NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

APPENDICES

Novartis Pharmaceuticals UK Limited

December 2015

File name	Version	Contains confidential information	Date
		Yes	01/12/2015

Appendices

Appendix 8.1: European public assessment report, SmPC/IFU, scientific discussion or drafts (section 2.2)

The Summary of Product Characteristics for Mekinist (trametinib) and Tafinlar (dabrafenib) can be found in the reference pack accompanying this submission.

The EMA's assessment report for the licence variation for the use of trametinib in combination with dabrafenib can be found in the reference pack accompanying this submission.

Appendix 8.2: Search strategy for relevant clinical studies (section 4.1.2)

This appendix describes the methods of the systematic reviews conducted to identify clinical studies of relevance to the decision problem. Further detail can be found in the full Systematic Review report available upon request.

Table 1: Search strategy for Embase® and MEDLINE® database for clinical review searched via Embase.com platform (searched on 13 July 2015)

#	Query	Facet	Results
1	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomized controlled trial' OR 'randomized controlled trial' OR 'randomized controlled trials' OR 'randomized controlled trials' OR 'randomization' OR 'randomization' OR random* OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR allocated NEAR/2 random OR assign* NEAR/2 random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	Randomized controlled trials	6 413 391
2	('melanoma'/exp OR melanoma) OR (melanocarcinoma OR melanomatosis OR melanomalignoma OR n?evocarcinoma OR 'pigmentary cancer') OR melanom* NEAR/1 (malign* OR nodular OR metasta* OR advanc* OR disseminat* OR recurr* OR unresect* OR 'stage iii' OR 'stage 3' OR 'stage iiic' OR 'stage 3c' OR 'stage iv' OR 'stage 4')	Disease (metastatic malignant melanoma)	145 203
3	('ipilimumab'/exp OR ipilimumab OR 'mdx 010' OR 'mdx 101' OR 'bms 734016' OR yervoy) OR ('vemurafenib'/exp OR vemurafenib OR plx4032 OR rg7204 OR ro5185426 OR zelboraf OR 'plx 4032') OR ('dabrafenib'/exp OR dabrafenib OR gsk2118436 OR gsk*436 OR tafinlar) OR ('trametinib'/exp OR trametinib OR gsk1120212 OR gsk*212 OR mekinist)	Intervention	7451
4	'nivolumab'/syn OR 'nivolumab'/exp OR 'bms 936558' OR bms936558 OR 'mdx 1106' OR mdx1106 OR 'ono 4538' OR ono4538 OR opdivo		896
5	'pembrolizumab'/syn OR 'pembrolizumab'/exp OR keytruda OR lambrolizumab OR 'mk 3475' OR mk3475		497
6	#4 OR #5		1060
7	#1 AND #2 AND #3		3072
8	#1 AND #2 AND #3 AND [28-12-2014]/sd		438
9	#1 AND #2 AND #6		531
10	#7 OR #9	From database start to present	3163
11	#8 OR #9 (date limits applied to interventions searched in previous review and no date limits for pembrolizumab and nivolumab)	Final numbers	827

Table 2: Search strategy for Cochrane database for clinical review (searched on 13 July 2015)

#	Query	Facet	Results
1	MeSH descriptor: [Melanoma] explode all trees	Disease (metastatic malignant melanoma)	1148
2	Melanoma OR (melanom* near (malign* or nodular or metasta* or advanc* or disseminat* or recurr* or unresect*)) OR melanom* near ("stage iii" or "stage 3" or "stage iiic" or "stage 3c" or "stage iv" or "stage 4")		2594
3	#1 OR #2		2607
4	ipilimumab or mdx-010 or yervoy or vemurafenib or plx4032 or zelboraf or dabrafenib or gsk2118436 or gsk*436 or tafinlar or tramefinib or gsk1120212 or gsk*212 or Mekinist	Intervention	171
5	pembrolizumab or keytruda or lambrolizumab or "mk 3475" or mk3475 or nivolumab or 'bms 936558' or bms936558 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo		30
6	#3 AND #4, in Trials		117
7	#3 AND #4 Publication Year from 2014 to 2015, in Trials		26
8	#3 AND #5, in Trials		10
9	#6 OR #8	From database start to present	121
10	#7 OR #8 (date limits applied to interventions searched in previous review and no date limits for pembrolizumab and nivolumab)	Final numbers	32

Table 3: Search strategy for MEDLINE® In-Process searched via PubMed® platform for clinical review (searched on 13 July 2015)

#	Search term	Facet	Hits
1	melanoma	Disease (metastatic malignant melanoma)	101 811
2	melanom* AND (malign* OR nodular OR metasta* OR advanc* OR disseminat* OR recurr* OR unresect*)		57 667
3	melanom* AND (“stage iii” OR “stage 3” OR “stage iiic” OR “stage 3c” OR “stage iv” OR “stage 4”)		1835
4	#1 OR #2 OR #3		102 787
5	ipilimumab OR mdx-010 OR yervoy OR vemurafenib OR plx4032 or zelboraf OR gsk2118436 OR dabrafenib OR tafinlar OR gsk1120212 OR trametinib OR mekinist	Intervention	2221
6	pembrolizumab or keytruda or lambrolizumab or "mk 3475" or mk3475 or nivolumab or 'bms 936558' or bms936558 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo		252
7	#4 AND #5		1707
8	#4 AND #5 Filters: Publication date from 2014/11/28		376
9	#4 AND #6		151
10	#7 OR #9 AND (pubstatusaheadofprint OR inprocess[sb])	From database start to present	359
11	#8 OR #9 AND (pubstatusaheadofprint OR inprocess[sb]) Date limits applied to interventions searched in previous review and no date limits for pembrolizumab and nivolumab	Final numbers	296

Appendix 8.3: Quality assessment of randomised controlled trials (RCTs)

The quality assessments for the three RCTs of relevance to this submission (COMBI-d [MEK115306]; COMBI-d [MEK116513]; BRF113220 [Part C]) are provided in Section 4.6.

Appendix 8.4: Subgroup analysis

Results from subgroup analyses from the three RCTs relevant to this submission are presented and discussed in Section 4.8.

Appendix 8.5: Search strategy for indirect and mixed treatment comparisons

Comparative efficacy and safety data for the intervention under review, trametinib + dabrafenib combination therapy, versus the comparators for this appraisal, dabrafenib or vemurafenib, are drawn directly from the head-to-head RCTs (COMBI-d [MEK115306]; COMBI-d [MEK116513]; BRF113220 [Part C]). Thus, it has not been necessary to utilise an indirect/mixed treatment comparison in this submission. (See section 4.10.1)

Appendix 8.6: Methods, results, outcomes and quality assessment of the relevant trials in the indirect or mixed treatment comparison (section 4.10.9-10)

See above.

Appendix 8.7: Programming language used in the analysis (section 4.10.13)

Not applicable. An indirect/mixed treatment comparison has not been utilised in this submission.

Appendix 8.8: Relevant non-randomised and non-controlled evidence

There is no non-RCT evidence of relevance to this submission i.e. additional data that provides value to the decision problem over and above the robust RCT evidence for trametinib + dabrafenib combination therapy provided by the Phase III COMBI-d and COMBI-v studies, and the randomised Phase II BRF1132220 trial.

For completeness, the results for the crossover group in study BRF113220 are presented below. This comprises a population who had progressed on dabrafenib monotherapy and who switched to receive trametinib + dabrafenib combination therapy.

Of the 162 patients enrolled onto BRF113220 Part C, 54 were assigned to receive dabrafenib monotherapy, and 45 (described here) crossed over to combination therapy with dabrafenib 150mg b.d. + trametinib 2mg o.d. (combination 150/2) upon independently-confirmed disease progression. Baseline patient demographics and disease characteristics for the crossover population at the time of initiation of combination therapy are presented in Table 4 below; these were consistent with the ITT population (Table 25 in the main body of the submission).[1]

Table 4: Baseline patient demographic and clinical characteristics for crossover population in BRF113220

	Crossover population n=45
Age, mean (range)	51 (18-82)
Male gender, n (%)	23 (51)
ECOG Performance Status, n (%)	
1	26 (58)
2	19 (42)
Stage, n (%)	
IIIc	1 (2)
Iva	9 (20)
IVb	5 (11)
IVc	30 (67)
Prior brain metastases, n (%)	4 (9)
Baseline LDH, n (%)	
<ULN	36 (80)
≥ULN	9 (20)
BRAF mutation type, n (%)	
V600 E	38 (84)
V660 K	7 (16)
Prior systemic therapy, n (%)	
Immunotherapy	5 (11)
Chemotherapy	4 (9)
Duration of prior BRAF inhibitor therapy, months	
<6	22 (49)
≥6	23 (51)
Best response to prior BRAF inhibitor	
Complete response or Partial response	26 (58)
Stable Disease	16 (36)
Progressive Disease	3 (7)

Efficacy outcomes for crossover population

From the first dose of combination therapy, median PFS was 3.6 months for crossover patients in Part C (95% CI: 2 to 4 months) and median OS from start of combination therapy was 11.8 months (95% CI: 8 to 25 months).[1] The confirmed ORR was 13% (one CR and 5 PRs; 95%CI: 5 to 27), and an additional 20 patients (44%) had stable disease for at least 8 weeks (Table 5). Among patients with evaluable tumour responses, 53% (34 of 64) had some degree of tumour shrinkage as best response to combination 150/2 therapy after experiencing progression with single-agent BRAF inhibitor.[1]

Table 5: Best response for crossover population in BRF113220

	Crossover population n=45 n (%)
Complete response (CR)	1 (2)
Partial response (PR)	5 (11)
Stable Disease (SD)*	20 (44)
Progressive Disease (PD)	17 (38)
Not evaluable (NE)	2 (4)
Response rate, % (95% CI)	13 (5, 27)
This includes two patients with best response of non-CR/non-PD who had no baseline measurable disease at time of cross-over.	

Appendix 8.9: Search strategy for adverse reactions (section 4.12.3)

Not applicable. All relevant evidence for adverse reactions/safety of trametinib + dabrafenib combination therapy is provided by the RCTs (COMBI-d [MEK115306]; COMBI-d [MEK116513]; BRF113220 [Part C]) and is presented and discussed fully in section 4.12. We are not aware of any additional evidence that provides information on adverse reactions/safety of relevance to this appraisal.

Appendix 8.10: Quality assessment of adverse reaction data (section 4.12.3)

Not applicable – see above.

Appendix 8.11: Systematic Reviews of Economic Literature and HRQoL literature

This appendix describes the methods of the systematic reviews conducted to identify economic and HRQoL literature associated with treatments for metastatic melanoma. Further detail is available in a separate Parexel report upon request.

Search strategies

Economic review

Table 6: Search strategy for Embase® and MEDLINE® database for economic review searched via Embase.com platform (searched on 13 July 2015)

#	Query	Facet	Results
1	'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'economic evaluation'/exp OR 'socioeconomics'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR cost NEXT/1 estimate* OR 'fee'/exp OR 'budget'/exp OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'hospital finance'/de OR 'financial management'/de OR price*:ab,ti OR pricing:ab,ti OR cost* NEAR/3 (treat* OR therap*) OR 'cost-effectiveness' OR 'cost-utility' OR 'cost utility' OR 'cost benefit' OR 'cost minimization' OR 'cost minimization' OR 'budget impact' OR 'cost consequence' OR 'health care utilisation'/de OR health*care NEXT/1 (utilisation OR utilisation) OR 'health care' NEXT/1 (utilisation OR utilisation) OR resource NEXT/1 (utilisation OR utilisation OR use)	Economic study design	1 053 775
2	('melanoma'/exp OR melanoma) OR (melanocarcinoma OR melanomatosis OR melanomalignoma OR n?evocarcinoma OR 'pigmentary cancer') OR melanom* NEAR/1 (malign* OR nodular OR metasta* OR advanc* OR disseminat* OR recurr* OR unresect* OR 'stage iii' OR 'stage 3' OR 'stage iiic' OR 'stage 3c' OR 'stage iv' OR 'stage 4')	Disease (metastatic malignant melanoma)	145 203
3	#1 AND #2	From database start to present	2380
4	**#1 AND #2 AND [28-11-2014]/sd**	**Final numbers**	**183**

Table 7: Search strategy for Cochrane database for economic review (searched on 13 July 2015)

#	Query	Facet	Results
1	MeSH descriptor: [Melanoma] explode all trees	Disease (metastatic malignant melanoma)	1148
2	Melanoma OR (melanom* near (malign* or nodular or metasta* or advanc* or disseminat* or recurr* or unresect*)) OR melanom* near ("stage iii" or "stage 3" or "stage iiic" or "stage 3c" or "stage iv" or "stage 4")		2594
3	#1 OR #2		2607
4	#3, in Economic Evaluations	From database start to present	49
5	**#3 Publication Year from 2014 to 2015, in Economic Evaluations**	**Final numbers**	**6**

Table 8: Search strategy for MEDLINE® In-Process searched via PubMed® platform for economic and utility review (searched on 13 July 2015)

#	Search term	Facet	Hits
1	melanoma	Disease (metastatic malignant melanoma)	101 811
2	melanom* AND (malign* OR nodular OR metasta* OR advanc* OR disseminat* OR recurr* OR unresect*)		57 667
3	melanom* AND (“stage iii” OR “stage 3” OR “stage iiic” OR “stage 3c” OR “stage iv” OR “stage 4”)		1835
4	#1 OR #2 OR #3		102 787
5	Economics or Cost or Pharmacoeconomics or Socioeconomics or fee or budget or (“cost-effectiveness” OR “cost-utility” OR “cost utility” OR “Cost benefit” OR “Cost minimisation” OR “Cost minimization” OR “budget impact” OR “cost consequence”) or "economic aspect" or "health care cost" or "drug cost" or "hospital cost" or "economic evaluation" or “health economics" or "health care financing" or "low cost" or "high cost" or "cost estimate" or "cost variable" or "unit cost" or economic* or pharmacoeconomic* or price* or pricing or "hospital finance" or "financial management" or "health care utilisation" or "health care utilisation" or "resource use" or "resource utilisation" or "resource utilisation"	Economic study design	1 210 516
6	#4 AND #5 AND (pubstatusaheadofprint OR inprocess[sb])	From database start to present	80
7	**#4 AND #5 AND (pubstatusaheadofprint OR inprocess[sb]) Publication date from 2014/11/28**	**Final numbers**	**66**

Quality of life review

Table 9: Search strategy for Embase® and MEDLINE® database searched via Embase.com platform (searched on 13 July 2015)

#	Query	Facet	Results
1	utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis OR scale) OR 'health utility index' OR 'hui' OR 'hrqol' OR 'hqol' OR 'quality of life'/exp OR 'quality of life' OR 'quality-of-life' OR qol OR utilit* NEXT/1 (score* OR value* OR evaluation*) OR health NEXT/2 utilit* OR ('health'/exp OR 'health' AND state NEXT/1 utilit*) OR (health NEXT/1 state* AND state* NEXT/1 preference*) OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'quality adjusted life' OR 'quality adjusted' NEXT/1 survival* OR qaly* OR qald* OR qale* OR qtime* OR 'disability adjusted life' OR daly* OR 'health survey'/exp OR 'health survey' OR hye* OR health*year*equivalent OR health NEAR/2 utility* OR health NEAR/2 measurement OR 'wellbeing'/exp OR 'wellbeing' OR quality NEAR/2 well*being OR qwb OR willingness NEAR/2 pay OR standard NEAR/2 gamble OR disutili* OR 'multi attribute' OR multiattribute OR health NEAR/2 ind* OR (time OR person) NEAR/2 trade* OR 'discrete choice' NEXT/1 experiment* OR 'short form 36'/exp OR 'short form 36' OR 'sf36' OR 'sf-36' OR 'sf 36' OR 'short form 12'/exp OR 'short form 12' OR 'sf12' OR 'sf-12' OR 'sf 12' OR 'short form 6' OR 'sf6' OR 'sf-6' OR 'sf 6' OR 'euroqol' OR euro*qol OR 'eq5d' OR 'eq-5d' OR 'eq 5d' OR rosser OR qlq* OR (visual OR linear) NEXT/1 analog* OR analog* NEXT/1 scale* OR 'visual analog scale'/exp OR 'fact m' OR 'fact g' OR 'functional assessment of cancer therapy melanoma' OR fact NEXT/1 melano* OR 'functional assessment of cancer therapy' OR 'fact brm' OR 'glq 8' OR 'quality of well being self administered questionnaire' OR 'qwb sa' OR 'brief symptom inventory' OR bsi OR 'chronic strains survey' OR css OR 'health and activities limitation index' OR halex OR 'ways of coping' OR woc OR 'cancer specific social support' OR 'structural functional social support' OR sfss OR 'anger expression scale' OR 'life experience survey' OR 'rotterdam symptom checklist' OR rscl OR 'depression anxiety scale' OR deps OR 'hospital anxiety and depression' OR hads OR 'impact of event scale' OR isel OR 'interpersonal support evaluation list' OR mcsds OR 'marlowe crowne social desirability scale' OR mcsd OR 'psychosocial adjustment of illness scale' OR 'pais sr' OR 'classification of illness states' OR 'well years' OR 'well year' OR 'state trait anxiety inventory' OR stai	QoL study design	899 552
2	('melanoma'/exp OR melanoma) OR (melanocarcinoma OR melanomatosis OR melanomalignoma OR n?evocarcinoma OR 'pigmentary cancer') OR melanom* NEAR/1 (malign* OR nodular OR metasta* OR advanc* OR disseminat* OR recurr* OR unresect* OR 'stage iii' OR 'stage 3' OR 'stage iiic' OR 'stage 3c' OR 'stage iv' OR 'stage 4')	Disease (metastatic malignant melanoma)	145 203
3	#1 AND #2	From database start to present	3611
4	**#1 AND #2 AND [28-11-2014]/sd**	**Final numbers**	**351**

Table 10: Search strategy for Cochrane database (searched on 13 July 2015)

#	Query	Facet	Results
1	MeSH descriptor: [Melanoma] explode all trees	Disease (metastatic malignant melanoma)	1148
2	Melanoma OR (melanom* near (malign* or nodular or metasta* or advanc* or disseminat* or recurr* or unresect*)) OR melanom* near ("stage iii" or "stage 3" or "stage iiic" or "stage 3c" or "stage iv" or "stage 4")		2594
3	#1 OR #2		2620
4	((utilit*) NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)) OR "health utility index" OR hui OR hrqol OR hqol OR "quality of life" or qol OR (utilit* NEXT/1 (score* OR value* OR evaluation*)) OR (health NEXT/2 utilit*) OR ('health' AND state NEXT/1 utilit*) OR "quality adjusted life year" OR "quality adjusted life" OR ("quality adjusted" NEXT/1 survival*) OR qaly* OR qald* OR qale* OR qtime* OR "disability adjusted life" OR daly* OR "health survey" OR hye* OR "health year equivalent" OR (health NEAR/2 utility*) OR "wellbeing" OR (quality	QoL study design	68 987

	NEAR/2 well*being) OR qwb OR (willingness NEAR/2 pay) OR (standard NEAR/2 gamble) OR disutili* OR (time NEAR/2 trade*off) OR tto OR "short form 36" OR "sf36" OR "sf-36" OR "sf 36" OR "short form 12" OR "sf12" OR "sf-12" OR "sf 12" OR "short form 6" OR "sf6" OR "sf-6" OR "sf 6" OR "euroqol" OR euro*qol OR "eq5d" OR "eq-5d" OR "eq 5d" OR Rosser OR qlq* OR "visual analogue scale" or (visual analog*) OR "fact m" OR "fact g" OR "functional assessment of cancer therapy melanoma" OR fact NEXT/1 melano* OR "functional assessment of cancer therapy" OR "fact brm" OR "glq 8" OR "quality of well being self administered questionnaire" OR "qwb sa" OR "brief symptom inventory" OR bsi OR "chronic strains survey" OR css OR "health and activities limitation index" OR halex OR "ways of coping" OR woc OR "structural functional social support" OR sfss OR "anger expression scale" OR "life experience survey" OR "rotterdam symptom checklist" OR rscl OR "depression anxiety scale" OR deps OR "hospital anxiety and depression" OR hads OR "impact of event scale" OR isel OR "interpersonal support evaluation list" OR "marlowe crowne social desirability scale" OR mcsds OR "profile of mood states" OR poms OR "psychosocial adjustment of illness scale" OR "pais sr" OR "state trait anxiety inventory" OR stai		
5	MeSH descriptor: [Quality of Life] explode all trees		15 292
6	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees		3930
7	MeSH descriptor: [Health Care Surveys] explode all trees		334
8	#4 OR #5 OR #6 OR #7		76 392
9	#3 AND #8, in Trials	From database start to present	119
10	**#3 AND #8 Publication Year from 2014 to 2015, in Trials**	**Final numbers**	**19**

Table 11: Search strategy for MEDLINE® In-Process searched via PubMed® platform (searched on 13 July 2015)

#	Search term	Facet	Hits
1	melanoma	Disease (metastatic malignant melanoma)	101 811
2	melanom* AND (malign* OR nodular OR metasta* OR advanc* OR disseminat* OR recurr* OR unresect*)		57 667
3	melanom* AND ("stage iii" OR "stage 3" OR "stage iiic" OR "stage 3c" OR "stage iv" OR "stage 4")		1835
4	#1 OR #2 OR #3		102 787
5	"quality of life" OR "health related quality of life" OR hrqol OR utilit* OR "health gain" or hui* OR "health measurement scale" OR "health measurement scales" OR "health measurements scale"OR "health measurements scales" OR "health measurement questionnaire" OR "health measurement questionnaires" OR "health measurements questionnaire" OR "health measurements questionnaires" OR "standard gamble" OR "standard gambles" OR (category* AND scal*) OR (linear AND analog*) OR (visual AND scal*) OR (magnitude AND estimate*) OR "time trade off" OR "time trade offs" OR "time tradeoffs" OR rosser* OR hrqol OR "index of wellbeing" OR "quality of wellbeing" OR qwb OR multiattribute* OR "health indices" OR "health index" OR "health utility index" OR "health utilities index" OR "health utility indices" OR "health utilities indices" OR "quality adjusted life year" or "quality adjusted life years" OR qaly OR qald* OR qale* OR qtime* OR "disability adjusted life" OR daly*	QoL study design	491 262
6	hye OR hyes OR "health year equivalent" OR "health year equivalents" OR "health years equivalent" OR "health years equivalents" OR "person trade off" OR "person trade offs" OR "person tradeoff" OR "person tradeoffs" OR "health survey" or "health surveys" OR wellbeing or "well being" OR disutilit* OR "short form 36" OR "sf36" OR "sf-36" OR "sf 36" OR "short form 12" OR "sf12" OR "sf-12" OR "sf 12" OR "short form 6" OR "sf6" OR "sf-6" OR "sf 6" OR "euroqol" OR euro*qol OR "eq5d" OR "eq-5d" OR "eq 5d" OR qlq* OR "visual analog scale" OR "linear analog scale" OR "visual analogue scale" OR "linear analogue scale"		174 399
7	"fact m" or "fact-m" or "fact-melanoma" OR "fact g" OR "functional assessment of cancer therapy melanoma" OR "fact melanoma" OR "functional assessment of cancer therapy" OR "fact brm" OR "glq 8" OR		46 003

	"quality of well being self administered questionnaire" OR "qwb sa"OR "brief symptom inventory" OR bsi OR "chronic strains survey" OR css OR "health and activities limitation index" OR halex OR "ways of coping" OR woc OR "cancer specific social support" OR "structural functional social support" OR sfss OR "anger expression scale" OR "life experience survey" OR "rotterdam symptom checklist" OR rscl OR "depression anxiety scale" OR deps OR "hospital anxiety and depression" OR hads OR "impact of event scale" OR isel OR "interpersonal support evaluation list" OR "marlowe crowne social desirability scale" OR mcsds OR "profile of mood states" OR poms OR "psychosocial adjustment of illness scale" OR "pais sr" OR "classification of illness states" OR "well years" OR "well year" OR "state trait anxiety inventory" OR stai		
8	#5 OR #6 OR #7		628 127
9	#4 AND #8 AND (pubstatusaheadofprint OR inprocess[sb])	From database start to present	131
10	**#4 AND #8 AND (pubstatusaheadofprint OR inprocess[sb]) Publication date from 2014/11/28**	**Final numbers**	**98**

Results

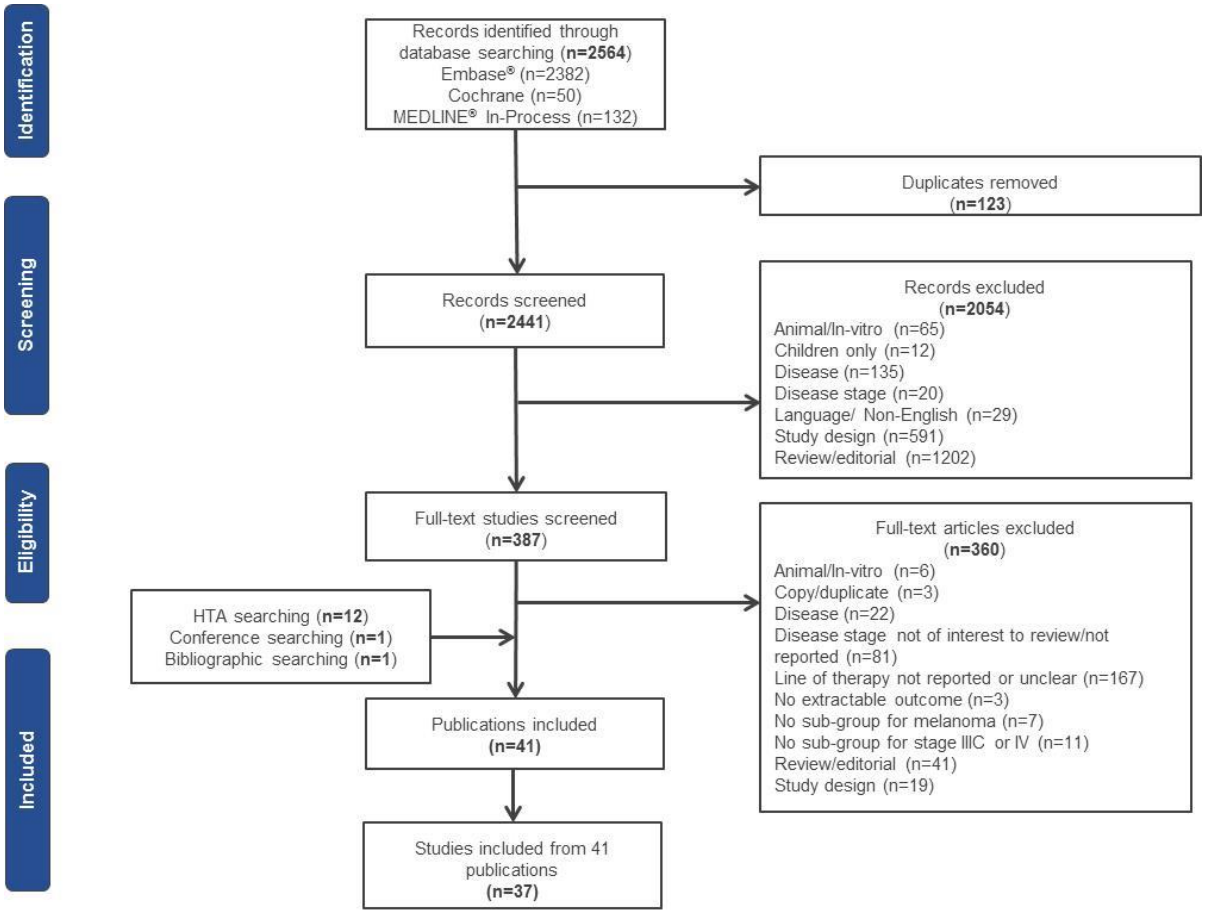
Economic review

Details of the flow of studies included at each step of the review are shown in the PRISMA flow diagram in Figure 1 below. A systematic search of Embase®, Cochrane, and MEDLINE® databases yielded 2564 separate references, of which 123 references were found to be duplicates and were removed.

Following first pass of the remaining 2441 citations, 387 potentially relevant references were identified. Full-text reports of these citations were obtained for a more detailed evaluation. Additional references (n=14) meeting the inclusion criteria for this review were identified from conference proceedings (n=1), HTA searching (n=12), and bibliographic searching (n=1). Following detailed examination of these 401 articles, 359 citations were excluded for not meeting the eligibility criteria.

Following full-text screening and linking of multiple publications, 37 studies (reported in 41 publications) were included for extraction. Of these 26 studies were economic evaluations and the remaining 11 studies were cost/resource studies. The majority of studies were published as conference abstracts (n=18), while seven studies were published as journal articles. The remaining 12 studies were manufacturers' submission to HTA agencies across Canada (4 studies), the UK (3 studies), Australia (3 studies), and Scotland (2 studies).

Figure 1: PRISMA diagram for economic literature review



The complete list of studies that met the eligibility criteria and were included in the review is provided below.

Table 12: List of studies included in the full economic review

Study name	Type of publication
Economic evaluations	
Canada	
Amdahl, 2014	Conference abstract
Delea, 2015 [2]	Journal article
Dabrafenib pCODR, 2013[3]	HTA submission
Ipilimumab pCODR, 2014[4]	HTA submission
Trametinib pCODR, 2013 [5]	HTA submission
Vemurafenib pCODR, 2012[6]	HTA submission
USA	
Curl, 2014 [7]	Journal article
Shih 2015[8]	Journal article
Hillner, 2000[9]	Journal article
Barzey, 2014[10; 9]	Journal article

UK	
Delea, 2014[11; 9]	Conference abstract
Ipilimumab NICE STA, 2014[9; 12]	HTA submission
Dabrafenib NICE STA, 2014[9; 13]	HTA submission
Vemurafenib NICE STA, 2012 [14]	HTA submission
Australia	
PBAC submission Dabrafenib	HTA submission
PBAC submission Vemurafenib	HTA submission
PBAC submission Pembrolizumab	HTA submission
Scotland	
Lee, 2014[15]	Conference abstract
Vemurafenib SMC, 2013[16]	HTA submission
Dabrafenib SMC, 2015[17]	HTA submission
Sweden	
Ohna, 2014[18]	Conference abstract
Barzey, 2014[10]	Conference abstract
Spain	
Aceituno, 2014[19]	Conference abstract
Netherland	
Retel, 2014[20]	Conference abstract
Peru	
Garrido, 2015[21]	Conference abstract
Chile	
Rovegno, 2015[22]	Conference abstract
Cost/Resource use studies	
Canada	
MELODY study; Osenenko, 2011[23]	Conference abstract
USA	
Tarhini, 2014 [24]	Conference abstract
Agarwala, 2013[25]	Conference abstract
Chang, 2015 [26]	Journal article
Davis, 2009 [27]	Journal article
Brazil	
Tsuchiya, 2013 [28]	Conference abstract
MELODY study; Schmerling, 2011[29]	Conference abstract
Slovakia	
Ondrusova, 2014[30]	Conference abstract
Italy	
Maio 2012; MELODY study[31]	Journal article
France	
MELODY study; Bedane, 2010[32]	Conference abstract

Mexico	
Silva 2012 [33]	Conference abstract

HTA: Health Technology Assessment; NICE: National Institute for Health and Clinical Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; pCODR: PAN-Canadian Oncology Drug Review; SMC: Scottish Medicines Consortium; STA: Single Technology Appraisal; UK; United Kingdom; USA: United States of America

For the purposes of this submission a further filter was applied to retrieved studies. Only those describing cost-effectiveness analyses from a UK perspective of the intervention of interest for this decision problem – namely, dabrafenib-trametinib combination, is described.

UK	
Delea, 2014 [11]	Conference abstract

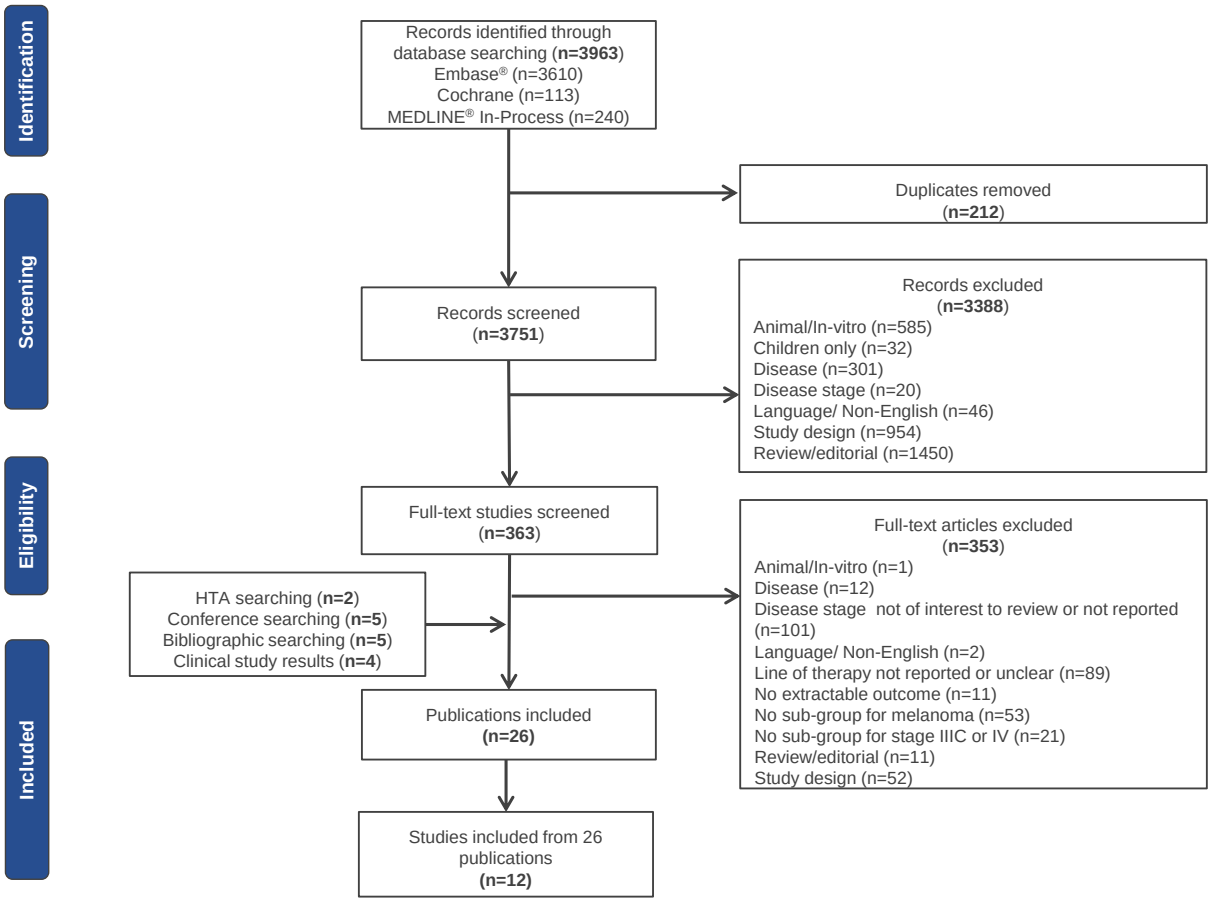
HRQoL review

Details of the flow of studies included at each step of the review are shown in the PRISMA flow diagram in Figure 2 below. A systematic search of Embase®, Cochrane, and MEDLINE® databases yielded 3963 separate references, of which 212 references were found to be duplicates and were removed.

Following first pass of the remaining 3751 citations in the HERON systematic review database, 363 potentially relevant references were identified. Full-text reports of these citations were obtained for a more detailed evaluation. Additional references (n=16) meeting the inclusion criteria for this review were identified from conference proceedings, HTA searching, bibliographic searching, and clinical study reports provided by Novartis. Following detailed examination of these 379 articles, 353 citations were excluded for not meeting the eligibility criteria.

Following full-text screening and linking of multiple publications, twelve studies (reported in 26 publications) were included for extraction.

Figure 2: Study flow diagram for the quality of life review



Embase: *Excerpta Medica* Database; HTA: Health Technology Assessment; LoT: Line of Therapy; MEDLINE: Medical Literature Analysis and Retrieval System Online; SGA: Sub-Group Analysis

The complete list of studies that met eligibility criteria and were included in the review is provided below.

Table 13: Full list of RCTs deemed eligible for the HRQL review

Study name	N	Interventions (n)	Patient population	Linked publications
BREAK-3 CSR[34]	250	• DTIC 1000 mg/m^2 q3w (N=63) • Dabrafenib 150 mg bid (N=187)	Age ≥18 years, histologically confirmed advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutation positive melanoma, ECOG PS 0-1	Grob, 2013, Grob, 2014 [35; 36]
BRIM-3 [37]	675	• DTIC 1000 mg/m^2 q3w (N=338) • Vemurafenib 960 mg bid (N=337) • DTIC 1000 mg/m^{2}q3W (BRAF V600E) (N=303) • Vemurafenib 960 mg bid (BRAF V600E) (N=295) • DTIC 1000 mg/m^{2}q3w (BRAF V600K) (N=24) • Vemurafenib 960 mg bid (BRAF V600K) (N=33)	Age≥18 years, unresectable, stage IIIC or IV melanoma tested positive for the BRAF V600E mutation on real-time polymerase-chain-reaction assay, ECOG PS of 0-1	Vemurafenib IQWiG,2013, Vemurafenib pCODR, 2012
COMBI-d CSR[38]	423	• Dabrafenib 150 mg bid + trametinib 2 mg od (N=211) • Dabrafenib 150 mg bid (N=212)	First-line patient population of BRAFV600E and V600K mutation-positive, unresectable and metastatic melanoma	Schadendorf, 2015[39]
METRIC CSR[34; 40]	322	• Trametinib 2 mg od (N=114) • DTIC 250 mg/m^2 q3w (N=62) • Paclitaxel 175 mg/m^2 q3w	Histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF V600E/K mutation-positive tumor, ECOG PS 0-1	Schadendorf, 2013; Schadendorf, 2014 [41; 42]
COMBI-v CSR[43]	704	• Dabrafenib 150 mg bid + trametinib 2 mg (N=352) • Vemurafenib 960 mg bid (N=352)	Age ≥18 years, histologically confirmed cutaneous melanoma Stage IIIC (unresectable) or Stage IV (metastatic), BRAF V600E or V600K mutations, measureable disease, ECOG PS 0 or 1, brain metastases treatment with no increase in lesion size for at least 12 weeks	Grob, 2015[44]
CoBRIM [45]	495	• •	Age ≥18 years, histologically confirmed unresectable, locally advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation, measurable disease, ECOG PS 0 or 1, adequate hematologic, hepatic, renal, and cardiac function, and if previously treated brain metastases, then, at least a 3-week history of stable disease was a must	Dréno, 2015[46]
CHECKMATE 066 [47]	418	• Nivolumab 3 mg/kg q2w (N=210) • DTIC 1000 mg/m^2 q3w (N=208)	Age ≥18 years, confirmed, unresectable, previously untreated stage III or IV melanoma without a BRAF mutation, ECOG PS 0-1	
CHECKMATE 069 [48]	142	• Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg q3w (N=95) • Ipilimumab 3mg/kg+C45 q3w (N=47)	Histologically confirmed, unresectable Stage III or Stage IV melanoma	

Study name	N	Interventions (n)	Patient population	Linked publications
Avril, 2004[49]	129	• Fotemustine 100 mg/m^2 q2w (N=112) • DTIC 250 mg/m^2/d for 5 days, q4w (N=117)	Age 18 to 75 years, histologically confirmed disseminated non-ocular metastatic melanoma, with or without brain metastases, ECOG PS ≤1, life expectancy greater than 3 months, adequate bone marrow function, and satisfactory hepatic and renal functions, no prior chemotherapy or immunotherapy	None
Chiarion-Sileni, 2003[50]	178	• Chemotherapy* (N=89) • Bio-chemotherapy# (N=89)	Advanced melanoma, not previously treated with systemic chemotherapy	None
CA182024 [51]	502	• DTIC 850 mg/m^2 i.v. q3w + ipilimumab 10 mg/kg q3w (N=250) • DTIC 850 mg/m^2 i.v. q3w (N=252)	Age≥18 years, previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions, an ECOG PS 0 or 1	Kotapati, 2011[52]
Middleton 2000[53]	305	• Temozolomide 200 mg/m^2/day for 5 days, q4w (N=156) • DTIC 250 mg/m^2/d for 5 days, q3w (N=149)	Age ≥18 years, histologically confirmed surgically incurable or unresectable, advanced metastatic melanoma, WHO PS 0, 1 or 2, normal renal, hepatic and bone marrow functions	None

For the purposes of this submission a further filter was applied to retrieved studies. Only those describing quality of life data phase III studies of the intervention of interest for this decision problem – namely, dabrafenib-trametinib combination are described.

UK	
COMBI-V	CSR and Grob, 2015[44]
COMBI-D	CSR and Schadendorf, 2014[39]

The quality assessment of COMBI-V and COMBI-D trials is discussed in depth in Section 4.6.3 of the main submission document.

Appendix 8.12: Comparability of COMBI-v and COMBI-d studies

Design & methodology

The design and methodology of the COMBI-d and COMBI-v studies were identical in most rspects.[54; 55] Both were multicentre, phase III, two-arm controlled trials involving the same randomisation process to trametinib + dabrafenib combination therapy or BRAF inhibitor monotherapy. They were conducted in similar geographical regions (including Europe, N. America and Australia) in the same time frame such that any differences in supportive care/treatments available is likely to be minimal.

Both studies included PFS and OS as key endpoints and the statistical analyses undertaken were identical. Crossover was initially prohibited in both studies in order to preserve the integrity of the OS endpoint. However, the COMBI-v protocol was amended following a planned interim analysis which met the pre-specified stopping boundary and the study was stopped for efficacy.[55] A small number of patients (21/352=6%) randomised to vemurafenib then switched to receive trametinib + dabrafenib.

The frequency of study visits was the same in both studies as was the nature and timing of all assessments undertaken. Tumour assessments were conducted every 8 weeks until week 56, and every 12 weeks thereafter. Tumour response and progression was assessed according to RECIST v1.1 in both studies and all responses were confirmed with a scan at least 4 weeks after the first RECIST response.[54; 55]

Median follow-up times at the latest data cut-offs are very similar: 20.0 months and 19.0 months for the combination arms in COMBI-d and COMBI-v respectively, and 16.0 and 15.0 months for the BRAF inhibitor monotherapy arms.[56; 57]

Patient population

The eligibility criteria for COMBI-d and COMBI-v were identical (see Table 14 in the main submission document) resulting in the patient populations enrolled in the two studies having highly overlapping baseline demographic and disease characteristics (Table 14 overleaf). Treatment arms were well balanced within the individual studies and are also comparable across the studies (see Table 14 overleaf). Minor exceptions include a slightly lower proportion of patients with visceral disease in the dabrafenib monotherapy arm in COMBI-d, and slightly more patients with ≥3 disease sites in the combination arm in COMBI-v. Overall, the majority of subjects in the studies had Stage IV M1c disease (59-67%), LDH ≤ULN (63-68%), ECOG performance status of 0 (70-73%), visceral disease (68-79%), and 85-90% had a BRAF V600E mutation.[54; 55] Additionally, the CHMP has acknowledged that the patient populations in the two studies were comparable and any minor imbalances between treatment arms did not affect the reliability of the study results.[58]

Table 14: Characteristics of participants in COMBI-d and COMBI-v studies

Study	COMBI-d[54]		COMBI-v[55]	
Intervention	**Trametinib + dabrafenib**	**Dabrafenib monotherapy**	**Trametinib + dabrafenib**	**Vemurafenib monotherapy**
	211	**212**	**352**	**352**
Age, mean (yrs)	55.1 (13.33)	55.3 (13.75)	54.1 (13.83)	54.3 (14.06)
Male, n (%)	111 (53)	114 (54)	208 (59)	180 (51)
ECOG PS, n (%)				
0	155 (73)	150 (71)	248 (71)	248 (70)
1	55 (26)	61 (29)	102 (29)	104 (30)
BRAF mutation status, n (%)				
BRAF V600E	179 (85)	181 (85)	312 (90)	317 (90)
BRAF V600K[a]	32 (15)	30 (14)	34 (10)	34 (10)
Baseline LDH, n (%)				
≤ULN	133 (63)	140 (66)	233 (66)	238 (68)
>ULN	77 (36)	71 (33)	118 (34)	114 (32)
Baseline disease stage, n (%)				
M0[b]	5 (2)	10 (5)	14 (4)	26 (7)
M1a	19 (9)	31 (15)	55 (16)	50 (14)
M1b	45 (21)	32 (15)	61 (17)	67 (19)
M1c	142 (67)	138 (65)	221 (63)	208 (59)
No. disease sites, n (%)[b]				
≥3 sites	92 (43)	92 (43)	174 (50)	151 (43)
< 3	119 (56)	119 (56)	177 (50)	201 (57)
Visceral disease at baseline, n (%)				
No	46 (22)	66 (31)	73 (21)	81 (23)
Yes	165 (78)	145 (68)	278 (79)	271 (77)

a. One patient in COMBI-d was both BRAF V600E and BRAF V600K mutation positive and is included in the BRAF V600K subset in this display

b. Number of body sites of disease based on unique RECIST target and non-target lesions identified by the investigator, not the number of metastases.

Appendix 8.13: Comparability efficacy of the BRAF inhibitor monotherapies (dabrafenib and vemurafenib)

Background

For the purposes of the economic evaluation, we chose to pool data from the two phase III studies, COMBI-d [MEK115306] and COMBI-v [MEK116513]) using individual patient level data in order to provide a more precise estimate of treatment effect for trametinib + dabrafenib combination therapy versus BRAF inhibitor monotherapy.

Assumption of comparable efficacy between dabrafenib and vemurafenib

The pooling assumes that the BRAF inhibitor monotherapies - dabrafenib and vemurafenib – have:

- Comparable efficacy (PFS and OS)
- Distinct adverse event profiles (therefore distinct impacts on quality of life)

Although there are no controlled trials directly comparing the two drugs, a naïve comparison of efficacy results from the respective phase III studies (BREAK-3 and BRIM-3) indicates that their efficacy is very similar (Table 15). ORR was 59% for dabrafenib in BREAK-3 and 57% for vemurafenib in BRIM-3.[59; 60] Best tumour response for dabrafenib and vemurafenib in these studies as illustrated by waterfall plots were remarkably similar (Figure 3).[61; 37] Based on digitisation of these figures, the approximate average tumour reduction with dabrafenib in BREAK-3 was similar to that for vemurafenib in BRIM-3 (46% vs. 42%). The HRs for PFS for dabrafenib vs. dacarbazine and for vemurafenib vs. dacarbazine were 0.37 and 0.38 respectively. The HRs for unadjusted OS are also similar (0.81 for dabrafenib vs. dacarbazine and 0.76 for vemurafenib vs. dacarbazine).[59; 60]

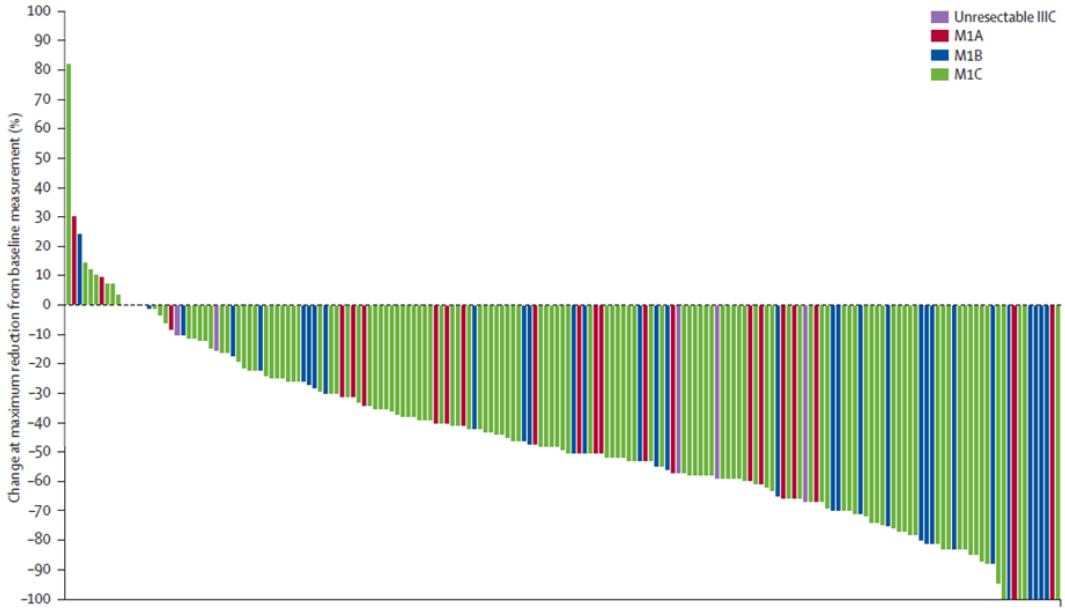
Table 15: Comparison of efficacy results from BREAK-3 and BRIM-3 trials (based on latest available data)

	BREAK-3[59; 62]		**BRIM-3[60]**	
	Dabrafenib N=187	**Dacarbazine N=63**	**Vemurafenib N=337**	**Dacarbazine N=338**
ORR	**June 2012 cut-off**		**February 2012 cut-off**	
	110 (59%)	15 (24%)	192 (57%)	29 (9%)
PFS	**June 2012 cut-off**		**February 2012 cut-off**	
Median, months (95% CI)	6.9 (5.2, 9.0)	2.7 (1.5, 3.2)	6.9 (6.1, 7.0)	1.6 (1.6, 2.1)
HR (95% CI)	0.37 (0.23-0.57)		0.38 (0.32, 0.46)	
OS (unadjusted)	**August 2014 cut-off**		**February 2012 cut-off**	
Median, months (95% CI)	20.1 (16.7, 24.4)	15.6 (11.9, 21.2)	13.6 (12.0-15.2)	10.3 (9.1, 12.8)
HR (95% CI)	0.81 (0.56, 1.18)*		0.76 (0.63, 0.93)	

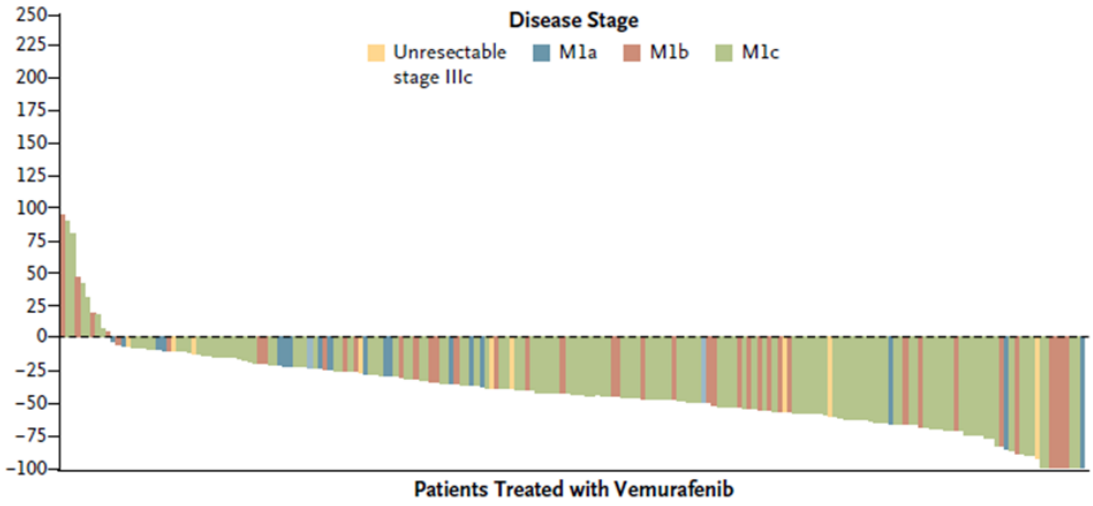
*confounded by crossover of 37/63=59% patients randomised to dacarbazine to receive dabrafenib after confirmed disease progressed

Figure 3: Maximum tumour percent change from baseline in patients treated with dabrafenib in BREAK-3 (A) and for patients treated with vemurafenib in BRIM-3 (B)

A: Dabrafenib n=187; Dacarbazine n=63 (December 2011 cut-off) (Hauschild 2012 *et al*.[61])



B: Vemurafenib n=337; Dacarbazine n=338 (December 2010 cut-off) (Chapman *et al*. 2011)



An indirect comparison of the BREAK-3 and BRIM-3 studies using the Bucher method was undertaken by GSK for the NICE single technology appraisal (STA) of dabrafenib monotherapy in patients with BRAF V600 mutation-positive metastatic melanoma. This analysis found no difference between dabrafenib and vemurafenib in PFS (HR 0.97 [95% CI: 0.59 to 1.60]) or OS (unadjusted HR 1.00 [95% CI 0.62 to 1.62]; crossover-adjusted HR 0.86 [95% CI 0.32 to 2.29]).[13]

The same indirect comparison was provided to the Scottish Medicines Consortium (SMC) for their assessment of dabrafenib in the same indication. The SMC also noted that the results of the indirect comparison suggest that there is no significant difference between dabrafenib and vemurafenib for PFS and overall survival.[17]

Consistently, there is clinical consensus that the effectiveness of the two agents is comparable in clinical practice and that a clinician's choice of treatment is largely driven by the different AE profiles of the treatments.[13] Clinicians participating in the SMC's patient and clinician engagement (PACE) meeting also acknowledged the similar efficacy of dabrafenib and vemurafenib.[17]

Finally, the Appraisal Committee for the dabrafenib STA concluded that there was no clear evidence that dabrafenib and vemurafenib differed in clinical effectiveness and that it would not be unreasonable to assume that they have similar treatment effects.[13]

For the above reasons, an assumption of comparable efficacy was deemed reasonable and time-to-event data were pooled in a one-stage meta-analysis for the purposes of economic modelling.

Appendix 8.14: Assessing possibility of parallel cumulative hazards

The cumulative hazard function was examined to determine whether there any apparent shift to the right for the experimental treatment group around the origin followed by parallel cumulative hazard functions thereafter. If such a shift can be identified, Bagust and Beale [63] suggest that "a good estimate of the expected health gain can be obtained without any resort to projective modelling".

As shown in Figure 4, the cumulative hazard functions for overall survival for the combination does exhibit a shift of 2-3 months initially. However, the cumulative hazard functions for the combination and monotherapy after the shift do not appear to be parallel. In light of these results, we did not pursue this approach to modelling survival.

Figure 4 [redacted]

Appendix 8.15: Technical detail: model cheat sheet.

Overview of model

The economic model was developed by Policy Analysis Inc. (part of the Minerva Group). The model is their house offering which has been customised to address the question of interest for this NICE appraisal. The excel workbook is a framework which can accept a range of different treatments, analyses perspectives and allows for a variety of potential approaches to estimating survival distributions. This explains upfront why there may be unused functionality in the model (e.g. space to accommodate other regimens or inputs), and some superfluous cells, sheets and functionality. Where possible this has been stripped out to avoid distraction. Where it remains,

redundant input cells are shaded in a light blue for clarity; they can be ignored and should not be deemed an error.

This document is a user guide for those attempting to understand the structure and functionality of the model as it applies to the case set out in this NICE appraisal.

Model worksheets

1. Run Analyses

Base case and other analyses can be run from here.

- Base case analysis is run, applying specified discounts to the treatments of interest (the discounts relate to the unit prices specified on the 'Regimen details' sheet)

- Results will display:

    - Table of pair-wise comparison of base-case results
    - Table of incremental comparison of base-case results
    - A scatter plot of efficiency frontier for all comparators considered in the model
    - Plots of survival distributions used for PFS and OS for each comparator

- Tornado Plot Analysis / DSA can be run (the scenarios that will run here are set up on the 'Tornado Plot Inputs' sheet. Results will display:

    - Tornado diagrams providing results for pre-specified analyses
- PSA can be run, with a pre-specified number of simulations at the pre-specified CE threshold **(NB: with 1000 simulations this can take approximate 30-50 minutes to run).** Results will display:
    - Table of statistical summary in expected costs and QALYs, and differences in costs and QALYs between dabrafenib and the comparators
    - Table of outcomes (costs and QALYs) with each row of table represents results of one simulation
    - Scatter plot of ICERs with percent of simulations in each quadrant of cost-effectiveness plane, and CIs for costs, QALYs and cost-effectiveness
    - Scatter plot of pair-wise acceptability curves
    - Scatter plot of incremental acceptability curves

2. Comparators

This sheet sets up the comparisons of interest.

- Enabled : This functionality allows the user to select which interventions/comparators to include

- Referent: Select the referent treatment in the pairwise and incremental analyses
- Active: The model runs in real time on the worksheets and this selection allows the user to select which treatment's data are visible at any one instant

There will be no need to change any of the settings on this sheet as it is set up to represent the specified decision problem for this assessment.

3. Main inputs

This sheet summarises the model inputs for:

- Effectiveness
- Safety
- Costs
- Utility

Greyed out boxes hold inputs that are estimated outside of the model (detailed in the submission document as referenced), whilst cells without shading have drop down menus.

In turn:

a. Effectiveness

PFS and OS profiles can be selected from the drop down menus for each comparator. The names of these profiles are simply labels which reflect a profile that has been set up for each treatment on PFS Profiles! and OS Profiles! sheets (see Section 1.3.10 below for more detail on how the effectiveness profiles are set up).

It will only be necessary to change the drop down in cell C6 to re-run the model with the scenario analysis option selected for the combination (i.e. the no-continuing PFS benefit assumption).

b. Safety

The safety inputs specify a ‘reference’ profile and a ‘relative risk’ profile for each comparator. The way they are set up reflect the way that AE incidences are incorporated (namely using the pooled AE incidences for the combination arm and relative risks of these AEs for the monotherapies). Again these are labels referring to details on the Safety Profiles! and Relative Risk Profiles! sheets respectively.

c. Costs

- Relative dose intensity is a scalar estimated outside of the model (see Section 5.5.5 in submission for a description of the calculation of RDIs). These are specified in cells C14, C15, C17, C18, H14, H15, M14 and M15.

- One-time costs are incorporated for treatment initiation and for death. The estimation of these inputs is detailed in Section 5.5.6. of the submission document. Costs are also applied in the progression state for post-study anti-cancer therapies, as estimated in Section 5.5.8. of the submission.

- Monthly costs are applied in both the progression-free and post-progression health states to account for monitoring and follow up. The calculations behind inputs in cells C33, C37, H33, H37, M33 and M37 are detailed in Section 5.5.6 of the submission document.

d. Utilities

Pre- and post-progression health state utilities are estimated outside of the model (see Section 5.4.12 of the submission). In the model, the health state utilities are input as a decrement vs. perfect health and a decrement vs. progression free, respectively. This approach is to simplify model calculations, but the health state utilities that these decrements represent are as described in the submission.

4. Regimen details

This sheet provides the details of the regimens included in the model as specified in Section 5.2.4.

5. Settings

- Trial, extrapolation and AJCC data used until, Years
    - Specifies the time for which underlying trial, exponential and AJCC data are used
- Model time horizon:
    - Specifies the full model horizon
- Discount rates:
    - Pre-specified at 3.5% per annum for both costs and benefits.
- Sensitivity analysis scalars:

- Functionality is not implemented in this model (it is there to allow further flexibility in the way that sensitivity analyses can be conducted). In this model we set up our sensitivity analyses in the Tornado Plot Inputs sheet.

- BSA and weight:
  - These inputs are derived from the BREAK-3 study and are utilised in estimation of some PSACT costs.

6. Tornado Plot Inputs

On this sheet, the DSA parameters are specified on the basis of the underlying variables that will be tested. Section 5.8.5. details the analyses undertaken here.

7. Safety Profiles

Sets out the detail called up from reference profile on MainInputs! sheet (see above). The dabrafenib-trametinib combination safety profile (estimated on the basis of the incidence of G3+ AEs in the pooled combination dataset) is the reference profile for both dabrafenib and vemurafenib AE incidence (which are incorporated on the basis of indirect treatment comparisons). Section 5.5.7. details how these incidences were estimated.

8. Relative Risk Profiles

An understanding of the relative risks of the various adverse events with both dabrafenib and vemurafenib is necessary in order to estimate the cost of AEs with these BRAF inhibitor monotherapies, as detailed in Section 5.5.7 in the submission.

9. Cost of AEs

This sheet holds the inputs of the per event cost of treating the adverse events of interest. The calculations behind these estimates are described in Section 5.5.7 and Appendix 8.19. For the purposes of sensitivity analyses, standard error is assumed to be 25% of the estimate.

10. PFS and OS profile sheets

These sheets are set up sheets where the user selects the PFS and OS distributions to apply for the trial period and the projection period (out to 20 years). The following table describes which distributions are applied in this model for PFS and OS for the treatment and comparators.

Progression free survival	Trial period (until end of trial follow up)		Projection phase (until 20 years)	
	Profile name and definition	Explanation	Profile name and definition	Explanation
BASE CASE: PFS: D+T KM + Exp, Cont, Benefit	D + T PFS1 Kaplan-Meier + Exponential. The data behind this profile is on the Empirical Survival Inputs! Sheet.	As described in Section 5.3.1.3. KM trametinib + dabrafenib combination data are used until the established break point of 11.82 months (model variable *parametric4_param2)* followed by an exponential distribution using the hazards at that time point. This distribution, i.e. KM to the break point and exponential thereafter is detailed on the Empirical Survival Inputs sheet under the respective profile name, i.e. "D + T PFS1 Kaplan-Meier + Exponential". It is a blend of the KM data (also detailed on that sheet) and the exponential distribution (detailed on Parametric Survival Inputs! sheet) pivoting about the predetermined break point (*parametric4_param2*)	Uses D + T PFS1 Kaplan-Meier + Exponential	As described in Section 5.3.1.3, exponential distribution is used for the entire projection phase
SCENARIO1: PFS: D+T KM + Exp, No Cont. Benefit	D + T PFS1 Kaplan-Meier + Exponential. The data behind this profile is on the Empirical Survival Inputs! Sheet.	As above for the trial period	BRAF Inhibitor PFS1 Kaplan-Meier + Exponential	As described in Section 5.8.8, the scenario analysis uses combination KM data and exponential extrapolation during the trial period and then switches to the monotherapy exponential projection.
PFS: BRAF KM + Exp	BRAF Inhibitor PFS1 Kaplan-Meier + Exponential The data behind this profile is on the Empirical Survival Inputs! Sheet.	As described in Section 5.3.1.3. KM BRAF inhibitor monotherapy data are used until the established break point of 12.48 months (model variable *parametric3_param2)* followed by an exponential distribution using the hazards at that time point. This distribution, i.e. KM to the break point and exponential thereafter is detailed on the Empirical Survival Inputs sheet under the respective profile name, i.e. "BRAF Inhibitor PFS1 Kaplan-Meier + Exponential". It is a blend of the KM data (also detailed on that sheet) and the exponential distribution (detailed on Parametric Survival Inputs! sheet) pivoting about the predetermined break point (*parametric3_param2*)	BRAF Inhibitor PFS1 Kaplan-Meier + Exponential	As described in Section 5.3.1.3, exponential distribution is used for the entire projection phase

OS Profiles	Trial period (until end of trial follow up)		Projection phase (until 20 years)	
	Profile name and definition	Explanation	Profile name and definition	Explanation
OS: D+T KM + Exp + AJCC	D + T OS Kaplan-Meier + Exponential The data behind this profile is on the Empirical Survival Inputs! Sheet.	As described in Section 5.3.1.4. KM trametinib + dabrafenib combination data are used until the established break point of 18.6 months (model variable *parametric2_param2)* followed by an exponential distribution using the hazards at that time point. This distribution, i.e. KM to the break point and exponential thereafter is detailed on the Empirical Survival Inputs sheet under the respective profile name, i.e. "D + T OS Kaplan-Meier + Exponential". It is a blend of the KM data (also detailed on that sheet) and the exponential distribution (detailed on Parametric Survival Inputs! sheet) pivoting about the predetermined break point (*parametric2_param2*)	AJCC Case-Mix Adjusted RCS Normal	As described in Section 5.3.1.4, the modelling using the exponential extrapolation from the break point to the end of the trial and then gradually transitions to the hazards seen in the AJCC dataset at 5 years. This transition is accommodated by inputting a start and end time for the transition (end of follow up and 60 months respectively) and by hazard ratios based on the parameter from exponential projection and the hazard rate from AJCC curve (hardcoded) at end of follow-up.
OS: BRAF KM + Exp + AJCC	BRAF Inhibitor OS Kaplan-Meier + Exponential	As described in Section 5.3.1.4. KM BRAF inhibitor monotherapy data are used until the established break point of 3.2 months (model variable *parametric1_param2)* followed by an exponential distribution using the hazards at that time point. This distribution, i.e. KM to the break point and exponential thereafter is detailed on the Empirical Survival Inputs sheet under the respective profile name, i.e. "BRAF Inhibitor OS Kaplan-Meier + Exponential". It is a blend of the KM data (also detailed on that sheet) and the exponential distribution (detailed on Parametric Survival Inputs! sheet) pivoting	AJCC Case-Mix Adjusted RCS Normal	As described in Section 5.3.1.4, the modelling using the exponential extrapolation from the break point to the end of the trial and then gradually transitions to the hazards seen in the AJCC dataset at 5 years. This transition is accommodated by inputting a start and end time for the transition (end

		about the predetermined break point (*parametric1_param2*)		of follow up and 60 months respectively) and by hazard ratios based on the parameter from exponential projection and the hazard rate from AJCC curve (hardcoded) at end of follow-up.

11. Parametric Survival Inputs

This sheet specifies the parameters for the exponential distributions that are used in the PFS and OS extrapolation to project beyond the break points.

Location parameter for these distributions is the break point and scale parameter is the hazards at the break point for each arm for each outcome.

12. Empirical Survival Inputs

This sheet details the underlying KM curves for the AUC analyses. As described above, the profile that is used depends upon selections in MainInputs! sheet.

13. Bootstrap KM and Bootstrap Inputs

Stores bootstrapped estimates of Kaplan-Meier curves defined in empirical survival inputs sheet and for other parameters for the bootstrap sampling.

14. CostQalyCalc, SurvCalc, MedCalc, AECalc and LifeTableCalc

These sheets are all live calculation sheets which display the ‘results’ for whichever treatment is selected as ‘active’ on the Comparators worksheet.

None of these sheets contain any input cells and they should therefore not be changed.

15. Variables

Presents a full list of the variables generated throughout the model. This sheet should not be changed.

Appendix 8.16: Literature on long-term survival in metastatic melanoma

In both SEER and AJCC, survival for stage IV patients was approximately 15% after 5 years and 10% after 10 years. These data suggest an annual average probability of death of approximately 32% for years 1-5 post-diagnosis and 8% for years 6-10 post-diagnosis. Assuming an age of approximately 60 years, the 5-10 mortality rates from SEER and AJCC still exceed corresponding age-specific general population mortality rates (approximately 1-2% annually for 65 year old persons in the US and UK), suggesting that a substantial residual elevated risk of death still remains after 5 years.

Long-term data from controlled trials represents an alternative to the use of registry data and demonstrate a similar pattern. The longest reported follow-up analyses of survival in Phase III trials of metastatic melanoma in the current era are from trials of ipilimumab.[64; 65; 66; 67] Schadendorf et al have reported results of a pooled analysis of OS data for 1,861 patients from 10 prospective and two retrospective studies of ipilimumab, including two phase III trials. Patients were previously treated (n=1,257) or treatment naive (n=604), with a maximum follow-up of approximately 10 years. Among treatment-naïve patients, survival at 3 and 5 years were 26% and approximately 23%, respectively. Annual probabilities of death declined over time from approximately 47% in year 1 to approximately 5% in years 5 to 7. The pattern among previously treated patients was similar, with a relatively higher mortality during years 1-3, but with a similar plateau in mortality rates between years 3 to 5.

Recently, OS data from a milestone analysis of 5 year survival in the CA184-024 trial of ipilimumab+DTIC vs. placebo+DTIC in treatment naïve patients with metastatic melanoma has recently been reported.[64] In this study, 5-year survival was 18.2% (95%CI 13.6% to 23.4%) with ipilimumab+DTIC vs 8.8% (95%CI 5.7 %to 12.8%) with placebo +DTIC. Thus, survival among ipilimumab patients in this study was similar to that for treatment-naïve patients in the pooled analysis described above Schadendorf, 2015.[67] Survival at 5 years among patients receiving DTIC in this study was similar, but slightly lower, than survival in the AJCC and SEER registries. As with the AJCC and SEER registries, annual mortality among DTIC patients diminished over time, from 64% in in the first year to 9% in year 5. The authors noted that survival plateaued in both arms suggesting that some proportion of patients in both arms achieve “long-term survival” but that long term survival is approximately 10% greater patients receiving ipilimumab. They further attribute this to a shift in the survival curves at year 1.

Taken as a whole, long-term data from the SEER and AJCC registries as well as from long-term follow-up in ipilimumab trials suggest the following. First, among patients with metastatic melanoma receiving traditional chemotherapy, survival drops rapidly during the first three years from around 40% at one year to a plateau of 10% to 15% at 5 years. Annual probability of death declines correspondingly during this period from approximately 60% in year one to approximately 10% at 5 years. After five years, survival plateaus, although the annual probability of death remains elevated relative to the general population. Between 5 and 10 years, annual probability of death is likely between 5% and 10%. Data on survival after 10 years in patients with metastatic disease are unavailable so it is uncertain whether there are further declines. The reason for the decline in mortality is uncertain but likely

relates in part to winnowing of patients at highest risk of death from the cohort over time so that only those patients at lowest risk remain in the long term.

The AJCC Melanoma Registry data were used because they represent a large sample of (relatively) geographically-diverse patients with metastatic melanoma and provide the longest duration of follow-up among the various sources of long-term data. Also, as mortality data from AJCC Melanoma Registry are available by M stage, it is therefore possible to calculate case-mix adjusted estimates of survival for each arm of the pooled dataset trials using the AJCC data and the distribution of patients by M stage in the two studies. Five years was chosen as the point at which the mortality rates would converge because data from the long-term studies consistently show that survival plateaus by approximately 5 years.

Appendix 8.17: Health state unit costs and resource use

One off costs applied in the model are presented in Table 9 and are derived from the MELODY study as presented to NICE in the ipilimumab second-line melanoma submission. They have been updated using 2013-2014 reference costs and 2014 PSSRU costs as detailed here.

Service	Unit cost	Mean utilisation	Source	Expected cost (£)
General practitioner outpatient visit	38.00	0.08	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.04
Plastic surgeon outpatient visit	93.14	0.03	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	2.79
Oncology/general ward inpatient stay	536.25	0.17	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	90.09
Complete blood count lab test	3.00	1.20	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.60
Complete metabolic panel lab test	1.18	1.20	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.42
Lactate dehydrogenase lab test	1.18	1.20	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.42
CT scan of abdomen/pelvis	97.95	1.00	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	97.95

CT scan of chest	97.95	1.00	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	97.95
MRI of brain	151.64	0.06	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	9.10
CT scan of brain	97.95	0.41	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	40.16
PET/CT scan	151.64	0.05	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	7.58
Bone scintigraphy	188.29	0.19	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	35.78
Echography	54.35	0.06	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.26
Chest X-Ray	29.60	0.20	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	5.92
Total				**400.05**

Monthly health state costs as presented in Table 9 are derived from the MELODY study as presented to NICE in the ipilimumab second-line melanoma submission and have been updated using 2013-2014 reference costs and 2014 PSSRU costs. They are estimated by multiplying the unit cost of each event by its frequency (detailed in the tables below).

Monthly PFS treatment costs

Service	Unit cost	Mean utilisation	Source	Expected cost (£)
General practitioner outpatient visit	38.00	0.08	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.04
Plastic surgeon outpatient visit	93.14	0.03	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	2.79
Oncology/general ward inpatient stay	536.25	0.07	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	34.86
Complete blood count lab test	3.00	1.30	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.90
Complete metabolic panel lab test	1.18	1.24	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.46
Lactate dehydrogenase lab test	1.18	1.24	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.46
CT scan of abdomen/pelvis	97.95	0.38	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	37.61

CT scan of chest	97.95	0.38	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	37.61
MRI of brain	151.64	0.06	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	9.55
CT scan of brain	97.95	0.02	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	2.15
PET/CT scan	151.64	0.01	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.21
Bone scintigraphy	188.29	0.00	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	0.56
Echography	54.35	0.04	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.96
Chest X-Ray	29.60	0.33	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	9.77
Total				**147.94***

*In PSA, distribution is assumed to be Lognormal with SE set at 25% of total costs

Monthly PPS treatment costs

Service	Unit cost	Mean utilisation	Source	Expected cost (£)
Medical oncologist outpatient visit	143.04	1.63	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	233.73
Radiation oncologist outpatient visit	131.11	0.06	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	7.87
General practitioner outpatient visit	38.00	0.08	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.04
Plastic surgeon outpatient visit	93.14	0.03	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	2.79
Oncology/general ward inpatient stay	536.25	0.07	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	34.86
Complete blood count lab test	3.00	1.30	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	3.90
Complete metabolic panel lab test	1.18	1.24	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.46
Lactate dehydrogenase lab test	1.18	1.24	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.46

CT scan of abdomen/pelvis	97.95	0.38	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	37.61
CT scan of chest	97.95	0.38	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	37.61
MRI of brain	151.64	0.06	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	9.55
CT scan of brain	97.95	0.02	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	2.15
PET/CT scan	151.64	0.01	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.21
Bone scintigraphy	188.29	0.00	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	0.56
Echography	54.35	0.04	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	1.96
Chest X-Ray	29.60	0.33	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 37.	9.77
Total				**389.54***

*In PSA, distribution is assumed to be Lognormal with SE set at 25% of total costs

Appendix 8.18: Calculation of inpatient costs

Table 16 below provides the calculations for the costs of inpatients costs for hypertension.

Table 16: Calculation of Cost of Inpatient Stays for hypertension and pyrexia

Currency Code	Currency Description	Non-Elective Inpatient						Weighted Average Cost, £
		Long Stay		Excess Bed Day		Short Stay		
		FCEs	Avg Cost, £	FCEs	Avg Cost, £	FCEs	Avg Cost, £	
Hypertension								
EB15A	Primary Pulmonary Hypertension with CC Score 9+	113	4,181	57	384	40	455	
EB15B	Primary Pulmonary Hypertension with CC Score 4-8	162	2,724	106	231	86	1,712	
EB15C	Primary Pulmonary Hypertension with CC Score 0-3	46	2,959	45	263	58	591	
Weighted average								**2,590**
Pyrexia								
WA04Z	Acute Febrile Illness with length of stay 4 days or less	4,106	1,259	1	415	10,314	461	
WA05Z	Pyrexia of Unknown Origin with length of stay 5 days or more	1,724	3,515	1,679	259	16	475	
Weighted average								**1,017**

Appendix 8.19: Calculation of PSACT costs

The estimation of PSACT costs in the economic model utilised underlying data from the COMBI-v and COMBI-d trials. Expected costs of PSACT were calculated by taking the sum of the product of the estimated mean utilisation of various PSACTs and corresponding estimates of the cost of a single course of each therapy. The cost per course of therapy for each PSACT included the costs of medication and therapy administration.

The utilisation of PSACT reported in COMBI-v and COMBI-d is presented in Table 17. Utilisation of cross-over treatment with dabrafenib-trametinib combination in the vemurafenib monotherapy arm was not included.

Table 17. Utilisation of post-study anti-cancer therapy in COMBI-v and COMBI-d

Therapy	COMBI-V		COMBI-D	
	Dabrafenib-Trametinib Combination N=350	Vemurafenib N=349	Dabrafenib-Trametinib Combination N=211	Dabrafenib N=212
Vemurafenib	8.9%	9.7%	7.6%	10.8%
Ipilimumab	21.4%	29.2%	17.5%	27.8%
DTIC*	5.1%	11.2%	7.6%	11.8%
Temozolomide	1.7%	4.3%	4.7%	2.4%
Paclitaxel (175 mg)	2.6%	2.0%	3.8%	6.1%
Carboplatin (1125 mg)	2.9%	2.6%	3.8%	3.3%
Lomustine	0.0%	2.0%	1.4%	2.4%
Interferon alfa-2b	0.0%	0.3%	0.5%	0.9%
IL-2	0.3%	1.1%	0.0%	0.5%
Cisplatin	0.9%	2.3%	1.9%	3.3%
Vinblastine	0.9%	1.4%	0.9%	1.4%
Bleomycin	0.3%	1.7%	0.5%	0.9%
Cytarabine	0.3%	0.3%	0.5%	0.0%
Vincristine	0.0%	1.1%	0.9%	0.9%
Bevacizumab	--	--	0.5%	2.4%
Cetuximab	--	--	0.0%	0.5%

Gemcitabine	--	--	0.0%	0.5%
Trametinib	0.9%	4.0%	0.5%	1.9%
Dabrafenib	5.1%	13.5%	2.4%	3.8%
Doxorubicin	--	--	0.0%	0.5%
Docetaxel	--	--	0.9%	0.9%
Pembrolizumab	5.1%	6.9%	2.4%	5.2%
Methotrexate	0.3%	0.0%	--	--
Cyclophosphamide	0.0%	0.6%	--	--
Etoposide	0.0%	0.3%	--	--

*Fotemustine is not available in the UK and was combined with DTIC.
SOURCE: COMBI-v CSR . Table 1.4230 Summary of Follow-up Biologic, Chemo, Immun, Small Molecule Targeted, and Hormonal Therapy Medications
SOURCE: COMBI-d CSR: Table 1.4230 Summary of Follow-up Biologic, Chemo, Immun, Small Molecule Targeted, and Hormonal Therapy Medications

Patients who did not progress are not at risk of receiving PSACT, so it was necessary to adjust the estimates of PSACT reported in these underlying trials for censoring. This was accomplished by dividing the unadjusted estimates of utilisation by the proportion of patients who progressed or died during the study to obtain estimates of utilisation of PSACTs among patients who progressed (Table 18).

Table 18. Percentage of patients who progressed or died in COMBI-v and COMBI-d

Trial	COMBI-v		COMBI-d	
	Dabrafenib-trametinib	Vemurafenib	Dabrafenib-trametinib	Dabrafenib
N	352	352	211	212
Progressed or died (%)	47%	62%	66%	76%

The expected cost per course of therapy for each PSACT was calculated by combining estimates of the mean duration of treatment with dosage schedules and estimated unit cost for medication and administration. Dosages were based on published studies in patients with unresectable or metastatic melanoma (Table 19). Fotemustine was assigned the same cost as DTIC. For medications that were dosed based on weight, mean body weight was obtained from BREAK-3. Mean time to discontinuation for dabrafenib and trametinib monotherapy were assumed to equal the mean PFS for dabrafenib estimated in a cost-effectiveness analysis of dabrafenib as first-line treatment in patients with BRAF V600 mutation-positive unresectable or

metastatic melanoma (49 weeks). Time to discontinuation for vemurafenib was assumed to be equal to the estimated mean PFS for vemurafenib in that study (48 weeks). Time to discontinuation for ipilimumab was assumed to be 29 weeks, based on the mean value reported in the manufacturer submission to NICE for ipilimumab for previously treated unresectable malignant melanoma (ipilimumab second line submission). Pembrolizumab and nivolumab were assumed to have the same time to discontinuation as ipilimumab. The time to discontinuation for DTIC and the remaining PSACTs were assumed to equal the mean PFS of DTIC aforementioned cost-effectiveness analysis of dabrafenib (24 weeks). RDIs for medication and administration cost were set to 100%.

Table 19. Characteristics of PSACT regimens considered in the analyses comparing dabrafenib-trametinib vs. vemurafenib

				Cost per dose				Expected cost per course		
Treatment	**Cost per mg**	**Duration of Tx**	**Source**	**Medication**	**Admin/ dispensing**	**Total**	**No. of doses per course**	**Medication**	**Admin/ dispensing**	**Total cost**
Vemurafenib	0.1302	48.07	Based on PFLYs for VEM from Delea et al. Pharmacoeconomics 2015 Apr;33(4):367-80.	250.00	0.49	250.49	350	87,617	170	87,787
Ipilimumab	75.0000	28.86	NICE. Ipilimumab for previously treated unresectable malignant melanoma. Single technology appraisal (STA). 2011. Manufacturer's submission. Table 42.	18,750.00	367.75	19,117.75	4	75,000	1,471	76,471
DTIC	0.0348	23.55	Based on the PFLYs for DTIC in Delea et al. Pharmacoeconomics 2015 Apr;33(4):367-80.	66.93	245.17	312.10	8	559	2,047	2,606
Temozolomide	0.0911	23.55	Same as DTIC	26.32	1.94	28.26	86	2,261	167	2,428
Paclitaxel	0.2372	23.55	Same as DTIC	79.96	735.51	815.47	8	668	6,141	6,809
Carboplatin	0.0448	23.55	Same as DTIC	50.43	122.58	173.01	8	421	1,024	1,445
Paclitaxel+ carboplatin	0.2372	23.55	Same as DTIC	102.80	735.51	838.31	8	858	6,141	6,999
	0.0448	23.55	Same as DTIC	40.34	122.58	162.92	8	337	1,024	1,360
Lomustine	0.5695	23.55	Same as DTIC	142.60	13.60	156.20	4	631	60	691
Interferon alfa-2b	4.1550	23.55	Same as DTIC	80.03	0.00	80.03	72	5,774	0	5,774
Vindesine	15.6600	23.55	Same as DTIC	90.49	0.00	90.49	24	2,176	0	2,176
IL-2	101.8182	23.55	Same as DTIC	299.16	61.29	360.46	28	8,377	1,716	10,093
Cisplatin	0.1560	23.55	Same as DTIC	30.05	1,961.36	1,991.40	6	192	12,527	12,719
Vinblastine	1.3000	23.55	Same as DTIC	18.53	0.00	18.53	5	93	0	93
Bleomycin	0.0010	23.55	Same as DTIC	0.03	0.00	0.03	10	0	0	0
Cytarabine	0.0056	23.55	Same as DTIC	0.90	0.00	0.90	10	9	0	9
Denosumab	2.6039	23.55	Same as DTIC	312.46	0.00	312.46	6	1,996	0	1,996
Vincristine	3.0860	23.55	Same as DTIC	8.92	0.00	8.92	24	214	0	214

Bevacizumab	2.3110	23.55	Same as DTIC	1,851.88	367.75	2,219.64	12	22,730	4,514	27,244
Cetuximab	1.7810	23.55	Same as DTIC	1,372.12	490.34	1,862.45	1	1,372	490	1,862
	1.7810	23.55	Same as DTIC	857.57	245.17	1,102.74	24	20,623	5,896	26,519
Gemcitabine	0.0091	23.55	Same as DTIC	17.58	122.58	140.17	6	112	783	895
Trametinib	80.0000	49.30	Same as dabrafenib.	160.00	0.49	160.49	359	57,454	174	57,629
Dabrafenib	0.6667	49.30	Based on PFLYs for dabrafenib from Delea et al. Pharmacoeconomics 2015 Apr;33(4):367-80.	200.00	0.49	200.49	359	71,818	174	71,992
Docetaxel	0.2209	23.55	Same as DTIC	42.55	245.17	287.72	8	355	2,047	2,402
Pembrolizumab	26.3000	28.86	Same as ipilimumab.	4,215.02	122.58	4,337.61	10	42,652	1,240	43,892
Methotrexate	0.0225	23.55	Same as DTIC	311.92	1,471.02	1,782.94	8	2,495	11,768	14,263
Cyclophosphamide	0.0165	23.55	Same as DTIC	19.06	0.00	19.06	24	458	0	458
Etoposide	0.0144	23.55	Same as DTIC	3.32	0.00	3.32	42	139	0	139
Dabrafenib+Trametinib	0.6667	49.30	Same as dabrafenib.	200.00	0.49	200.49	359	71,818	174	71,992
	80.0000	49.30	Same as dabrafenib.	160.00	0.49	160.49	359	57,454	174	57,629
Doxorubicin	0.0955	23.55	Same as DTIC	9.19	306.46	315.65	8	77	2,559	2,636

Costs of all PSACT medications were obtained from the Drugs and Pharmaceutical Electronic Market Information (eMit) database, if available, or the BNF otherwise. When multiple formulations for a single drug were available, the formulation with the lowest cost per mg was used.

The expected costs of PSACT per patient with progression treated with combination is estimated using the mean utilisation of the different PSACTs in the pooled COMBI-v and COMBI-d combination data. For the monotherapies, utilisation is based on indirect treatment comparisons. Costs were then calculated by multiplying the estimated utilisation of each regimen among patients with progression by corresponding estimates of cost per course for each regimen, and summing across regimens. The expected costs of PSACT per patient with progression in each arm of COMBI-v and COMBI-d and are reported in Table 20.

Table 20. Estimated expected costs of PSACT per patient with progression receiving dabrafenib-trametinib, vemurafenib, or dabrafenib in COMBI-v and COMBI-d

A: Trametinib+ dabrafenib combination

PSACT	Cost per course	Mean utilisation	Source	Expected cost (£)
Ipilimumab	76,471.02	0.38	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	29,334.56
Vemurafenib	87,787.30	0.16	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	14,087.08
Dabrafenib	71,992.05	0.08	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	5,872.11
DTIC	2,605.84	0.11	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	290.11
Pembrolizumab	43,892.43	0.08	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	3,580.14
Carboplatin	1,444.53	0.06	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	85.87
Paclitaxel	6,808.66	0.06	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	379.01
Temozolomide	2,428.26	0.05	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	120.78
Trametinib	57,628.52	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	809.41
Cisplatin	12,719.19	0.02	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	281.89

Vinblastine	92.64	0.02	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	1.55
Bleomycin	0.30	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	0.00
Cytarabine	9.02	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	0.06
IL-2	10,092.81	0.00	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	38.15
Methotrexate	14,263.50	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	86.42
Lomustine	691.14	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	5.61
Bevacizumab	27,244.06	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	196.00
Docetaxel	2,402.31	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	34.57
Vincristine	214.41	0.01	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	1.16
Interferon alfa-2b	5,773.53	0.00	Pooled utilisation of PSACT among patients who progress in COMBI-v and COMBI-d.	15.62
Total				**55,220.09***

*In sensitivity analyses, distribution is assumed to be lognormal and SE set at 25% of total.

B: Vemurafenib

PSACT	Cost per course	Mean utilisation	Source	Expected cost (£)
Ipilimumab	76,471.02	0.40	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	30,840.85
Vemurafenib	87,787.30	0.13	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	11,472.31
Dabrafenib	71,992.05	0.19	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	13,747.92

DTIC	2,605.84	0.18	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	478.29
Pembrolizumab	43,892.43	0.08	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	3,689.71
Carboplatin	1,444.53	0.04	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	58.78
Paclitaxel	6,808.66	0.03	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	229.27
Temozolomide	2,428.26	0.08	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	201.80
Trametinib	57,628.52	0.06	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	3,511.91
Cisplatin	12,719.19	0.04	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	523.66
Vinblastine	92.64	0.02	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	2.02
Bleomycin	0.30	0.03	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	0.01
Cytarabine	9.02	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	0.05
IL-2	10,092.81	0.02	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	164.64
Cyclophosphamide	458.27	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	4.26

Etoposide	138.58	0.00	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	0.64
Interferon alfa-2b	5,773.53	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	42.46
Lomustine	691.14	0.04	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	28.10
Vincristine	214.41	0.02	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and V in COMBI-v	5.15
Total				**65,001.83***

*In sensitivity analyses, distribution is assumed to be lognormal and SE set at 25% of total.

C: Dabrafenib

PSACT	Cost per course	Mean utilisation	Source	Expected cost (£)
Ipilimumab	76,471.02	0.48	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	36,829.52
DTIC	2,605.84	0.15	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	392.29
Vemurafenib	87,787.30	0.19	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	16,445.69
Paclitaxel	6,808.66	0.08	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	533.51
Carboplatin	1,444.53	0.05	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	65.15
Temozolomide	2,428.26	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	21.03

Dabrafenib	71,992.05	0.09	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	6,837.63
Cisplatin	12,719.19	0.04	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	465.47
Lomustine	691.14	0.02	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	12.03
Bevacizumab	27,244.06	0.03	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	840.87
Vinblastine	92.64	0.02	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	1.93
Docetaxel	2,402.31	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	29.66
Bleomycin	0.30	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	0.00
Vincristine	214.41	0.00	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	0.72
Interferon alfa-2b	5,773.53	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	45.36
Trametinib	57,628.52	0.03	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	1,817.74
Cetuximab	28,381.40	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	175.19
Doxorubicin	2,635.71	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	16.27

Gemcitabine	895.27	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	5.53
IL-2	10,092.81	0.01	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	100.45
Pembrolizumab	43,892.43	0.11	Calculated based on the utilisation in pooled analysis of COMBI-v and COMBI-d and the difference in utilisation between D+T and D in COMBI-d	4,981.62
Total				**69,617.68**

Appendix 8.20: Quality assessment of de novo cost-effectiveness analysis

Table 21: Summary of the quality assessment of included studies (in this appraisal) based on Drummond's checklist

Drummond's checklist for Economic evaluation studies										
Study Name	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
De novo model	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table 22: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q1-Q2.2)

Study name	Q1	Q1.1	Q1.2	Q1.3	Q2	Q2.1	Q2.2
De novo economic model	Yes; A well-defined question was posed in answerable form	Yes; The study examines both costs and effects of the service	Yes; The study involved comparison of alternatives	Yes; The viewpoint for the analysis was stated. The perspective considered was NHS/PSS perspective	Yes; the description of alternatives was described	No; There was no omission of relevent alternatives	No; Only Active interventions was compared

N: No; NC: Not Clear; Y: Yes; Q1: Was a well-defined question posed in answerable form?; Q1.1: Did the study examine both costs and effects of the service(s) or program(s)?; Q1.2: Did the study involve a comparison of alternatives?; Q1.3: Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?; Q2: Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?; Q2.1: Were there any important alternatives omitted?; Q2.2: Was (should) a do-nothing alternative be considered?

Table 23: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q3-Q4.3)

Study name	3	3.1	3.2	3.3	4	4.1	4.2	4.3
De novo economic model	Yes; The effectiveness of the programme were established	Yes; Data from randomised controlled trials was used.	Yes; The effectiveness was established through an overview of clinical studies	Yes; Observational data or assumptions were used to establish effectiveness	Yes; the impact of all relevant costs and consequences for each alternative were identified	Yes; the range was wide enough for the research question at hand.	Yes; The perspective was clearly stated	Yes; Where relevant all costs were included

Q3: Was the effectiveness of the program or services established?; Q3.1: Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?; Q3.2: Was effectiveness established through an overview of clinical studies?; Q3.3: Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?; Q4: Were all the important and relevant costs and consequences for each alternative identified?; Q4.1: Was the range wide enough for the research question at hand?; Q4.2: Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.); Q4.3: Were the capital costs, as well as operating costs, included?

Table 24: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q5-Q6.4)

Study name	Q5	Q5.1	Q5.2	Q6	Q6.1	Q6.2	Q6.3	Q6.4
De novo economic model	Yes; costs and consequences were measured appropriately	No; there were no omissions from measurement	Yes; market values were applied for costs	Yes; cost and consequences were credibly valued	Yes; The sources of all values were clearly identified	Yes; The costs were discounted at 3.5% per annum.	N/A	Yes; Cost-utility method was used

Q5: Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?; Q5.1: Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?; Q5.2: Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?; Q6: Were the cost and consequences valued credibly?; Q6.1: Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgments); Q6.2: Were market values employed for changes involving resources gained or depleted?; Q6.3: Where market values were absent (e.g. volunteer labor), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?; Q6.4: Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?

Table 25: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q7-Q9.3)

Study name	Q7	Q7.1	Q7.2	Q8	Q8.1	Q9	Q9.1	Q9.2	Q9.3
De novo economic model	Yes; Costs and consequences were adjusted for differential timing	Yes; The costs were discounted at 3.5% per annum.	Yes; discount rate was consistent with NICE reference case	Yes; an incremental analysis was provided	Yes; incremental costs were compared to additional QALYs gained	Yes; allowance was made for uncertainty	Yes;	Yes; Sensitivity analysis was employed	Yes; The results were sensitive to change in values.

Q7: Were costs and consequences adjusted for differential timing?; Q7.1: Were costs and consequences that occur in the future 'discounted' to their present values?; Q7.2: Was there any justification given for the discount rate used?; Q8: Was an incremental analysis of costs and consequences of alternatives performed?; Q8.1: Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?; Q9: Was allowance made for uncertainty in the estimates of costs and consequences?; Q9.1: If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?; Q9.2: If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?; Q9.3: Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

Table 26: Summary of critical appraisal of included studies (in this appraisal) based on Drummond's checklist (Q10-10.5)

Study name	Q10	Q10.1	Q10.2	Q10.3	Q10.4	Q10.5
De novo economic	Yes; the discussion	Yes; conclusions	Yes; results were	Yes; generalisability	Yes; all relevant	Yes; feasibility was

model	includes issues of concern	were based on ICERs	compared with literature where possible	of findings was discussed	factors were discussed	discussed.

Q10: Did the presentation and discussion of study results include all issues of concern to users?; Q10.1: Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?; Q10.2: Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?; Q10.3: Did the study discuss the generalizability of the results to other settings and patient/client groups?; Q10.4: Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?; Q10.5: Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' program given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programs?

References:

1. Johnson et al. Combined BRAF (Dabrafenib) and MEK inhibition (Trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. J.Clin.Oncol. 2014 Nov.;32(33):3697-3704.

2. Delea et al. Cost effectiveness of dabrafenib as a first-line treatment in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in Canada. Pharmacoeconomics. 2015 Apr.;33(4):367-380.

3. pCODR. 2013. Dabrafenib pCODR expert review committee recommendation.

4. pCODR. 2014. Ipilimumab pCODR expert review committee recommendation.

5. pCODR. 2013. Trametinib pCODR expert review committee recommendation.

6. pCODR. 2012. Vemurafenib - pCODR expert review committee recommendation.

7. Curl et al. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. PLoS.One. 2014;9(9):e107255.

8. Shih et al. Targeted Therapies Compared to Dacarbazine for Treatment of BRAF(V600E) Metastatic Melanoma: A Cost-Effectiveness Analysis. J.Skin Cancer 2015; Article ID 5505302.

9. Hillner et al. Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. J.Clin.Oncol. 2000 Apr.;18(7):1474-1480.

10. Barzey et al. Cost-effectiveness of ipilimumab in previously untreated patients for advanced melanoma in Sweden. Value Health 2014;17(7):A642-A643.

11. Delea et al. COST-UTILITY ANALYSIS OF DABRAFENIB/TRAMETINIB COMBINATION (D+T) FOR BRAFV600 MUTATION-POSITIVE METASTATIC MELANOMA (MM) FROM THE UNITED KINGDOM (UK) NATIONAL HEALTH SERVICE (NHS) PERSPECTIVE. Value Health 2014 May;17(3):A88.

12. National Institute for Health and Care ExcellenceIpilimumab for previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance TA319. 2014 July.

13. National Institute for Health and Care ExcellenceDabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. NICE technology appraisal guidance TA321. 2014 Oct.

14. National Institute for Health and Care ExcellenceVemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. NICE technology appraisal guidance 269. 2012 Dec.

15. Lee et al. Cost-effectiveness analysis of ipilimumab in previously untreated patients with unresectable malignant melanoma in Scotland. Value Health 2014;17(7):A549.

16. Scottish Medicines ConsortiumVemurafenib 240mg film-coated tablet (Zelboraf®) SMC No. (792/12). 2013 Nov.

17. Scottish Medicines ConsortiumDabrafenib, 50mg and 75mg hard capsules (Tafinlar®) SMC No. (No.1023/15). 2015 Feb.

18. Ohna et al. Cost-effectiveness of dabrafenib versus dacarbazine (DTIC) in patients with BRAF V600 mutation-positive advanced or metastatic melanoma (BRAF+MM) in Sweden. Society for Melanoma Research (SMR) Congress 2014 2014.

19. Aceituno et al. Cost-effectiveness of ipilimumab for previously untreated patients with advanced metastatic melanoma in Spain. Value Health 2014;17(7):A631.

20. Retel et al. Early cost-effectiveness modeling for tumor infiltrating lymphocytes (TIL)-treatment versus ipilimumab in metastatic melanoma patients. Value Health 2014;17(7):A640.

21. Garrido et al. Cost-efficacy analysis of ipilumumab in Peru. Value Health 2015;18(3):A206.

22. Rovegno et al. Cost-efficacy study for ipilimumab in the chilean market. Value Health 2015;18(3):A201.

23. Osenenko et al. A retrospective longitudinal study of treatment patterns and outcomes among patients with unresectable stage IIIC/IV melanoma in Canada (Melody). Value Health 2011;14(7):A433.

24. Tarhini et al. Impact of adverse events (AEs) on healthcare costs during ipilimumab therapy in advanced melanoma: A US multisite patient chart review. Pigment Cell & Melanoma Research 2014;27(6):1233.

25. Agarwala et al. Efficacy and cost of nab-paclitaxel (nab-P) in metastatic melanoma (mM). Journal of Clinical Oncology 2013;31(15):

26. Chang et al. Comparative healthcare costs in patients with metastatic melanoma in the USA. Melanoma Research 2015;25(4):312-320.

27. Davis et al. Direct economic burden of high-risk and metastatic melanoma in the elderly: evidence from the SEER-Medicare linked database. Appl.Health Econ.Health Policy 2009;7(1):31-41.

28. Tsuchiya et al. Estimating the potential budget impact of zelboraf (vemurafenib) for advanced melanoma treatment in brazilian private health care system. Value Health 2013 May;16(3):A132.

29. Schmerling et al. Melody Brazil-treatment patterns in Brazilian health care system. Value Health 2012 Nov.;15(7):A438-A439.

30. Ondrusova et al. Resource use and health care costs of metastatic malignant melanoma in Slovakia. Value Health 2014;17(7):A630.

31. Maio et al. The cost of unresectable stage III or stage IV melanoma in Italy. Journal of Experimental and Clinical Cancer Research 2012;31(1 Article Number):

32. Bedane et al. Treatment patterns and outcomes in patients with advanced melanoma in France. Curr.Med.Res.Opin. 2013;29(10):1297-1305.

33. Silva et al. Treatment patterns and outcomes among patients with unresectable stage III or stage IV melanoma in Mexico. Value Health 2012 June;15(4):A234.

34. GSK and Novartis. Clinical Study Report (CSR) for BRF113683 (2011N119043_00): A Phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma (Dec 2011 cut-off) . 2012 June.

35. Grob et al. Dabrafenib vs dacarbazine (DTIC) in patients with BRAF V600+ advanced and metastatic melanoma in BREAK-3: Quality of life (QOL) analysis. Pigment Cell and Melanoma Research 2013 Jan.;26(1):152.

36. Grob et al. 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. Ann.Oncol. 2014 July;25(7):1428-1436.

37. Chapman et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N.Engl.J.Med. 2011 June;364(26):2507-2516.

38. GSK and NovartisClinical Study Report (CSR). (2013N176386_00) for MEK115306: A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma (COMBI-d; August 2013 cut-off) . 2014 July.

39. Schadendorf et al. 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. Eur.J.Cancer 2015 May;51(7):833-840.

40. GSK and Novartis. Clinical Study Report (CSR) for MEK114267 (2011N125978_00):MEK114267, a Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutationpositive melanoma (Oct 2011 cut-off). 2012 June.

41. Schadendorf et al. Trametinib (T) vs chemotherapy (C) in patients with BRAF V600E+ metastatic melanoma (MM): Quality of life (QOL) analysis. Pigment Cell and Melanoma Research 2013 Jan.;26(1):154.

42. Schadendorf et al. Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann.Oncol. 2014 Mar.;25(3):700-706.

43. GSK and Novartis. Clinical Study Report (CSR) (2014N210212_00) for MEK116513: A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma (COMBI-v; April 2014 cut-off) . 2015 Jan.

44. Grobb et al. COMBI-v: health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). ESMO 2015.

45. Larkin et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N.Engl.J.Med. 2014 Nov.;371(20):1867-1876.

46. Dreno. Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). Journal of Clinical Oncology 2015;33(S)

47. Robert et al. Nivolumab in previously untreated melanoma without BRAF mutation. N.Engl.J.Med. 2015 Jan.;372(4):320-330.

48. Postow et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N.Engl.J Med. 2015 May;372(21):2006-2017.

49. Avril et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J.Clin.Oncol. 2004 Mar.;22(6):1118-1125.

50. Chiarion-Sileni et al. Quality of life evaluation in a randomised trial of chemotherapy versus bio-chemotherapy in advanced melanoma patients. Eur.J.Cancer 2003 July;39(11):1577-1585.

51. Robert et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N.Engl.J.Med. 2011 June;364(26):2517-2526.

52. Kotapati S et al. Health related quality of life (HRQL) of patients receiving ipilimumba with dacarbazine as first-line treatment for unresectable stage III/IV melanoma. International Melanoma Congress 2011;1037.

53. Middleton et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J.Clin.Oncol. 2000 Jan.;18(1):158-166.

54. Long et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N.Engl.J.Med. 2014 Nov.;371(20):1877-1888 (and supplementary appendix).

55. Robert et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N.Engl.J.Med. 2015 Jan.;372(1):30-39.

56. Long et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015 Aug.;386(9992):444-451 (and supplementary appendix).

57. Robert et al. Two year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib and trametinib with vemurafenib as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. European Cancer Congress 2015 (Vienna, 25-29 September 2015).Oral presentation.Abstract no.3301. 2015 Sept.

58. European Medicines Agency and Committee for Medicinal Products for Human Use (CHMP)Assessment report for Tafinlar + Mekinist. Procedure No. EMEA/H/C/WS/0736. EMA/589140/2015 . 2015 Nov.

59. Hauschild et al. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). Journal of Clinical Oncology 2013;31(15 SUPPL. 1.).

60. McArthur et al. 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. Lancet Oncol. 2014 Mar.;15(3):323-332.

61. Hauschild et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012 July;380(9839):358-365.

62. Grob et al. A Landmark Analysis of 3-year Overall Survival (OS) and Follow-On Therapies in BREAK-3, a Phase III, Randomized Trial: Dabrafenib vs. Dacarbazine (DTIC) in Patients (pts) with BRAF V600E Mutation-Positive Metastatic Melanoma. 2014 Nov.

63. Bagust and BealeSurvival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med.Decis.Making 2014 Apr.;34(3):343-351.

64. Maio et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol 2015 Apr.;33(10):1191-1196.

65. Maio et al. Four-year survival update for metastatic melanoma (MM) patients (PTS) treated with ipilimumab (IPI) + dacarbazine (DTIC) on phase 3 study CA184-024. Asia-Pacific Journal of Clinical Oncology 2012;8 SUPPL. 3303.

66. Prieto et al. CTLA-4 blockade with ipilimumab: Long-term follow-up of 177 patients with metastatic melanoma. Clinical Cancer Research 2012;18(7):2039-2047.

67. Schadendorf et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J.Clin.Oncol. 2015 June;33(17):1889-1894.