and £30,000, respectively. The probabilities of cost-effectiveness at these thresholds were 80.0% and 81.8%, respectively, for the two-step Korn method.
Data sources				

Study	Fleeman et al. (2017) Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Outcomes: Survival data was taken from the OPTiM trial for T-VEC, and from a meta-analysis using the Korn methods on two trials (MDX010-20, CA184-024) for ipilimumab. AEs of grade 3 or more were included in the model, and informed by the trials. **Quality of life:** Health state utility values were taken from a previous NICE appraisal of dabrafenib in unresectable or metastatic BRAF V600 mutation positive melanoma. Adverse event disutilities were taken from a bespoke study commissioned by the company. **Costs:** Resource use and costs associated with treatment and disease progression were estimated based on information collected in the company's resource utilisation study, published sources and the views of clinical experts. Sources informing resource use and costs associated with AEs were not reported in the study but these costs were included in the model.				
Comments				
Source of funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project Number 14/206/04).				
Overall applicability: Directly applicable				
The study was based on a NICE technology appraisal.				
Overall quality: Minor limitations				
Due to a lack of direct comparative data alternative methods for obtaining indirect estimates of effect were used (modified Korn and two-step Korn, both using meta-analysis). One of the authors received fees for speaking for advisory board membership from GlaxoSmithKline, Novartis, Merck Sharp and Dohme and Bristol Myers Squibb and support with travel to conferences from Bristol Myers Squibb and GlaxoSmithKline.				

1 *1 The study was based on a NICE Technical Appraisal, and results of both the manufacturer submission and the ERG report were presented.*

2

Study	Houten et al. (2020) Encorafenib with Binimetinib for the Treatment of Patients with BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Three state partitioned survival model **Approach to analysis:** Health states were progression-free (PF), post-progression (PP), and death, and both PF and PP had substates for patients	**Population:** Patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma **Intervention:** Encorafenib plus binimetinib	**Cost difference:** Not reported – enco+bini was less costly than dab+tram in the base-case analysis. **Currency and cost year:** 2018 GBP	**QALY difference:** 0.453	**Incremental analysis:** Enco+bini dominated dab+tram (i.e. was less costly and more effective) (company estimate[1]) Enco+bini was less costly and as effective as dab+tram (ERG estimate[1]) **Analysis of uncertainty:**

Study	Houten et al. (2020) Encorafenib with Binimetinib for the Treatment of Patients with BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
who were on or off primary treatment. Survival data for enco+bini was taken from the COLUMBUS trial and parametric models were fitted. In the absence of direct evidence comparing enco+bini with dab+tram, NMAs were conducted to indirectly estimate treatment efficacy, safety and HRQoL. **Perspective:** UK NHS perspective **Time horizon:** 30 years **Discounting:** 3.5% for costs and outcomes	**Comparator:**.Dabrafenib plus trametinib	**Costs included:** Health state resource use costs, AE costs, treatment costs, administration costs, terminal care costs.		Probabilistic and deterministic sensitivity analyses were conducted. The base-case results were sensitive to the use of an estimated HR for time to treatment discontinuation and dose of dab+tram. There were only two scenarios where enco+bini was not dominant; discounted list price of dabrafenib and trametinib, and assuming equal safety and efficacy between enco+bini and dab+tram.
Data sources				
Outcomes: The survival curves for enco+bini were taken from the COLUMBUS trial, and parametric models were fitted to this data to extrapolate beyond the trial time horizon. These curves were adjusted using HRs generated by the company's NMA to obtain survival curves for dab+tram. The company assumed that the time on treatment was the same for patients receiving Enco+Bini and Dab+Tram and used primary time on treatment data for both treatment combinations from the Enco+Bini arm of the COLUMBUS trial. Relative dose intensity multipliers and adverse event rates were taken from the COLUMBUS trial for enco+bini and from the COMBI-v and COMBI d trials for dab+tram. **Quality of life:** Health state EQ-5D utility scores were derived from the NMA; progression-free on treatment utility values differed by treatment arm, and progression-free off treatment and post-progression utility values were the same between treatment arms. **Costs**: Resource use and costs were estimated based on information from the COLUMBUS trial (usage of primary and subsequent treatments, and AE rates), published sources – including an Australian study of people with melanoma to estimate health state resource use, with the unit costs of the resource use based on estimates from the NHS, estimates of AE costs and terminal care costs – and advice from experts in clinical practice in the NHS.				
Comments				
Source of funding: This project was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 17/109/14)				
Overall applicability: Directly applicable				
The study was based on a NICE technology appraisal.				
Overall quality: Minor limitations				
The full breakdown of costs and outcomes was not presented in the study, but the overall outcome of the cost-effectiveness analysis was presented (intervention was dominant) and the incremental QALYs were reported.				

1 *1 The study was based on a NICE Technical Appraisal, and the main cost-effectiveness results of both the manufacturer submission and the ERG report were presented.*

1

Study	Pike et al. (2017) Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Probabilistic discrete-time Markov cohort model. **Approach to analysis:** The model has 3 mutually exclusive health states; progression-free disease (PFS), progressed disease (PD) and death. The model did not include treatment sequences. Network meta-analyses were conducted using both direct and indirect evidence with dacarbazine as a common comparator. Baseline OS and PFS cumulative density functions were fitted for the dacarbazine arm of a RCT, and transition probabilities calculated using the formula from Briggs et al. HRs from the NMA (relative to dacarbazine) were used to adjust the baseline transition probabilities for each intervention. In the base case analysis, the HRs are applied up to 2 years, assuming no treatment effects past 2 years of treatment for any of the interventions. **Perspective:** Norwegian healthcare payer **Time horizon:** 10 years **Discounting:** 4% for costs and outcomes	**Population:** Patients with metastatic and/or unresectable malignant melanoma – including both BRAF-mutant and BRAF-wild-type **Intervention:** Dacarbazine **Comparator:** (1) trametinib, (2) dabrafenib, (3) vemurafenib, (4) ipilimumab, (5) ipilimumab plus dacarbazine, (6) nivolumab, (7) pembrolizumab, (8) nivolumab plus ipilimumab, (9) vemurafenib plus cobimetinib, (10) dabrafenib plus trametinib	**Cost difference:** Costs compared pairwise with dacarbazine: (1) €82,714, (2) €87,334, (3) €87,399, (4) €88,793, (5) €89,077, (6) €100,798, (7) €103,330, (8) €150,537, (9) €258,460, (10) €259,654 **Currency and cost year:** 2015 Euro **Costs included:** BRAF testing, treatment costs, AE costs, monitoring costs	**QALY difference:** QALYs compared pairwise with dacarbazine (1) 0.28, (2) 0.35, (3) 0.31, (4) 0.48, (5) 0.40, (6) 0.82, (7) 0.80, (8) 0.81, (9) 0.89, (10) 0.83	**Incremental analysis:** Pairwise compared with dacarbazine: (1) €295,405, (2) €249,526, (3) €281,932, (4) €184,985, (5) €222,692, (6) €122,924, (7) €129,162, (8) €185,848, (9) €290,405, (10) €312,836 Fully incremental: (1) extended dominated (2) extended dominated (3) dominated (4) extended dominated (5) dominated (6) €122,923 (7) dominated (8) dominated (9) €2,252,329 (10) dominated **Analysis of uncertainty:** A probabilistic sensitivity analysis was conducted, in which all input parameters were randomly drawn from probability distributions and the model was run 10000 times. The PSA results showed that in the BRAF and MEK group, the combination therapies

Study	Pike et al. (2017) Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
				were more effective but more expensive than monotherapies. For the immunotherapies, the new available treatment alternatives (nivolumab and pembrolizumab) were more effective but more costly than ipilimumab monotherapy and ipilimumab in combination with dacarbazine. Scenario analyses were conducted for drug pricing, time horizon and HRQoL weights. The drug pricing analysis found that, for each treatment to be cost-effective at a threshold of €55850, the maximum pharmacy retail price would have to be reduced by approximately 79% for dabrafenib, 83% for trametinib, 84% for dabrafenib in combination with trametinib, 81% for vemurafenib, 84% for vemurafenib in combination with cobimetinib, 75% for ipilimumab, 63% for nivolumab and 64% for pembrolizumab. For the combination ipilimumab and dacarbazine, the drug cost of ipilimumab would need to be reduced by approximately 82%. For the combination nivolumab and ipilimumab, a combined price reduction of about 76% would be necessary An EVPI analysis indicated that the treatment efficacy data was the most influential source of uncertainty, followed by the HRQoL data, costs and SAE hazard ratios.
Data sources				

Study	Pike et al. (2017) Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Outcomes: Baseline OS and PFS (for dacarbazine) were taken from a RCT, and HRs from an NMA were used to adjust these survival functions for each intervention. The average monthly rate of a SAE was estimated from patients included in the dacarbazine arm of the NCT00324155 trial published in Robert et al. The baseline risk of AE was adjusted for each arm using the RRs for AEs in the NMA. **Quality of life:** A systematic search was conducted for published utility weights relevant for the model population and treatment options. EQ-5D values from Grob et al were used for PFS and PD states for vemurafenib in monotherapy and dabrafenib and trametinib in combination therapy. Due to lack of data, these values were also used for dabrafenib monotherapy and the combination vemurafenib and cobimetinib. The EQ-5D values for the interventions involving immunotherapies were derived from a published single technology assessment of pembrolizumab compared with ipilimumab. **Costs:** It is current practice in Norway to test all patients with advanced melanoma for the BRAF gene mutation, and costs from this were based on data from Oslo university hospital. The medicine costs depend on the acquisition price, the dosages and duration of treatment. Drug costs included in the model reflect the maximum pharmacy retail price, including VAT. Dosages correspond to the information in the summary of Product Characteristics. The model included SAEs requiring hospitalisation, that is, adverse events grade 3 and 4. The monthly costs related to SAEs are determined by the cost of hospitalisation and the average monthly probability of such an event. Costs are informed by the Norwegian Medicines Agency, results of the systematic review, DRG codes, official Norwegian unit prices and expert opinion.				
Comments				
Source of funding: This work was supported by the Norwegian Knowledge Centre for the Health Services.				
Overall applicability: Partially applicable				
The study was based in Norway, which has a different healthcare system and perspective on costs than that of the UK. Costs and QALYs were discounted at 4% per annum which is not the same as the reference case (3.5%).				
Overall quality: Minor limitations				
Most of the resource use estimates were based on expert opinion and published literature rather than being taken from the trials.				

1

Study	Quon et al. (2019) Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Three state partitioned survival model **Approach to analysis:** Health states were progression-free (PFS), post-	**Population:** Patients with advanced melanoma **Intervention:** Nivolumab + ipilimumab	**Cost difference:** Costs compared pairwise with Nivolumab + ipilimumab ($289,085):	**QALY difference:** QALYs compared pairwise with Nivolumab + ipilimumab (4.05):	**Incremental analysis:** Pairwise ICERs relative to nivolumab + ipilimumab: (1) $47,119, (2) $66,750, (3) $85,436,

Study	Quon et al. (2019) Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
progression (PP) and death. OS and PFS were informed by the CheckMate-067 clinical trial and a chained indirect comparison, and data was extrapolated past the trial period using parametric and piecewise methods. Treatment duration for nivo+ipi and nivolumab was based in data from the CheckMate-067 trial. **Perspective:** Canadian public healthcare system **Time horizon:** 20 years **Discounting:** 5% for costs and outcomes	**Comparator:** (1) Nivolumab, (2) Ipilimumab, (3) Pembrolizumab (24-month maximum treatment) (4) Pembrolizumab (treatment until progression)	(1) $26,814, (2) $149,556, (3) $134,786, (4) -$46,549 **Currency and cost year:** 2016 $Can **Costs included:** Treatment costs, administration costs, health state resource use costs, AE costs	(1) 0.569, (2) 2.241, (3) 1.577, (4) 1.584	(4) Dominant Fully incremental analysis: (2) - (3) $22,406 (1) extended dominated (nivo+ipi) $85,296 (4) dominated **Analysis of uncertainty:** Multi-way and univariate sensitivity analyses, testing the effect of the high and low ranges of the model parameters were conducted to identify key model drivers. Key drivers included parameters associated with drug costs (e.g., treatment duration, patient weight, and drug wastage), parametric functions for projecting OS and PFS, relative treatment effect for pembrolizumab, time horizon, discounting, and inclusion of subsequent treatment costs. All scenarios yielded ICERs within the threshold of $CAN50,000–100,000 per QALY gained. The sensitivity analysis did not find that AEs influenced overall results. A probabilistic sensitivity analysis was conducted to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterized using probability distributions and analysed using Monte Carlo simulation (1000 iterations). Mean

Study	Quon et al. (2019) Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
				incremental QALYs and costs were in line with base-case results (vs. nivolumab: 0.558 QALYs [95% CI 0.135 to 1.204], $CAN26,961 [95% CI 9565–43,181]; vs. ipilimumab: 2.021 QALYs [95% CI 1.615–2.783], $CAN149,817 [95% CI 136,769–165,627]; vs. pembrolizumab with a 24-month treatment cap: 1.498 QALYs [95% CI 0.463–2.307], $CAN132,936 [95% CI 102,185–158,250]), suggesting that deterministic results were robust in light of uncertainty in all parameters.
Data sources				
Outcomes: OS and PFS were informed by the CheckMate-067 clinical trial and a chained indirect comparison, and data was extrapolated past the trial period using parametric and piecewise methods. Treatment duration for nivo+ipi and nivolumab was based in data from the CheckMate-067 trial. Best objective response rates to first line treatment were collected from each of the trials and were used as predictors for quality-of-life estimates in the model. Grade 3 and 4 adverse event data were informed by the clinical trial publications, manufacturers product monographs, and input from clinicians about events that had cost or utility impacts. **Quality of life:** Health state utilities were elicited from the Canadian general public using the standard gamble method. EQ-5D-3L data were collected during CheckMate-067 but were only used in a scenario analysis because the utilities from the Canadian study were considered to be more reflective of the Canadian population. **Costs:** For calculating the drug cost per dose, average weight and average body surface area were based on average patient characteristics reported in recent pCODR submissions for injectable immunotherapies in melanoma. Costs for routine follow-up care and unplanned medical care were assigned to each health state, and frequency of medical resource use was informed by an interview with a clinical expert in melanoma in Canada. Subsequent cancer treatments could have a significant impact on overall costs and, because of the uncertainty of the breakdown of treatments following pembrolizumab, the model did not include the cost of these treatments in post-progression. The costs of terminal care involved palliative care physician visits every 2 weeks for the last 2 months of life and hospice care. The costs of treating AEs were calculated as weighted averages using a clinician's assumptions of the split between inpatient and outpatient care in Canada. Inpatient and outpatient costs for each AE were identified through the Ontario Case Costing Initiative Tool, and these costs were applied in the model as one-time costs upon initiating treatment.			
Comments				
Source of funding: Bristol-Myers Squibb, of Quebec, Canada, provided the funding for the study described in this manuscript and for the manuscript itself.				

Study	Quon et al. (2019) Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Overall applicability: Partially applicable				
The study was based in Canada, which has a different healthcare system to that of the UK. Costs and QALYs were discounted at 5% per annum which is not the same as the reference case (3.5%). The utility values were obtained from a Canada specific elicitation exercise, using the standard gamble approach, not using the EQ-5D.				
Overall quality: Minor limitations				
The study was supported by Bristol-Myers Squibb, and multiple authors worked for Evidera, and received funding from Bristol-Myers Squibb.				

1

Study	Tarhini et al. (2018) Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Patient-level simulation **Approach to analysis:** The model was based on pooled patient-level data from multiple clinical trials, and included sequences of first-line and second-line therapies. A set of sequential risk equations were derived using pooled patient-level data from 891 patients with advanced melanoma included in the CheckMate 067 and CheckMate 069 trials to establish the impact of individual patient characteristics on long-term outcomes such as overall survival. For each patient in the model, the risk equations predicted time on first-line treatment, time to subsequent treatment and time on second-line treatment. The competing risk of death was estimated for each phase in the treatment sequences.	**Population:** Patients with treatment-naïve BRAF-mutant advanced melanoma **Intervention:** - **Comparator:** (1) 1L[1] BRAF+MEK inhibitors followed by 2L[1] anti-PD-1 (2) 1L anti-PD-1 followed by 2L BRAF+MEK inhibitors (3) 1L anti-PD-1+anti-CTLA-4 followed by 2L BRAF+MEK inhibitors	**Cost difference:** Costs compared pairwise with (1) ($345,693): (2) +$250,034 (3) +$60,965 **Currency and cost year:** 2016 USD **Costs included:** Drug administration and acquisition costs, disease management costs, AE costs	**QALY difference:** QALYs compared pairwise with (1) (2.6): (2) +2.8 (3) +1.1	**Incremental analysis:** Pairwise ICERs relative to (1): (2) $89,298 (3) $55,423 Fully incremental analysis: (1) - (2) extended dominated (3) $79,743 **Analysis of uncertainty:** A probabilistic analysis was conducted to estimate the impact of parameter uncertainty on results. The analysis inputs were varied per the standard guidelines by the International Society for Pharmacoeconomics and Outcomes Research – Society for Medical Decision Making task force. Efficacy risk equations used a variance–covariance matrix. Cost inputs assumed gamma distribution, and

Study	Tarhini et al. (2018) Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Perspective: US third-party payer **Time horizon:** Lifetime (30 years) **Discounting:** 3% for costs and outcomes				standard error was assumed to be 20% of the mean. Quality-of-life inputs used beta distribution, and standard error was assumed to be 10% of the mean. The cost-effectiveness acceptability curve showed that for up to a willingness-to-pay threshold of $80,000 per QALY, a 1L BRAF+MEK inhibitor followed by an anti-PD-1 was the most likely cost-effective treatment option. At higher willingness-to-pay values, 1L anti-PD-1 + anti-CTLA-4 followed by 2L BRAF + MEK inhibitors was the most likely cost–effective option with a probability of approximately 40–90%. In one-way sensitivity analysis, model results were most sensitive to the 1L and 2L treatment effects derived from the CheckMate trials on the 1L anti-PD-1 sequence, and the overall HRs on the 1L BRAF+MEK inhibitor sequence.
Data sources				
Outcomes: For treatment sequences initiated with immunotherapies, data were pooled and extrapolated from the CheckMate 067 and 069 studies. A set of sequential risk equations were derived to establish the impact of individual patient characteristics on long-term outcomes such as overall survival. In the absence of head-to-head clinical trial data for BRAF+MEK inhibitors, a matching adjusted indirect comparison was conducted, estimating the treatment effect of dabrafenib plus trametinib compared with nivolumab plus ipilimumab. HRs were estimated using this comparison, and for both overall survival and progression-free survival there was evidence of nonproportionality so separate HRs were applied over different time points (OS before and after 12 months as observed in the data on hazard of death, PFS 0-5 months, 5-12 months and after 12 months). The separate time dependent HR time periods were not justified in the study. **Quality of life:** The model considered utility values for progression-free (0.79) and progressed health states (0.75), estimated from responses to the EuroQoL-5 Dimensions in the CheckMate 067 trial. The utility index scores were estimated using the EQ-5D-3L UK tariff. Adverse-event-related disutilities were considered depending on the setting of care, and the incidence was obtained from clinical trials. The duration of disutility related to adverse events was based on the time to resolution of events reported in CheckMate 067.				

Study	Tarhini et al. (2018) Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Costs: Drug and administration costs per month were estimated using the drug acquisition cost, route of administration, unit costs for administration (payer reimbursement for intravenous drug administration in physician's office and hospital outpatient settings), recommended dose and dosing frequency based on publicly available sources (i.e., RedBook and Medicare Payment limits), prescribing information and clinical trials. Inclusion of AEs was limited to those of grade 3 or 4 due to their economic impact, and their management costs were obtained from published literature. A statistical analysis of CheckMate 067 and 069 was conducted to understand resource use patterns for routine disease management. Resource item unit costs were obtained from published sources, and drug costs were based on published wholesale acquisition costs.				
Comments				
Source of funding: Supported/ funded by Bristol-Myers Squibb.				
Overall applicability: Partially applicable				
The study was based in the US, which has a different healthcare system and perspective on costs than that of the UK. Costs and QALYs were discounted at 3% per annum which is not the same as the reference case (3.5%).				
Overall quality: Potentially serious limitations				
The study was supported by Bristol-Myers Squibb, and multiple authors have received research funding or participated in a consulting or advisory role for various relevant pharmaceutical companies. The rationale for applying separate time depend HRs for treatment duration in the comparison of BRAF+MEK inhibitors with immunotherapies was not explained in the study.				

1 *1 1L and 2L stand for first line therapy and second line therapy, respectively.*

2

Study	Tarhini et al. (2018) Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Discrete event simulation **Approach to analysis:** The model used available clinical trial data to evaluate treatment sequences for a cohort of patients in which each patient has a unique set of baseline characteristics. The model predicted the time to clinical	**Population:** Patients with advanced melanoma and wild-type BRAF tumours naive to systemic therapies **Intervention:** - **Comparator:** (1) 1L[1] anti-PD-1 followed by 2L[1] anti-	**Cost difference:** Costs compared pairwise with (1) ($319,082): (2) +$24,460 (3) +$6,165 (4) +$100,837	**QALY difference:** QALYs compared pairwise with (1) (4.91): (2) -1.27 (3) +2.26 (4) -0.06	**Incremental analysis:** Pairwise ICERs relative to (1): (2) dominated (3) $2,728 (4) dominated Fully incremental analysis: (1) -

Study	Tarhini et al. (2018) Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
events (start and end of therapy lines, time of death) for each line of treatment in a sequence. **Perspective:** US third party payer **Time horizon:** Lifetime (30 years) **Discounting:** 3% for costs and outcomes	CTLA-4 followed by 3L[1] chemo/BSC (2) 1L anti-CTLA-4 followed by 2L anti-PD-1 followed by 3L chemo/BSC (3) 1L anti-CTLA-4 + anti-PD-1 followed by 2L chemo followed by 3L chemo/BSC (4) 1L anti-CTLA-4 + anti-PD-1 followed by 2L anti-PD-1 followed by 3L chemo/BSC	**Currency and cost year:** 2016 USD **Costs included:** Drug acquisition, administration and adverse events while on treatment, as well as disease management over their entire lifetime.		(2) dominated (3) $30,934 (4) dominated **Analysis of uncertainty:** Sensitivity analyses were conducted where inputs were varied as per the standard guidelines by the International Society for Pharmacoeconomics and Outcomes Research — Society for Medical Decision Making task force. The impact of each varied input on the model outcomes was presented as a tornado graph. Probabilistic analyses, based on 1000 Monte Carlo simulations, were presented as cost–effectiveness acceptability curves to capture the impact of uncertainty around the input parameters on the probability of individual sequences being the most cost-effective strategy under various willingness-to-pay thresholds. The probabilistic analyses, representing the uncertainty in the input parameter estimates, resulted in a cost-effectiveness acceptability curve showing that above a willingness-to-pay value of $32,500, anti-PD-1 + anti-CTLA-4 followed by chemotherapy is the most cost-effective treatment strategy. Univariate sensitivity analysis showed that model outcomes were sensitive to the treatment effect coefficient of the risk equations for time on 1L treatment, time

Study	Tarhini et al. (2018) Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
				to subsequent treatment, time on 2L treatment, survival during treatment-free interval and survival after 2L treatment. Furthermore, the analysis results were influenced by utilities (pre- and post-progression), drug costs and disease management costs.
Data sources				
Outcomes: Outcomes were predicted using a set of statistical risk equations for anti-PD-1, anti-CTLA-4 and anti-PD-1 + anti-CTLA-4 initiating sequences, estimated using the pooled patient-level dataset for nivolumab, ipilimumab and nivolumab + ipilimumab from the Phase III CheckMate 067 and Phase II CheckMate 069 clinical trials and extensive discussions with clinicians. The efficacy of pembrolizumab first-line therapy was assumed to be equivalent to nivolumab, supported by clinical opinion, similar overall survival (OS) reported in a network meta-analysis of pembrolizumab versus nivolumab, and similar median treatment duration for pembrolizumab and nivolumab in the KEYNOTE-006 and CheckMate 067 trials. To generate results, real patient profiles based on baseline characteristics from the BRAF wild-type patient pool of the CheckMate 067 and CheckMate 069 trials were run through the simulation. **Quality of life:** HRQoL for PF and PD health states were estimated from EQ-5D responses collected in CheckMate 067. AE disutilities were considered, and were obtained from published literature. **Costs:** Drug and administrations costs per month were estimated using drug acquisition cost, route of administration, unit costs for administration (payer reimbursement), recommended dose, and dosing frequency based on publicly available sources, US FDA labels, and clinical trials. Adverse event management costs based on the inpatient and outpatient settings were obtained from published literature. Routine disease management costs were estimated from the CheckMate 067 and CheckMate 069 trial data, and unit costs for concomitant drugs, hospitalisations, surgeries, lab tests and disease management procedures were obtained from published sources.				
Comments				
Source of funding: This research was funded by Bristol-Myers Squibb.				
Overall applicability: Partially applicable				
The study was based in the US, which has a different healthcare system and perspective on costs than that of the UK. Costs and QALYs were discounted at 3% per annum which is not the same as the reference case (3.5%).				
Overall quality: Minor limitations				
The study was supported by Bristol-Myers Squibb, and multiple authors have received research funding or participated in a consulting or advisory role for various relevant pharmaceutical companies.				

1 *1 1L, 2L and 3L stand for first-, second-, and third-line therapy, respectively.*

1

Study	*De novo* **economic model 2021**			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Three state partitioned survival model **Approach to analysis:** Health states were progression-free disease, progressed disease, and death. PFS and OS for all treatments were derived from a network meta-analysis (NMA) which was developed for this guideline with the assistance of the TSU (2021). **Perspective:** UK NICE perspective **Time horizon:** Lifetime (101 years of age) **Discounting:** 3.5% for costs and outcomes	**Population:** People with previously untreated advanced melanoma **Intervention:** (1) nivolumab, (2) pembrolizumab, (3) ipilimumab + nivolumab, (4) encorafenib + binimetinib, (5) dabrafenib + trametinib **Comparator:** -	**Cost difference (incremental):** (1) – (3) £4,038 (2) £4,106 (5) £61,512 (4) £76,432 **Currency and cost year:** 2021 GBP **Costs included:** Treatment costs, administration costs, adverse event costs, health state costs, terminal and palliative care costs.	**QALY difference (incremental):** (1) – (3) 0.784 (2) -0.952 (5) -2.013 (4) -1.673	**Incremental analysis:** (1) – (3) £5,148 (2) dominated (5) dominated (4) dominated **Analysis of uncertainty:** Probabilistic sensitivity analysis and scenario analyses were conducted to examine uncertainty. The results of the probabilistic analysis indicated that the combination of nivolumab and ipilimumab remained most cost-effective, and dominant over the other strategies. In scenario analysis the only parameters that made a substantial difference to the results were those around the data used for second line treatment distribution and time on treatment.
Data sources				
Outcomes: Survival data was taken from the NMA. Grade 3+ adverse events were included in the model and the rates of these events were derived from an NMA conducted for this guideline. **Quality of life:** Health state utility values were taken from the previous NICE technology appraisals in advanced melanoma. Adverse event disutility was informed by a study used in previous NICE technology appraisals. **Costs:** Resource use and costs were estimated based on previous NICE TAs and published sources, and were validated by the guideline committee.				
Comments				
This analysis was conducted as part of the development of the update to the guideline for Melanoma: assessment and management.				
Overall applicability: Directly applicable				
The analysis was conducted specifically for the purpose of answering this review question.				

Study	*De novo* **economic model 2021**			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Overall quality: Minor limitations				

1

Study applicability and limitations checklists

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	People with previously untreated advanced melanoma
1.2 Are the interventions appropriate for the review question?	Yes	Talimogene Laherparepvec, ipilimumab and dacarbazine are listed in the protocol and are treatments available in the UK for advanced melanoma
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK study
1.4 Is the perspective for costs appropriate for the review question?	Yes	NICE perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	NICE perspective
1.6 Are all future costs and outcomes discounted appropriately?	Yes	3.5% as per NICE reference case
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 Overall judgement: Directly applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	3 state partitioned survival model (non-progressive disease,

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
		progressive disease, death)
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime (30 years)
2.3 Are all important and relevant outcomes included?	Yes	OS, PFS (considered to be a proxy for time to treatment failure), AEs, costs and QALYs, ICER
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Based on trial data
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Due to a lack of direct comparative data alternative methods for obtaining indirect estimates of effect were used (modified Korn and two-step Korn, both using meta-analysis)
2.6 Are all important and relevant costs included?	Yes	Costs associated with treatment and with disease progression were included. The ERG discussion in this study did not note any key costs that were missing from the analysis.
2.7 Are the estimates of resource use from the best available source?	Yes	Estimated based on a resource utilisation study, published sources and views of clinical experts.
2.8 Are the unit costs of resources from the best available source?	Yes	Estimated based on a resource utilisation study, published sources and views of clinical experts.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	The analysis only compared two treatments, T-VEC and ipilimumab, with scenarios comparing T-VEC with other comparators.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	A range of one-way deterministic sensitivity analyses and a probabilistic

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
		sensitivity analysis was conducted.
2.11 Has no potential financial conflict of interest been declared?	No	One author received fees for speaking for advisory board membership from GlaxoSmithKline, Novartis, Merck Sharp and Dohme and Bristol Myers Squibb and support with travel to conferences from Bristol Myers Squibb and GlaxoSmithKline.
2.12 Overall assessment: Minor limitations		
Study Identification: Houten 2020; Encorafenib with Binimetinib for the Treatment of Patients with BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma
1.2 Are the interventions appropriate for the review question?	Yes	Both regimens were combination therapy of BRAF inhibitor plus BRAF+MEK inhibitor
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK study
1.4 Is the perspective for costs appropriate for the review question?	Yes	NICE perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	NICE perspective
1.6 Are all future costs and outcomes discounted appropriately?	Yes	3.5% as per NICE reference case
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line	Yes	Utility values were taken from an NMA of relevant trials.

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
with analytical perspectives taken (item 1.5 above).		
1.8 Overall judgement: Directly applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	3 state partitioned survival model (progression-free, post-progression, death) with sub-states within the PF and PP states for on/off treatment
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	30 years
2.3 Are all important and relevant outcomes included?	Yes	OS, PFS, AEs, costs and QALYs, ICER
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Directly from trial data, extrapolated beyond trial time horizon with parametric models
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Hazard ratios were generated using an NMA, in the absence of direct comparisons between the interventions
2.6 Are all important and relevant costs included?	Yes	Primary and subsequent treatment costs, administration costs, AE costs, health state costs
2.7 Are the estimates of resource use from the best available source?	Yes	Resource use taken from the COLUMBUS trial and published sources
2.8 Are the unit costs of resources from the best available source?	Yes	Based on NHS estimates and advice from experts in clinical practice in the NHS
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	The full breakdown of costs and outcomes was not presented in the study, but the

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
		overall outcome of the cost-effectiveness analysis was presented (intervention was dominant) and the incremental QALYs were reported.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Probabilistic and deterministic sensitivity analyses were conducted.
2.11 Has no potential financial conflict of interest been declared?	Yes	No conflicts of interest.
2.12 Overall assessment: Minor limitations		
Study Identification: Pike 2017; Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Patients with advanced malignant melanoma aged 18 or older
1.2 Are the interventions appropriate for the review question?	Yes	Multiple comparisons between single agent and combination chemotherapy, BRAF inhibitors, MEK inhibitors and immunotherapies
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Study based in Norway, which is fairly similar to the system in the UK
1.4 Is the perspective for costs appropriate for the review question?	Partly	Healthcare payer perspective which is similar to the NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs and QALYS discounted at 4% annually

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	EQ-5D values, identified in a systematic search
1.8 Overall judgement: Partially applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	3 state partitioned survival model, described as a probabilistic decision-analytic model (progression-free disease, progressed disease, death)
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	10 years
2.3 Are all important and relevant outcomes included?	Yes	OS, PFS, AEs, costs and QALYs, ICER
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Hazard ratios from the NMA
2.6 Are all important and relevant costs included?	Yes	BRAF testing, treatment costs, AE costs, monitoring costs
2.7 Are the estimates of resource use from the best available source?	Partly	Expert opinion, assumptions, published literature, trial data
2.8 Are the unit costs of resources from the best available source?	Yes	Published sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Probabilistic sensitivity analysis of all input parameters was conducted.

Study Identification: Fleeman 2017; Talimogene Laherparepvec for Treating Metastatic Melanoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal		
		Scenario analyses were conducted for drug pricing, time horizon and HRQoL weights.
2.11 Has no potential financial conflict of interest been declared?	Yes	No competing interests
2.12 Overall assessment: Minor limitations		

Study Identification: Quon 2019; Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Advanced melanoma
1.2 Are the interventions appropriate for the review question?	Yes	Multiple comparisons between immunotherapies
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	The study was in a Canadian setting
1.4 Is the perspective for costs appropriate for the review question?	Yes	Canadian public healthcare perspective, direct medical costs
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Canadian public healthcare perspective
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs and QALYS discounted at 5% annually
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	The base-case analysis used a study that elicited health state utility values from the Canadian general public using the standard gamble method. EQ-5D data from the CheckMate 067 trial was used in a sensitivity analysis.

Study Identification: Quon 2019; Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada		
1.8 Overall judgement: Partially applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	3 state partitioned survival model (progression-free, post-progression, death)
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	20 years
2.3 Are all important and relevant outcomes included?	Yes	OS, PFS, LYs, QALYs, ICERs, Incremental cost per additional life year, AEs
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	OS and PFS for 3 of the interventions was informed by the trial, with parametric curves fitted to extrapolate OS, and a piecewise approach was followed to extrapolate PFS.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	An indirect comparison was conducted for pembrolizumab, with ipilimumab as the common comparator.
2.6 Are all important and relevant costs included?	Yes	Treatment costs, administration costs, health state resource use costs, AE costs
2.7 Are the estimates of resource use from the best available source?	Yes	Clinical trials, expert opinion, published chart review study reviewed and adjusted by a clinician.
2.8 Are the unit costs of resources from the best available source?	Yes	Published sources, Ontario Case Costing Initiative Tool, Drug manufacturer, Pan-Canadian Oncology Drug Review, Ontario

Study Identification: Quon 2019; Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada		
		Ministry of Health and Long-Term Care
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Univariate, multi-variate and probabilistic sensitivity analyses were conducted.
2.11 Has no potential financial conflict of interest been declared?	No	This study was sponsored by Bristol-Myers Squibb. At the time the study or analysis was conducted, Amir Abbas Tahami Monfared was an employee and shareholder of Bristol-Myers Squibb, Canada. Peter Quon, Ying Xiao, and Sonja Sorensen are all employees of Evidera, which provides consulting and other research services to pharmaceutical, medical device, and other organizations. Evidera received funding from Bristol-Myers Squibb, of Quebec, Canada, for the involvement of their employees.
2.12 Overall assessment: Minor limitations		

Study Identification: Tarhini 2018; Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**

Study Identification: Tarhini 2018; Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma		
1.1 Is the study population appropriate for the review question?	Yes	Patients with treatment-naïve BRAF-mutant advanced melanoma
1.2 Are the interventions appropriate for the review question?	Yes	Sequences with first line options of combination and single agent immunotherapies and combination BRAF+MEK inhibitors
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US study, the healthcare system in the US is quite different to that in the UK.
1.4 Is the perspective for costs appropriate for the review question?	Partly	US third-party payer perspective, including drug administration, disease management and adverse events.
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs and outcomes discounted at 3% annually
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Utility values were estimated from EQ-5D reported in the CheckMate trial using TTO
1.8 Overall judgement: Partially applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Patient-level simulation incorporating detailed clinical trial data based on patient characteristics.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime (30 years)
2.3 Are all important and relevant outcomes included?	Yes	OS, AEs, costs and QALYs, ICERs

Study Identification: Tarhini 2018; Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma		
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	From the CheckMate 067 and CheckMate 069 trials
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From clinical trials where possible, and matching adjusted indirect comparison in the absence of head-to-head trial data. The rationale for applying time-dependent HRs for treatment duration between BRAF+MEK inhibitors and immunotherapies was not explained in the study.
2.6 Are all important and relevant costs included?	Yes	Drug administration and acquisition costs, disease management costs, AE costs
2.7 Are the estimates of resource use from the best available source?	Yes	Analysis of the CheckMate 067 and 069 trials, publicly available sources and prescribing information.
2.8 Are the unit costs of resources from the best available source?	Yes	Healthcare Cost and Utilization Project National Inpatient Sample database, published sources and published wholesale acquisition costs.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Probabilistic and one-way sensitivity analyses were conducted, as well as scenario analyses around treatment duration.
2.11 Has no potential financial conflict of interest been declared?	No	The study was supported by Bristol-Myers Squibb, and multiple authors have received research funding or participated in a consulting or advisory role for various

Study Identification: Tarhini 2018; Clinical and economic outcomes associated with treatment sequences in patients with BRAF-mutant advanced melanoma		
		relevant pharmaceutical companies.
2.12 Overall assessment: Potentially serious limitations		

Study Identification: Tarhini 2018; Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Patients with advanced melanoma and wild-type BRAF tumours naive to systemic therapies
1.2 Are the interventions appropriate for the review question?	Yes	Sequences with first line options of combination and single agent immunotherapies
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US study, the healthcare system in the US is quite different to that in the UK.
1.4 Is the perspective for costs appropriate for the review question?	Partly	US third-party payer perspective, including drug administration, disease management and adverse events.
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Included quality of life by disease phase and disutility due to adverse events
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs and outcomes discounted at 3% annually
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Utility values were estimated from EQ-5D reported in the CheckMate trial
1.8 Overall judgement: Partially applicable		

Study Identification: Tarhini 2018; Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis		
There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Discrete event simulation, predicting time to clinical events (start and end of lines of therapy, and death)
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime (30 years)
2.3 Are all important and relevant outcomes included?	Yes	OS, AEs, costs and QALYs, ICERs
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Statistical risk equations were estimated using pooled patient-level data from the phase III CheckMate 067 and phase II CheckMate 069 trials, alongside extensive discussion with clinical experts.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Statistical risk equations were estimated using pooled patient-level data from the phase III CheckMate 067 and phase II CheckMate 069 trials, alongside extensive discussion with clinical experts.
2.6 Are all important and relevant costs included?	Yes	Drug costs, administration costs, disease management costs, AE costs.
2.7 Are the estimates of resource use from the best available source?	Yes	Publicly available sources and trial data
2.8 Are the unit costs of resources from the best available source?	Yes	Publicly available sources, US FDA labels and clinical trials
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	

Study Identification: Tarhini 2018; Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost–effectiveness analysis		
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Probabilistic and univariate sensitivity analyses were conducted.
2.11 Has no potential financial conflict of interest been declared?	No	The study was supported by Bristol-Myers Squibb, and multiple authors have received research funding or participated in a consulting or advisory role for various relevant pharmaceutical companies.
2.12 Overall assessment: Minor limitations		

Study Identification: *De novo* cost-utility analysis (2021)		
Guidance topic: Skin tumours including melanoma		**Question no: 5.1**
Checklist completed by: Hannah Lomax		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Patients with advanced melanoma
1.2 Are the interventions appropriate for the review question?	Yes	NICE TA approved therapies for first-line treatment of advanced melanoma
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK NICE context
1.4 Is the perspective for costs appropriate for the review question?	Yes	UK NICE perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	UK NICE perspective
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Costs and outcomes discounted at 3.5% annually
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Utility values were taken from previous NICE TAs which were deemed appropriate by the ERG.

Study Identification: *De novo* cost-utility analysis (2021)		
1.8 Overall judgement: Directly applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Partitioned survival model
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime (maximum 101 years of age)
2.3 Are all important and relevant outcomes included?	Yes	OS, PFS, costs and QALYs, ICERs
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	An NMA was conducted to address this review question.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	An NMA was conducted to address this review question.
2.6 Are all important and relevant costs included?	Yes	Drug costs, administration costs, disease management costs, AE costs, palliative and terminal care costs.
2.7 Are the estimates of resource use from the best available source?	Yes	Publicly available sources and previous NICE TAs
2.8 Are the unit costs of resources from the best available source?	Yes	Publicly available sources and previous NICE TAs
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 Overall assessment: Minor limitations		

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Appendix J – Health economic model

A de novo economic analysis was conducted for this review question and is detailed in the economic model report for review F .

Appendix K – Excluded studies

Clinical studies

Study	Reason for exclusion
Algazi, A.P., Othus, M., Daud, A.I. et al. (2020) Continuous versus intermittent BRAF and MEK inhibition in patients with BRAF-mutated melanoma: a randomized phase 2 trial. Nature Medicine 26(10): 1564-1568	- Study does not contain a relevant intervention
Ascierto, Paolo A, McArthur, Grant A, Dreno, Brigitte et al. (2016) Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. The Lancet. Oncology 17(9): 1248-60	- Not recommended by NICE Cobimetinib in combination with vemurafenib
Atkins, MB, Stephen Hodi, F, Thompson, JA et al. (2018) Pembrolizumab plus pegylated interferon alfa-2b or ipilimumab for advanced melanoma or renal cell carcinoma: dose-finding results from the phase Ib KEYNOTE-029 Study. Clinical cancer research 24(8): 1805-1815	- Study does not contain a relevant intervention pembrolizumab plus ipilimumab vs. pembrolizumab plus PEG-IFN
Bagge, Ann-Sophie Lindqvist, Ben-Shabat, Ilan, Belgrano, Valerio et al. (2016) Health-Related Quality of Life for Patients Who have In-Transit Melanoma Metastases Treated with Isolated Limb Perfusion. Annals of surgical oncology 23(6): 2062-9	- Single arm trial Single arm prospective study of ILP
Blank, CU, Larkin, J, Arance, AM et al. (2017) Open-label, multicentre safety study of vemurafenib in 3219 patients with BRAFV600 mutation-positive metastatic melanoma: 2-year follow-up data and long-term responders' analysis. European journal of cancer 79: 176-184	- Single arm trial
Campana, L G, Testori, A, Curatolo, P et al. (2016) Treatment efficacy with electrochemotherapy: A multi-institutional prospective observational study on 376 patients with superficial tumors. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 42(12): 1914-1923	- Single arm prospective study
Caraco, Corrado, Mozzillo, Nicola, Marone, Ugo et al. (2013) Long-lasting response to electrochemotherapy in melanoma patients with cutaneous metastasis. BMC cancer 13: 564	- Single arm prospective study
Carlino, Matteo S, Long, Georgina V, Schadendorf, Dirk et al. (2018) Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: A randomised clinical trial. European journal of cancer (Oxford, England : 1990) 101: 236-243	- Secondary publication of an included study that does not provide any additional relevant information
Chesney, Jason, Awasthi, Sanjay, Curti, Brendan et al. (2018) Phase IIIb safety results from an expanded-access protocol of talimogene laherparepvec for patients with unresected, stage IIIB-IVM1c melanoma. Melanoma research 28(1): 44-51	- Single arm prospective study

Study	Reason for exclusion
Chesney, Jason, Puzanov, Igor, Collichio, Frances et al. (2019) Patterns of response with talimogene laherparepvec in combination with ipilimumab or ipilimumab alone in metastatic unresectable melanoma. British journal of cancer 121(5): 417-420	- Outcome - not within protocol Patients with an objective response were evaluated for pseudoprogression
Clover, A.J.P., de Terlizzi, F., Bertino, G. et al. (2020) Electrochemotherapy in the treatment of cutaneous malignancy: Outcomes and subgroup analysis from the cumulative results from the pan-European International Network for Sharing Practice in Electrochemotherapy database for 2482 lesions in 987 patients (2008-2019). European Journal of Cancer 138: 30-40	- Single arm prospective study
Daud, AI, Wolchok, JD, Robert, C et al. (2016) Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. Journal of clinical oncology 34(34): 4102-4109	- Single arm trial
De La Cruz-Merino, L, Di Guardo, L, Grob, J-J et al. (2015) Clinical features of cobimetinib (COBI)-associated serous retinopathy (SR) in BRAF-mutated melanoma patients (pts) treated in the coBRIM study. Journal of clinical oncology 33(15suppl1)	- Not recommended by NICE Cobimetinib in combination with vemurafenib
Dreno, B, Ribas, A, Larkin, J et al. (2017) Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Annals of oncology: official journal of the European Society for Medical Oncology 28(5): 1137-1144	- Not recommended by NICE Cobimetinib in combination with vemurafenib
Dreno, Brigitte, Ascierto, Paolo A, Atkinson, Victoria et al. (2018) Health-related quality of life impact of cobimetinib in combination with vemurafenib in patients with advanced or metastatic BRAFV600 mutation-positive melanoma. British journal of cancer 118(6): 777-784	- Not recommended by NICE Cobimetinib in combination with vemurafenib
Eggermont, A.M.M., Kicinski, M., Blank, C.U. et al. (2020) Association between Immune-Related Adverse Events and Recurrence-Free Survival among Patients with Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncology 6(4): 519-527	- Resected melanoma Completely resected histologically confirmed cutaneous melanoma metastatic to regional lymph nodes; either stage IIIA, IIIB, or IIIC
Falk, H., Matthiessen, L.W., Wooler, G. et al. (2018) Calcium electroporation for treatment of cutaneous metastases; a randomized double-blinded phase II study, comparing the effect of calcium electroporation with electrochemotherapy. Acta Oncologica 57(3): 311-319	- Does not contain a population of people with unresectable stage 3 or 4 melanoma Only one participant with melanoma (stage not reported)
Franke, Viola, Berger, Danique M S, Klop, W Martin C et al. (2019) High response rates for T-VEC in early metastatic melanoma (stage IIIB/C-IVM1a). International journal of cancer 145(4): 974-978	- Single arm prospective study
Gogas, Helen J, Flaherty, Keith T, Dummer, Reinhard et al. (2019) Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. European journal of cancer (Oxford, England: 1990) 119: 97-106	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Goldberg, Sarah B, Gettinger, Scott N, Mahajan, Amit et al. (2016) Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. The Lancet. Oncology 17(7): 976-983	- Single arm trial
Gutzmer, Ralf, Stroyakovskiy, Daniil, Gogas, Helen et al. (2020) Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England) 395(10240): 1835-1844	- Not recommended by NICE Cobimetinib in combination with vemurafenib plus atezolizumab
Hamid, O, Robert, C, Daud, A et al. (2019) Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Annals of oncology: official journal of the European Society for Medical Oncology 30(4): 582-588	- Single arm trial
Hauschild, Axel, Ascierto, Paolo A, Schadendorf, Dirk et al. (2020) Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib monotherapy: Analysis from phase 2 and 3 clinical trials. European journal of cancer (Oxford, England: 1990) 125: 114-120	- Secondary publication of an included study that does not provide any additional relevant information
Hodi, F.S., Chapman, P.B., Sznol, M. et al. (2020) Safety and efficacy of combination nivolumab plus ipilimumab in patients with advanced melanoma: results from a North American expanded access program (CheckMate 218). Melanoma research	- Not a relevant study design Expanded access program designNivolumab was used in combination with ipilimumab (induction phase). Single agent nivolumab was subsequently administered during the maintenance phase.
Jiang, Betty S, Speicher, Paul J, Thomas, Samantha et al. (2015) Quality of life after isolated limb infusion for in-transit melanoma of the extremity. Annals of surgical oncology 22(5): 1694-700	- Single arm trial
Johnson, DB, Flaherty, KT, Weber, JS et al. (2014) Combined BRAF (dabrafenib) and MEK inhibition (trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. Journal of clinical oncology 32(33): 3697-3704	- Secondary publication of an included study that does not provide any additional relevant information Related to Long 2018 (NCT01072175, BRF113220)
Kunte, C, Letule, V, Gehl, J et al. (2017) Electrochemotherapy in the treatment of metastatic malignant melanoma: a prospective cohort study by InspECT. The British journal of dermatology 176(6): 1475-1485	- Does not contain a population of people with unresectable stage 3 or 4 melanoma
Larkin, James, Ascierto, Paolo A, Dreno, Brigitte et al. (2014) Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. The New England journal of medicine 371(20): 1867-76	- Not recommended by NICE Cobimetinib in combination with vemurafenib
Latimer, Nicholas R, Amonkar, Mayur M, Stapelkamp, Ceilidh et al. (2015) Adjusting for confounding effects of treatment switching in a randomized phase II study of dabrafenib plus trametinib in BRAF V600+ metastatic melanoma. Melanoma research 25(6): 528-36	- Secondary publication of an included study that does not provide any additional relevant information Related to Long 2018 (NCT01072175, BRF113220)

Study	Reason for exclusion
Latimer, Nicholas R, Bell, Helen, Abrams, Keith R et al. (2016) Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer medicine 5(5): 806-15	- Study does not contain a relevant intervention
Long, G V, Flaherty, K T, Stroyakovskiy, D et al. (2017) Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Annals of oncology: official journal of the European Society for Medical Oncology 28(7): 1631-1639	- Secondary publication of an included study that does not provide any additional relevant information
Long, Georgina V, Dummer, Reinhard, Hamid, Omid et al. (2019) Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. The Lancet. Oncology 20(8): 1083-1097	- Comparator in study does not match that specified in protocol
Long, Georgina V, Weber, Jeffrey S, Infante, Jeffrey R et al. (2016) Overall Survival and Durable Responses in Patients With BRAF V600-Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 34(8): 871-8	- Secondary publication of an included study that does not provide any additional relevant information Related to Long 2018 (NCT01072175, BRF113220)
Maio, Michele, Grob, Jean-Jacques, Aamdal, Steinar et al. (2015) Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(10): 1191-6	- Study does not contain a relevant intervention ipilimumab plus dacarbazine vs placebo plus dacarbazine
McDermott, D, Haanen, J, Chen, T-T et al. (2013) Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Annals of oncology: official journal of the European Society for Medical Oncology 24(10): 2694-2698	- Comparator in study does not match that specified in protocol
McDermott, David F, Shah, Ruchit, Gupte-Singh, Komal et al. (2019) Quality-adjusted survival of nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone among treatment-naive patients with advanced melanoma: a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation 28(1): 109-119	- Secondary publication of an included study that does not provide any additional relevant information Related to Larkin 2019 (CheckMate 067 trial)
Nebot, N., Arkenau, H.-T., Infante, J.R. et al. (2018) Evaluation of the effect of dabrafenib and metabolites on QTc interval in patients with BRAF V600-mutant tumours. British Journal of Clinical Pharmacology 84(4): 764-775	- Outcome - not within protocol
Puzanov, I, Milhem, MM, Minor, D et al. (2016) Talimogene laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIB-IV melanoma. Journal of clinical oncology 34(22): 2619-2626	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Revicki, D.A., van den Eertwegh, A.J., Lorigan, P. et al. (2012) Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. Health and quality of life outcomes 10: 66	- Comparator in study does not match that specified in protocol
Ribas, A, Lawrence, D, Atkinson, V et al. (2019) Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in BRAF-mutant melanoma. Nature medicine 25(6): 936-940	- Outcome - not within protocol
Ribas, Antoni, Gonzalez, Rene, Pavlick, Anna et al. (2014) Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. The Lancet. Oncology 15(9): 954-65	- Not recommended by NICE Cobimetinib in combination with vemurafenib
Ricotti, F, Giuliodori, K, Cataldi, I et al. (2014) Electrochemotherapy: an effective local treatment of cutaneous and subcutaneous melanoma metastases. Dermatologic therapy 27(3): 148-52	- Single arm prospective study
Robert, Caroline, Flaherty, Keith, Nathan, Paul et al. (2019) Five-year outcomes from a phase 3 METRIC study in patients with BRAF V600 E/K-mutant advanced or metastatic melanoma. European journal of cancer (Oxford, England : 1990) 109: 61-69	- Study does not contain a relevant intervention
Robert, Caroline, Ribas, Antoni, Hamid, Omid et al. (2018) Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36(17): 1668-1674	- Not a relevant study design
Schadendorf, D, Amonkar, M M, Milhem, M et al. (2014) Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Annals of oncology: official journal of the European Society for Medical Oncology 25(3): 700-706	- Study does not contain a relevant intervention Trametinib alone compared to chemotherapy
Shetty, Gina, Beasley, Georgia M, Sparks, Sara et al. (2013) Plasma cytokine analysis in patients with advanced extremity melanoma undergoing isolated limb infusion. Annals of surgical oncology 20(4): 1128-35	- Data not reported in an extractable format
Simioni, Andrea, Valpione, Sara, Granziera, Elisa et al. (2020) Ablation of soft tissue tumours by long needle variable electrode-geometry electrochemotherapy: final report from a single-arm, single-centre phase-2 study. Scientific reports 10(1): 2291	- Single arm trial
Smith, H.G., Wilkinson, M.J., Smith, M.J.F. et al. (2018) The effect of age on outcomes after isolated limb perfusion for advanced extremity malignancies. European Journal of Cancer 100: 46-54	- Does not contain a population of people with unresectable stage 3 or 4 melanoma
Solari, Nicola, Spagnolo, Francesco, Ponte, Erica et al. (2014) Electrochemotherapy for the management of cutaneous and subcutaneous metastasis: a series of 39 patients treated with palliative intent. Journal of surgical oncology 109(3): 270-4	- Single arm prospective study All patients underwent ECT

Study	Reason for exclusion
Stamatiou, Dimitrios, Ioannou, Christos V, Kontopodis, Nikolaos et al. (2017) Hyperthermic isolated limb perfusion. The switch from Steinmann pins to Omni-tract assisted isolation. The Journal of surgical research 213: 147-157	- Prospective, multi-arm evaluation of variations of same Tx
Tarhini, Ahmad A, Lee, Sandra J, Li, Xiaoxue et al. (2019) E3611-A Randomized Phase II Study of Ipilimumab at 3 or 10 mg/kg Alone or in Combination with High-Dose Interferon-alpha2b in Advanced Melanoma. Clinical cancer research: an official journal of the American Association for Cancer Research 25(2): 524-532	- Comparator in study does not match that specified in protocol
Theurich, Sebastian, Rothschild, Sacha I, Hoffmann, Michael et al. (2016) Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma. Cancer immunology research 4(9): 744-54	- Study does not contain a relevant intervention
Tomassini, Gian M, Covarelli, Piero, Tomassini, Marco A et al. (2016) Electrochemotherapy with intravenous bleomycin for advanced non-melanoma skin cancers and for cutaneous and subcutaneous metastases from melanoma. Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia 151(5): 499-506	- Single arm prospective study
Weber, Jeffrey S, Dummer, Reinhard, de Pril, Veerle et al. (2013) Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 119(9): 1675-82	- Comparator in study does not match that specified in protocol
Wong, Joyce, Chen, Y Ann, Fisher, Kate J et al. (2014) Resection of residual disease after isolated limb infusion (ILI) is equivalent to a complete response after ILI-alone in advanced extremity melanoma. Annals of surgical oncology 21(2): 650-5	- Comparator in study does not match that specified in protocol -Surgical resection of remaining disease following ILI

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2 Economic studies

Study reference	Reason for exclusion
Almutairi, Abdulaali R, Alkhatib, Nimer S, Oh, Mok et al. (2019) Economic Evaluation of Talimogene Laherparepvec Plus Ipilimumab Combination Therapy vs Ipilimumab Monotherapy in Patients With Advanced Unresectable Melanoma. JAMA dermatology 155(1): 22-28	Non-relevant comparison
Barzey V, Atkins MB, Garrison LP, Asukai Y, Kotapati S, Penrod JR (2013) Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. Journal of Medical Economics 16(2): 202-212	Non-relevant comparison
Bohensky, Megan A, Pasupathi, Kumar, Gorelik, Alexandra et al. (2016) A Cost-Effectiveness Analysis of Nivolumab Compared with Ipilimumab for the Treatment of BRAF Wild-Type Advanced	Non-relevant comparison

Study reference	Reason for exclusion
Melanoma in Australia. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 19(8): 1009-1015	
CADTH (2015) Yervoy for first line advanced melanoma. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)	Non-relevant comparison
Curl, Patti, Vujic, Igor, van 't Veer, Laura J et al. (2014) Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. PloS one 9(9): e107255	Non-relevant comparison
De Francesco, M., Lamotte, M., Ascierto, P.A. et al. (2016) Economic evaluation of ipilimumab in first line treatment of advanced melanoma in Italy. Global and Regional Health Technology Assessment 3(2): 67-79	Non-relevant comparison
Delea, Thomas E, Amdahl, Jordan, Wang, Alice et al. (2015) Cost effectiveness of dabrafenib as a first-line treatment in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in Canada. PharmacoEconomics 33(4): 367-80	Non-relevant comparison
Fleeman, Nigel, Bagust, Adrian, Beale, Sophie et al. (2015) Dabrafenib for Treating Unresectable, Advanced or Metastatic BRAF V600 Mutation-Positive Melanoma: An Evidence Review Group Perspective. PharmacoEconomics 33(9): 893-904	Non-relevant comparison
Giannopoulou, Christina, Sideris, Eleftherios, Wade, Ros et al. (2015) Ipilimumab for Previously Untreated Unresectable Malignant Melanoma: A Critique of the Evidence. PharmacoEconomics 33(12): 1269-79	Non-relevant comparison
Gibson, E.J., Begum, N., Koblbauer, I. et al. (2020) Economic evaluation of single versus combination immuno-oncology therapies: Application of a novel modelling approach in metastatic melanoma. ClinicoEconomics and Outcomes Research 12: 241-252	Non-relevant comparison
Guglieri-Lopez, Beatriz, Perez-Pitarch, Alejandro, Porta Oltra, Begona et al. (2016) Effectiveness, toxicity, and economic evaluation of ipilimumab for the treatment of patients with metastatic melanoma in the Spanish outpatient setting. Anti-cancer drugs 27(7): 679-84	Non-QALY outcomes
Jensen, Ivar S, Zacherle, Emily, Blanchette, Christopher M et al. (2016) Evaluating cost benefits of combination therapies for advanced melanoma. Drugs in context 5: 212297	Non-QALY outcomes
Kohn, Christine G, Zeichner, Simon B, Chen, Qiushi et al. (2017) Cost-Effectiveness of Immune Checkpoint Inhibition in BRAF Wild-Type Advanced Melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 35(11): 1194-1202	Unrealistic treatments for UK setting
Lee, D., Amadi, A., Sabater, J. et al. (2019) Can We Accurately Predict Cost Effectiveness Without Access to Overall Survival Data? The Case Study of Nivolumab in Combination with Ipilimumab for the Treatment of Patients with Advanced Melanoma in England. PharmacoEconomics - Open 3(1): 43-54	Non-relevant comparison

Study reference	Reason for exclusion
Loong, H.H., Wong, C.K.H., Leung, L.K.S. et al. (2020) Cost-effectiveness analysis of pembrolizumab compared to standard of care as first line treatment for patients with advanced melanoma in Hong Kong. Cost Effectiveness and Resource Allocation 18(1): 2	Non-relevant comparison and not comparable setting
Matter-Walstra, K, Braun, R, Kolb, C et al. (2015) A cost-effectiveness analysis of trametinib plus dabrafenib as first-line therapy for metastatic BRAF V600-mutated melanoma in the Swiss setting. The British journal of dermatology 173(6): 1462-70	Non-relevant comparison
Meng, Yang, Hertel, Nadine, Ellis, John et al. (2018) The cost-effectiveness of nivolumab monotherapy for the treatment of advanced melanoma patients in England. The European journal of health economics : HEPAC : health economics in prevention and care 19(8): 1163-1172	Non-relevant comparison
Miguel, Luis Silva, Lopes, Francisca Vargas, Pinheiro, Bernardete et al. (2017) Cost Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 20(8): 1065-1073	Non-relevant comparison
Oh, Anna, Tran, Dang M, McDowell, Leann C et al. (2017) Cost-Effectiveness of Nivolumab-Ipilimumab Combination Therapy Compared with Monotherapy for First-Line Treatment of Metastatic Melanoma in the United States. Journal of managed care & specialty pharmacy 23(6): 653-664	Non-relevant comparison
Othus, Megan, Bansal, Aasthaa, Koepl, Lisel et al. (2017) Accounting for Cured Patients in Cost-Effectiveness Analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 20(4): 705-709	Non-relevant comparison
Retel, Valesca P, Steuten, Lotte M G, Geukes Foppen, Marnix H et al. (2018) Early cost-effectiveness of tumor infiltrating lymphocytes (TIL) for second line treatment in advanced melanoma: a model-based economic evaluation. BMC cancer 18(1): 895	Non-relevant comparison
Shih, Vanessa, Ten Ham, Renske M, Bui, Christine T et al. (2015) Targeted Therapies Compared to Dacarbazine for Treatment of BRAF(V600E) Metastatic Melanoma: A Cost-Effectiveness Analysis. Journal of skin cancer 2015: 505302	Non-relevant comparison
Tartari, Francesca, Santoni, Matteo, Burattini, Luciano et al. (2016) Economic sustainability of anti-PD-1 agents nivolumab and pembrolizumab in cancer patients: Recent insights and future challenges. Cancer treatment reviews 48: 20-4	Non-QALY outcomes
Wang, Jingshu, Chmielowski, Bartosz, Pellissier, James et al. (2017) Cost-Effectiveness of Pembrolizumab Versus Ipilimumab in Ipilimumab-Naive Patients with Advanced Melanoma in the United States. Journal of managed care & specialty pharmacy 23(2): 184-194	Non-relevant comparison
Aceituno, S, Canal, C, Paz, S et al. (2014) Cost-Effectiveness of Ipilimumab for Previously Untreated Patients with Advanced Metastatic Melanoma in Spain. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a631	Abstract only

Study reference	Reason for exclusion
Andalusian Agency for Health Technology, Assessment (2001) Efficacy and safety of immunotherapy with activated killer cells using interleukins (LAK) in metastatic melanoma: rapid response. Seville: Andalusian Agency for Health Technology Assessment (AETSA)	Bibliographic record only (does not give any information about cost effectiveness)
Ipilimumab for previously treated unresectable malignant melanoma. Health Technology Assessment	Bibliographic record only (does not give any information about cost effectiveness)
Vemurafenib for the treatment of locally advanced or metastatic, BRAFV600E mutation-positive malignant melanoma. Health Technology Assessment	Bibliographic record only (does not give any information about cost effectiveness)
(2011) Abraxane for malignant melanoma first line. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
Dabrafenib and trametinib for treating advance unresectable or metastatic BRAFV600 mutation-positive melanoma (ID605). Health Technology Assessment	Bibliographic record only (does not give any information about cost effectiveness)
Dabrafenib for treating advance unresectable or metastatic BRAFV600 mutation-positive melanoma (ID605). Health Technology Assessment	Bibliographic record only (does not give any information about cost effectiveness)
Ipilimumab in combination with dacarbazine within its licensed indication for previously untreated unresectable stage III or IV malignant melanoma (ID74). Health Technology Assessment	Bibliographic record only (does not give any information about cost effectiveness)
Barzey, V, Asukai, Y, Gueron, B et al. (2014) Cost-Effectiveness of Ipilimumab in Previously Untreated Patients for Advanced Melanoma in Sweden. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a642-3	Abstract only
Chang, Chun-Lan, Schabert, Vernon F, Munakata, Julie et al. (2015) Comparative healthcare costs in patients with metastatic melanoma in the USA. Melanoma research 25(4): 312-20	Cost analysis only
Couchoud, C., Fagnoni, P., Aubin, F. et al. (2020) Economic evaluations of cancer immunotherapy: a systematic review and quality evaluation. Cancer Immunology, Immunotherapy	Systematic review
Curl, P.K. (2015) Navigating uncertainty: A valuable cost-effectiveness analysis in the rapidly changing field of metastatic melanoma treatment. British Journal of Dermatology 173(6): 1365-1366	Editorial only
Dixon S, Walters S J, Turner L, Hancock B W (2006) Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. British Journal of Cancer 94(4): 492-498	Different decision problem
Gao, Tianfu; Liu, Jia; Wu, Jing (2021) Cost-effectiveness analysis of dabrafenib plus trametinib and vemurafenib as first-line treatment in patients with braf v600 mutation-positive unresectable or metastatic melanoma in china. International Journal of Environmental Research and Public Health 18(12): 6194	Not applicable - country

Study reference	Reason for exclusion
Gibson, Edward J, Begum, Najida, Koblbauer, Ian et al. (2019) Cohort versus patient level simulation for the economic evaluation of single versus combination immuno-oncology therapies in metastatic melanoma. Journal of medical economics 22(6): 531-544	Different decision problem
Goldstein, D. (2018) Weight-based dosing vs fixed dosing of pembrolizumab: An economic analysis. Clinical Advances in Hematology and Oncology 16(8): 549-551	Different decision problem
GonzÃ¡lez L, Pichon-Riviere A, Augustovski F, GarcÃa MartÃ S, Alcaraz A, Bardach A, Ciapponi A (2017) [Nivolumab for the treatment of advanced melanoma]. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS)	Bibliographic record only (does not give any information about cost effectiveness)
Gorry, Claire; McCullagh, Laura; Barry, Michael (2020) Economic Evaluation of Systemic Treatments for Advanced Melanoma: A Systematic Review. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 23(1): 52-60	Systematic review
Guerra, Renata Leborato, Correa, Flavia de Miranda, Fernandes, Ricardo Ribeiro Alves et al. (2019) Custo-utilidade de terapias-alvo comparadas a dacarbazina para o tratamento de primeira linha do melanoma avancado nao-cirurgico e metastatico no Sistema Unico de Saude do Brazil. Value in health regional issues 20: 103-109	Not in English
Hancock, Christie, Green, Linda, Lestingi, Timothy et al. (2018) An Attempt to Quantitate "Value" In Medical Oncologic Therapy. Cureus 10(6): e2810	Non economic evaluation
HAYES, Inc. (2016) Pembrolizumab (Keytruda) for unresectable or metastatic melanoma. Lansdale, PA: HAYES, Inc	Bibliographic record only (does not give any information about cost effectiveness)
HAYES, Inc. (2016) Talimogene laherparepvec (T-VEC; Imlygic) for treatment of unresectable melanoma lesions. Lansdale, PA: HAYES, Inc	Bibliographic record only (does not give any information about cost effectiveness)
HAYES, Inc. (2015) Nivolumab (Opdivo) for first-line treatment of advanced melanoma. Lansdale, PA: HAYES, Inc	Bibliographic record only (does not give any information about cost effectiveness)
Hillner B E, Agarwala S, Middleton M R (2000) Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. Journal of Clinical Oncology 18(7): 1474-1480	Different decision problem
Hren, R (2014) Cost-Effectiveness and Budget-Impact Analysis of Braf Inhibitors in Patients With Metastatic Malignant Melanoma (MMM) in Slovenia. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a623-4	Abstract only
Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen, (IQWiG) (2016) [Trametinib: benefit assessment according to 35a Social Code Book V (dossier assessment)]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)

Study reference	Reason for exclusion
Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen, (IQWiG) (2016) [Dabrafenib (new therapeutic indication): benefit assessment according to 35a Social Code Book V]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
Institut fuer Qualitaet und Wirtschaftlichkeit im, Gesundheitswesen (2017) [Nivolumab (melanoma) - benefit assessment according to 35a Social Code Book V (expiry of the decision)]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
Institut fuer Qualitaet und Wirtschaftlichkeit im, Gesundheitswesen (2016) [A16-05 dabrafenib/trametinib - addendum to commissions A15-39 and A15-40]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
Institut fuer Qualitaet und Wirtschaftlichkeit im, Gesundheitswesen (2016) [Cobimetinib - benefit assessment according to 35a Social Code Book V]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
IQWiG (2013) [Dabrafenib: benefit assessment according to 35a Social Code Book V (dossier assessment)]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
IQWiG (2014) [Ipilimumab (new therapeutic indication): benefit assessment according to 35a Social Code Book V (dossier assessment]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
IQWiG (2012) [Vemurafenib - Benefit assessment according to 35a Social Code Book V (dossier assessment)]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
IQWiG (2013) [Vemurafenib: benefit assessment according to 35a Social Code Book V (dossier assessment)]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Bibliographic record only (does not give any information about cost effectiveness)
Johnston, Karissa M, McPherson, Emily, Osenenko, Katherine et al. (2015) Cost-effectiveness of therapies for melanoma. Expert review of pharmacoeconomics & outcomes research 15(2): 229-42	Systematic review
Joppi R, Nachtnebel A (2012) Ipilimumab (Yervoy®) for the first-line therapy of advanced/metastatic cutaneous melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
Joppi R, Nachtnebel R (2012) Trametinib for advanced or metastatic BRAF V600E mutation-positive melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
Joppi R, Wild C (2012) Vemurafenib for the 1st line unresectable stage IIIC or IV melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
Kim, Hansoo, Liew, Danny, Cook, Greg et al. (2021) Comparison of EQ-5D-3L with QLU-C10D in Metastatic Melanoma Using Cost-Utility Analysis. PharmacoEconomics - Open	Different decision problem;Not applicable - country;

Study reference	Reason for exclusion
Klink, Andrew J, Chmielowski, Bartosz, Feinberg, Bruce et al. (2019) Health Care Resource Utilization and Costs in First-Line Treatments for Patients with Metastatic Melanoma in the United States. Journal of managed care & specialty pharmacy 25(8): 869-877	Cost analysis only
Lee, D, Porter, J, Hatswell, A J et al. (2014) Cost-Effectiveness Analysis of Ipilimumab in Previously Untreated Patients With Unresectable Malignant Melanoma in Scotland. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a549-50	Abstract only
Lester-Coll, Nataniel H, Rutter, Charles E, Bledsoe, Trevor J et al. (2016) Cost-Effectiveness of Surgery, Stereotactic Body Radiation Therapy, and Systemic Therapy for Pulmonary Oligometastases. International journal of radiation oncology, biology, physics 95(2): 663-72	Different decision problem
Li, Meng, Basu, Anirban, Bennette, Caroline et al. (2019) How Does Option Value Affect the Potential Cost-Effectiveness of a Treatment? The Case of Ipilimumab for Metastatic Melanoma. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 22(7): 777-784	Different decision problem
Lindenberg, Melanie, Retel, Valesca, Rohaan, Maartje et al. (2020) Evaluating different adoption scenarios for TIL-therapy and the influence on its (early) cost-effectiveness. BMC cancer 20(1): 712	Different decision problem
Ludwig Boltzmann Institut fuer Health Technology Assessment, (LBI-HTA) (2015) Pembrolizumab (Keytruda®) for the treatment of advanced melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
Ludwig Boltzmann Institute for Health Technology Assessment, (LBI-HTA) (2015) Nivolumab (Opdivo®) as single-agent first-line therapy for unresectable or metastatic melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
Medical Services Advisory, Committee (2002) M-VAX(TM) - a treatment for patients with advanced stage III melanoma. Canberra: Medical Services Advisory Committee (MSAC): 99isb0642821879	Bibliographic record only (does not give any information about cost effectiveness)
Mengarelli C, Ciapponi A, Pichon-Riviere A, Augustovski F, GarcÃa MartÃ S, Alcaraz A, Bardach A, LÃ³pez A, Rey-Ares L (2016) Pembrolizumab for the treatment of advanced melanoma. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS)	Bibliographic record only (does not give any information about cost effectiveness)
Moreno Ramirez D, de la Cruz Merino L, Ferrandiz Pulido L, Nieto Garcia A, Villegas Portero R (2010) [Isolated limb perfusion for locally advanced melanoma and soft tissue sarcoma]. Seville: Andalusian Agency for Health Technology Assessment (AETSA)	Bibliographic record only (does not give any information about cost effectiveness)
Nachtnebel, A (2011) Ipilimumab for pre-treated patients with advanced/metastatic melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
National Horizon Scanning, Centre (2010) OncoVEX GM-CSF for unresectable metastatic melanoma - first and second line treatment. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)

Study reference	Reason for exclusion
National Horizon Scanning, Centre (2010) RG7204 for BRAF V600E mutation positive metastatic malignant melanoma - first or second line. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
National Horizon Scanning, Centre (2008) Ipilimumab (MDX-010) for unresectable stage III or IV metastatic melanoma - first or second line treatment. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
National Horizon Scanning, Centre (2007) Temozolomide (Temodal) for advanced metastatic melanoma: horizon scanning technology briefing. Birmingham: National Horizon Scanning Centre (NHSC): 5	Bibliographic record only (does not give any information about cost effectiveness)
National Horizon Scanning, Centre (2011) GSK1120212 for unresectable or metastatic melanoma, BRAF V600 mutation-positive in adults. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
National Horizon Scanning, Centre (2011) GSK2118436 (dabrafenib) for malignant melanoma: advanced and/or metastatic (stage III or IV), BRAF V600E mutation - first line. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
National Institute for Health and Clinical, Excellence (2006) Improving outcomes for people with skin tumours including melanoma: the manual. London: National Institute for Health and Clinical Excellence (NICE): 177	Bibliographic record only (does not give any information about cost effectiveness)
NHSC (2003) Oblimersen for advanced malignant melanoma and refractory chronic lymphocytic leukaemia - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
NHSC (2003) Oncophage for renal cell carcinoma and malignant melanoma - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2014) Nivolumab with ipilimumab for advanced melanoma first line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2014) Nivolumab for BRAF V600 mutation-positive advanced melanoma first line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2014) Nivolumab for BRAF V600 mutation negative advanced melanoma first line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2014) Nivolumab for advanced melanoma second or third line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2012) Velimogene aliplasmid (Allovectin) for advanced or metastatic malignant melanoma. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)

Study reference	Reason for exclusion
NIHR, HSC (2014) Vemurafenib and cobimetinib for previously untreated BRAFV600-mutation positive, unresectable, locally advanced or metastatic melanoma first line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2014) Ecorafenib and binimetinib for BRAF V600 mutation-positive melanoma first and second line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2013) Lambrolizumab for advanced melanoma second line; refractory to ipilimumab. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2013) MEK162 for NRAS mutation positive advanced malignant melanoma first and second line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2013) MK-3475 for advanced melanoma first or second line, in patients naïve to ipilimumab. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSC (2012) Trametinib in combination with dabrafenib for V600 BRAF positive advanced malignant melanoma first line. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSRIC (2016) Masitinib for advanced or metastatic malignant melanoma with a c-kit juxtamembrane mutation. Birmingham: NIHR Horizon Scanning Research&Intelligence Centre	Bibliographic record only (does not give any information about cost effectiveness)
NIHR, HSRIC (2015) Vemurafenib (Zelboraf) for metastatic BRAF V600 mutation positive melanoma in children and adolescents. Birmingham: NIHR Horizon Scanning Research&Intelligence Centre	Bibliographic record only (does not give any information about cost effectiveness)
Paly, Victoria Federico, Baker, Timothy, Hikichi, Yusuke et al. (2020) Economic evaluation of nivolumab combined with ipilimumab in the first-line treatment of advanced melanoma in Japan. Journal of Medical Economics 23(12): 1542-1552	Different decision problem;Not applicable - country;
Pichon Riviere A, Augustovski F, Garcia Marti S, Glujovsky D, Alcaraz A, Lopez A, Bardach A, Ciapponi A, Rey-Ares L, Caccavo F (2012) [Ipilimumab for patients with metastatic melanoma]. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS)	Bibliographic record only (does not give any information about cost effectiveness)
Pike E, Torkilseng EB, SÃ¦terdal I, Jimenez E, Odgaard-Jensen J, Harboe I, Klemp M (2015) A health technology assessment of the new drugs for inoperable or metastatic malignant melanoma patients. Oslo: Norwegian Knowledge Centre for the Health Services (NOKC)	Bibliographic record only (does not give any information about cost effectiveness)
Pike, Eva, Torkilseng, Einar Bjorner, Saeterdal, Ingvil et al. (2015) No title provided.	Duplicate
Pike, Eva, Torkilseng, Einar Bjorner, Saeterdal, Ingvil et al. (2015) No title provided.	Not applicable - country
Pirc, Eva, Federici, Carlo, Bosnjak, Masa et al. (2020) Early Cost-effectiveness Analysis of Electrochemotherapy as a Prospect Treatment Modality for Skin Melanoma. Clinical therapeutics 42(8): 1535-1548e2	Different decision problem

Study reference	Reason for exclusion
Retel, V P, Steuten, L M G, Mewes, J C et al. (2014) Early Cost-Effectiveness Modeling for Tumor Infiltrating Lymphocytes (TIL) -Treatment Versus Ipilimumab in Metastatic Melanoma Patients. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a640	Abstract only
Rubio-Rodriguez, Dario, De Diego Blanco, Silvia, Perez, Maite et al. (2017) Cost-Effectiveness of Drug Treatments for Advanced Melanoma: A Systematic Literature Review. PharmacoEconomics 35(9): 879-893	Systematic review
Russi, Alberto, Chiarion-Sileni, Vanna, Damuzzo, Vera et al. (2017) CASE STUDY ON AN IPILIMUMAB COST-CONTAINMENT STRATEGY IN AN ITALIAN HOSPITAL. International journal of technology assessment in health care 33(2): 199-205	Cost analysis only
Semlitsch T, Zengerer A, Jeitler K (2013) Dabrafenib (Tafinlar®) in previously untreated subjects with BRAF mutation-positive advanced (stage III) or metastatic (stage IV) melanoma. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA)	Bibliographic record only (does not give any information about cost effectiveness)
Shepherd J, Milne R (1999) The use of interferon alfa in the treatment of metastatic cutaneous melanoma. Southampton: Wessex Institute for Health Research and Development (WIHRD): 29	Bibliographic record only (does not give any information about cost effectiveness)
Specenier, Pol (2021) Cost-effectiveness of nivolumab in advanced melanoma: a drug review. Expert review of pharmacoeconomics & outcomes research 21(1): 13-28	Non economic evaluation
Tapia-LÃ³pez E, Ciapponi A, Gonzalez L, Pichon-Riviere A, Augustovski F, GarcÃa MartÃ S, Alcaraz A, Bardach A, LÃ³pez A, Rey-Ares L (2016) Nivolumab in advanced melanoma treament. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS)	Bibliographic record only (does not give any information about cost effectiveness)
Toy, Edmond L, Vekeman, Francis, Lewis, Michael C et al. (2015) Costs, resource utilization, and treatment patterns for patients with metastatic melanoma in a commercially insured setting. Current medical research and opinion 31(8): 1561-72	Cost analysis only
Tran, A.D., Fogarty, G., Nowak, A.K. et al. (2020) Cost-Effectiveness of Subsequent Whole-Brain Radiotherapy or Hippocampal-Avoidant Whole-Brain Radiotherapy Versus Stereotactic Radiosurgery or Surgery Alone for Treatment of Melanoma Brain Metastases. Applied Health Economics and Health Policy	Different decision problem
van Boemmel-Wegmann, Sascha, Brown, Joshua D, Diaby, Vakaramoko et al. (2021) Health Care Utilization and Costs Associated With Systemic First-Line Metastatic Melanoma Therapies in the United States. JCO oncology practice: op2100140	Cost analysis only;Non economic evaluation;
Verma, V., Sprave, T., Haque, W. et al. (2018) A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors 11 Medical and Health Sciences 1112 Oncology and Carcinogenesis. Journal for ImmunoTherapy of Cancer 6(1): 128	Systematic review

Study reference	Reason for exclusion
Verma, Vivek, Sprave, Tanja, Haque, Waqar et al. (2018) A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. Journal for immunotherapy of cancer 6(1): 128	Systematic review
Winn, A.N., Ekwueme, D.U., Guy, G.P. et al. (2016) Cost-Utility Analysis of Cancer Prevention, Treatment, and Control: A Systematic Review. American Journal of Preventive Medicine 50(2): 241-248	Systematic review
Wise, J. (2016) NICE approves immunotherapy combination for advanced melanoma. BMJ (Clinical research ed.) 353	Non economic evaluation
Yousaf, Nadia, Davidson, Michael, Goode, Emily et al. (2015) The cost of ipilimumab toxicity: a single-centre analysis. Melanoma research 25(3): 259-64	Cost analysis only

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Appendix L – Research recommendations – full details

1.1 Localised treatments

Research recommendation 1 (localised treatment comparison)

1. What is the effectiveness of localised treatment for people with stage III-IV melanoma?

Why this is important

Localised treatments are typically used in specific cases, where the primary site is within an isolated area such as a limb and the tumour hasn't metastasized beyond the primary site. Different options of localised treatments are selected largely on the basis of clinical characteristics. For example, it is often used in patients who are unsuitable for systemic anti-cancer treatments. There is also a group of patients for whom multiple localised treatment options are possible. In these circumstances there is a lack of clarity as to which treatment to use. Additionally, there is uncertainty as to whether certain comorbidities and characteristics make one option preferable over others. The committee discussed the need for a matched-participant cohort study in which participants receiving localised treatments are matched on the basis of key characteristics relating to eligibility for alternative options.

Rationale for research recommendation 1

Importance to 'patients' or the population	There is very limited good quality evidence for localised treatments for people with melanoma and an almost complete lack of comparative studies in which two or more options are compared on a similar population.
Relevance to NICE guidance	NICE currently recommends considering the use of TVEC in specific populations. Additionally, it gives guidance on the use of ILI, ILP and ECT but due to limited data were limited in their ability to recommend specifically when these different options be used.
Relevance to the NHS	This evidence would allow for more optimal and individualised treatment.
National priorities	High
Current evidence base	Very limited comparative data
Equality considerations	None known

1 **Modified PICO table**

Population	People with a diagnosis of stage III-IV melanoma who are eligible for localised treatment.
Intervention (index test)	• TVEC • Isolated limb infusion • Isolated limb perfusion • Electrochemotherapy
Comparator (reference standard)	Compared to each other
Outcome	• Progression-free survival • Overall survival • Melanoma-specific survival • Adverse events • Quality of life • Complete response
Study design	• Retrospective cohort study • Prospective cohort study
Timeframe	Short-long term
Additional information	Subgroup analyses should be conducted to identify which patients would benefit the most from each treatment. Detailed images should be reported clearly showing extent of disease prior to treatment for each participant.

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