Appendix

Appendix 1. Search Methods

Databases: Ovid MEDLINE(R), Embase (Ovid), Cochrane Central Register of Controlled Trials (Central), Web of Science, PubMed, Google scholar.
Date: 2015.02.12.-16. (all searches)
Update: 2015.09.25. (all searches)
Year of publication: 2000-2015
Results: 621 references (2015.02.16.)
83 references (2015.09.25.)
Study design: Randomized controlled trials searched by using Ovids search filter "therapy (maximizes specificity)" and search filters for RCT's from Cochrane Handbook, chapter 6.4.11.1/2.
Searched by: Ingrid Harboe, research librarian

Search strategies:

Databases (federated search):
Embase 1974 to 2015 Week 06
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present

Codes used for subject headings:
Embase: oemez
MEDLINE: pmoz

#	Searches	Results
1	Melanoma/	166646
2	Metastatic melanoma/ use oemez	3401
3	((malignant or metasta* or advanced) adj6 (melanoma* or neoplasm* or tumo*r* or cancer*)).tw.	778494
4	((unresectable or inoperable) adj6 (melanoma* or neoplasm* or tumo*r* or cancer*)).tw.	22486
5	or/1-4	882325

6	ipilimumab/ use oemez	3407
7	pembrolizumab/ use oemez	160
8	nivolumab/ use oemez	549
9	cobimetinib/ use oemez	102
10	vemurafenib/ use oemez	2908
11	trametinib/ use oemez	884
12	dabrafenib/ use oemez	965
13	(Ipilimumab* or Pembrolizumab* or Nivolumab* or Cobimetinib* or Vemurafenib* or Trametinib* or Dabrafenib*).tw.	4502
14	or/6-13	7925
15	5 and 14	6043
16	exp animals/	37527209
17	humans/	29052404
18	16 not (16 and 17)	8474805
19	15 not 18	5984
20	randomized controlled trial.pt. use pmoz	384806
21	controlled clinical trial.pt. use pmoz	88621
22	randomized.ab. use pmoz	309240
23	placebo.ab. use pmoz	158103
24	clinical trials as topic.sh. use pmoz	170815
25	randomly.ab. use pmoz	224068
26	trial.ti. use pmoz	133103
27	or/20-26	935733
28	19 and 27	198
29	randomized controlled trial/ use oemez	361660

30	crossover-procedure/ use oemez	41457
31	double-blind procedure/ use oemez	120141
32	single-blind procedure/ use oemez	19436
33	randomized.ab. use oemez	414908
34	placebo.ab. use oemez	205278
35	randomly.ab. use oemez	280688
36	trial.ti. use oemez	175027
37	or/29-36	969327
38	37 and 19	507
39	limit 19 to "therapy (maximizes specificity)"	185
40	28 or 38 or 39	718
41	limit 40 to yr="2000 -Current"	718
42	remove duplicates from 41	606

Database: Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Melanoma] explode all tree	1122
#2	((malignant or metasta* or advanced) near/6 (melanoma* or neoplasm* or tumo*r* or cancer*)):ti,ab,kw	21000
#3	((unresectable or inoperable) near/6 (melanoma* or neoplasm* or tumo*r* or cancer*)):ti,ab,kw	1079
#4	#1 or #2 or #3	21930
#5	(Ipilimumab* or Pembrolizumab* or Nivolumab* or Cobimetinib* or Vemurafenib* or Trametinib* or Dabrafenib*):ti,ab,kw	150
#6	#4 and #5	125

Database: PubMed

Search:
(((((((("advanced melanoma*"[Title/Abstract] OR "unresectable melanoma*"[Title/Abstract] OR "inoperable melanoma*"[Title/Abstract])))) OR (("malignant melanoma*" OR "metasta* melanoma*"[Title/Abstract]))) OR "melanoma"[MeSH Major Topic]))
AND
((Ipilimumab*[Title/Abstract] OR Pembrolizumab*[Title/Abstract] OR Nivolumab*[Title/Abstract] OR Cobimetinib*[Title/Abstract] OR Vemurafenib*[Title/Abstract] OR Trametinib*[Title/Abstract] OR Dabrafenib*[Title/Abstract])))
AND
Pubstatusaheadofprint

Database: Web of Science

Set	Results	
# 5	72	#5 AND #4 Refined by: Databases: (WOS) AND DOCUMENT TYPES: (CLINICAL TRIAL) Timespan=2000-2015 Search language=Auto
# 4	1,139	#3 AND #2 AND #1 Timespan=All years Search language=Auto
# 3	Approximately 20,433,548	TOPIC: (trial) OR TITLE: (trial) OR TOPIC: (study) OR TITLE: (study) Timespan=All years Search language=Auto
# 2	Approximately 5,365	TOPIC: ((Ipilimumab* or Pembrolizumab* or Nivolumab* or Cobimetinib* or Vemurafenib* or Trametinib* or Dabrafenib*)) OR TITLE: ((Ipilimumab* or Pembrolizumab* or Nivolumab* or Cobimetinib* or Vemurafenib* or Trametinib* or Dabrafenib*)) Timespan=All years Search language=Auto
# 1	Approximately 95,539	TOPIC: (malignant melanoma) OR TITLE: (malignant melanoma) OR TOPIC: (metastatic melanoma) OR TITLE: (metastatic melanoma) Timespan=All years Search language=Auto

Source: Google Scholar

Search: All relevant drugs (seven) combined separately with "malignant metastatic melanoma" Anywhere in the article
Published: 2000-2015

Health Technology Assessment agencies (Appendix 3)

Search for ongoing studies (Appendix 4)

Appendix 2. Excluded trials

Excluded trials from our search, and the reasons for the exclusions

1. Improved survival ends nivolumab trial early. Cancer Discov 2014;4(9):979-980.
   Not RCT

2. Anonymous. Trial watch: ipilimumab success in melanoma provides boost for cancer immunotherapy. Nature Reviews Drug Discovery 2010;9(8):584.
   Not RCT

3. Anonymous. Vemurafenib (Zelboraf) for metastatic melanoma. Med Lett Drugs Ther 2011;53(1374):77-78.
   Not RCT

4. Anonymous. Ipilimumab. Immunostimulant; more assessment needed. Prescrire Int 2012;21(128):145-147.
   Not RCT

5. Chapman PB, Hauschild A, Robert C, Larkin JMG, Haanen J, Ribas A, et al. Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with V600EBRAF-mutated melanoma. J Clin Oncol 2011;29(18 suppl. 1).
   Similar results as in Chapman 2011, BRIM-3, full text, as we have included.

6. Chmielowski B, Hamid O, Minor DR, D'Angelo SP, Pennock GK, Grossmann K, et al. A phase III open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice in advanced melanoma patients progressing post anti-CTLA-4 therapy. J Clin Oncol 2013;1).
   No results

7. Coens C, Suciu S, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, et al. Phase III trial (EORTC 18071/CA184029) of postoperative adjuvant ipilimumab compared to placebo in patients with resected stage III cutaneous melanoma: Health related quality of life (HRQoL) results. Pigment Cell and Melanoma Research 2014;27 (6):1181-1182.
   Inappropiate population

8. Collichio F, Milhem MM, Andtbacka RHI, Puzanov I, Saenger Y, Chesney J, et al. A phase 1b/2 multicenter, open-label trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) versus ipi alone in previously untreated, unresected, stage IIIB-IV melanoma. Pigment Cell and Melanoma Research 2014;27 (6):1172.
   Inappropiate control

9. Curl P, Vujic I, t Veer LJ, Ortiz-Urda S, Kahn JG. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. PLoS One 2014;9(9).
   Inappropiate endpoints

10. Dales MJM. First-line ipilimumab bests placebo in trial using DTIC. Oncology Report 2011(JULY-AUGUST):30.
    Not RCT

11. Grob J, Algarra SM, Amonkar MM, Demidov LV, Goodman VL, Grotzinger K, 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;26 (1):152.
Abstract from meeting. We use Grob 2014 instead.

12. Haanen JB, Hodi FS, O'Day SJ, McDermott DF, Robert C, Schadendorf D, et al. Ipilimumab improves overall survival in patients with previously treated, advanced melanoma: Long-term survival results from a phase III trial. Ann Oncol 2010;21:viii402.
Abstract with similar data as in the full text publication, Hodi 2010, NCT 00094653, as we have included

13. Hamid O. Dose effect of ipilimumab in patients with advanced melanoma: Results from a phase II, randomized, dose-ranging study [abstract no. 9025]. Journal of Clinical Oncology: ASCO annual meeting proceedings 2008;26(15S part I):489.
Dose comparisons

14. Hamid O, Robert C, Ribas A, Wolchok JD, Hodi FS, Kefford R, et al. Randomized comparison of two doses of the anti-PD-1 monoclonal antibody MK-3475 for ipilimumab-refractory (IPI-R) and IPI-naive (IPI-N) melanoma (MEL). J Clin Oncol 2014;1).
Dose comparisons

15. Hamid O, Schmidt H, Nissan A, Ridolfi L, Aamdal S, Hansson J, et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. J Transl Med 2011;9(1).
Dose comparisons

16. Hammers HJ, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, et al. Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). J Clin Oncol 2014;1).
Inappropiate population

17. Harvey B, Lee D, Gaudin AF, Gueron B, Bregman B, Lebbe C, et al. Changes in the quality of life of advanced melanoma patients after 12 weeks of treatment with ipilimumab compared to gp100 in a phase III clinical trial. J Clin Oncol 2013;1).
We use Revicki 2012 instead (full text)

18. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Phase III, randomized, open-label, multicenter trial (BREAK-3) comparing the BRAF kinase inhibitor dabrafenib (GSK2118436) with dacarbazine (DTIC) in patients with BRAFV600E-mutated melanoma. J Clin Oncol 2012;1).
Use Hauschild in Lancet 2012 instead

19. Hersey P, Wolchock JD, Thomas L, Bondarenko IN, O'Day S, Weber J, et al. A second randomised ipilimumab phase III trial shows significant survival improvement in metastatic melanoma. Asia Pac J Clin Oncol 2011;7:111.
Use Robert 2011 instead

20. Hersh E, Weber J, Powderly J, Pavlik A, Nichol G, Yellin M, et al. Long-term survival of patients (pts) with advanced melanoma treated with

ipilimumab with or without dacarbazine. J Clin Oncol 2009;1):9038.
Not RCT

21. Hersh EM, Weber JS, Powderly JD, Khan K, Pavlick AC, Samlowski WE, et al. Disease control and long-term survival in chemotherapy-naive patients with advanced melanoma treated with ipilimumab (MDX- 010) with or without dacarbazine [abstract no. 9022]. Journal of Clinical Oncology: ASCO annual meeting proceedings 2008;26(15S part I):488.
Use Hersh 2011 instead

22. Hodi FS, Baudelet C, Chen AC, Weber JS. An open-label, randomized, phase II study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) given sequentially with ipilimumab in patients (pts) with advanced or metastatic melanoma (MEL). J Clin Oncol 2013;1).
Use Hersh 2011 instead

23. Hodi FS, Lee S, McDermott DF, Rao UN, Butterfield LH, Tarhini AA, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. JAMA 2014;312(17):1744-1753.
Inappropiate population

24. Hodi FS, Lee SJ, McDermott DF, Rao UNM, Butterfield LH, Tarhini AA, et al. Multicenter, randomized phase II trial of GM-CSF (GM) plus ipilimumab (Ipi) versus Ipi alone in metastatic melanoma: E1608. J Clin Oncol 2013;1).
Not our focus

25. Hodi FS, O'Day S, McDermott DF, Haanen JB, Robert C, Zhu X, et al. Re-induction with ipilimumab, gp100 peptide vaccine, or a combination of both from a phase III, randomized, double-blind, multicenter study of previously treated patients with unresectable stage III or IV melanoma. J Clin Oncol 2010;1).
No subanalysis

26. Infante JR, Falchook GS, Lawrence DP, Weber JS, Kefford RF, Bendell JC, et al. Phase I/II study to assess safety, pharmacokinetics, and efficacy of the oral MEK 1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral BRAF inhibitor GSK2118436 (GSK436). J Clin Oncol 2011;1).
Study not finalized

27. Jackson J, Whitney G, Hamid O, Schmidt H, Chasalow SD, Alaparthy S, et al. Assessment of association between BRAF mutation status in melanoma tumors and response to ipilimumab. J Clin Oncol 2011;1).
Not our focus

28. Jamal R, Belanger K, Friedmann JE, Ayoub JPM, Cocolakis E, Kazemi S, et al. A randomized phase II study of ipilimumab (IPI) with carboplatin and paclitaxel (CP) in patients with unresectable stage III or IV metastatic melanoma (MM). J Clin Oncol 2014;1).
Inappropiate endpoint

29. Kaufman H, Lutzky J, Clark J, Margolin KA, Lawson DH, Amin A, et al. Safety and efficacy of ipilimumab in melanoma patients who received prior immunotherapy on phase III study MDX010-020. J Clin Oncol 2013;31(15 suppl. 1).
Inappropiate endpoint

30. Kim G, McKee AE, Ning YM, Hazarika M, Theoret M, Johnson JR, et al. FDA approval summary: Vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation mutation. Clin Cancer Res 2014;20(19):4994-5000.
Not RCT

31. Latimer N, Abrams KR, Amonkar M, Stapelkamp C, Swann RS. Adjusting for treatment crossover in the BREAK-3 metastatic melanoma trial for dabrafenib: Preliminary analysis. J Clin Oncol 2013;31(15 suppl. 1).
Not our focus

32. Latimer N, Amonkar M, Stapelkamp C, Sun P. Adjusting for confounding effects of treatment crossover in a randomized phase 2 study of dabrafenib plus trametinib in BRAF V600+ metastatic melanoma. Cancer Res 2014;1).
Inappropiate endpoint

33. Lebbe C, Hoos A, Chin K, Li J, Neyns B, Linette G, et al. Effect of dose on efficacy and safety in ipilimumab-treated patients with advanced melanoma - Results from a phase II, randomized, dose-ranging study. Ann Oncol 2008;19 (S8):viii239-viii240.
Dose comparison

34. Lebbe C, McDermott DF, Robert C, Lorigan P, Ottensmeier CH, Wolchok J, et al. Ipilimumab improves survival in previously treated, advanced melanoma patients with poor prognostic factors: Subgroup analyses from a phase III trial. Ann Oncol 2010;21:viii401.
Not our focus

35. Lebbe C, Weber J, Maio M, Neyns B, Harmankaya K, Chin K, et al. Five-year survival rates for patients (PTS) with metastatic melanoma (MM) treated with ipilimumab (IPI) in phase II trials. Asia Pac J Clin Oncol 2012;8:309.
Not RCT

36. Lee B, Mukhi N, Liu D. Current management and novel agents for malignant melanoma. J Hematol Oncol 2012;5:3.
Not RCT

37. Lewis KD, Maio M, Mandala M, Nelson BJ, Goodman GR, Schadendorf D. BRIM8: A phase III, randomized, double-blind, placebo-controlled study of vemurafenib adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk for recurrence (NCT01667419). J Clin Oncol 2014;1).
Inappropiate population

38. Long GV, Stroyakovsky DL, Gogas H, Levchenko E, De Braud F, Larkin JMG, et al. COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAFV600E/Kmutation-positive cutaneous melanoma. J Clin Oncol 2014;1).
Use Long 2014 full text instead

39. Maio M, Bondarenko I, Robert C, Thomas L, Garbe C, Testori A, et al. Survival analysis with 5 years of follow-up in a phase III study of ipilimumab and dacarbazine in metastatic melanoma. Eur J Cancer 2013;49:S857.
Use Maio 2015 full text instead

40. Maio M, Lebbe C, Chiarion Sileni V, Siegel J, Hoos A, Humphrey R, et al. Long-term survival in advanced melanoma patients treated with ipilimumab at 10mg/kg: Ongoing analyses from completed Phase II trials. European Journal of Cancer, Supplement 2009;7 (2-3):578.
Inappropiate control

41. McArthur G, Hauschild A, Robert C, Larkin J, Haanen JB, Ribas A, et al. Efficacy of vemurafenib in BRAFV600K mutationpositive melanoma disease-results from the phase 3 clinical study BRIM3. Pigment Cell and Melanoma Research 2012;25 (6):871.
Not our focus

42. McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol 2013;24(10):2694-2698.
Not our focus

43. O'Day S, Hodi FS, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma. J Clin Oncol 2010;1).
Use Hodi 2010 full text instead

44. O'Day SJ, McDermott DF, Urba WJ, Wolchok JD, Robert C, Haanen JB, et al. Ipilimumab improves overall survival in previously treated, advanced melanoma patients with good and poor prognostic factors. J Immunother 2010;33 (8):905-906.
Not our focus

45. Ottensmeier C, Weber R, Haanen JB, Robert C, Schadendorf D, Lutzky J, et al. Ipilimumab produces durable objective responses in patients with previously treated, advanced melanoma: Results from a phase III trial. Ann Oncol 2010;21:viii401-viii402.
Use Hodi 2010 full text instead

46. Patrawala S, Puzanov I. Vemurafenib (RG67204, PLX4032): a potent, selective BRAF kinase inhibitor. Future Oncology 2012;8(5):509-523.
Not RCT

47. Porter J, Lee D, Hertel N, Hatswell AJ. Patient reported utilities in first-line advanced or metastatic melanoma: Analysis of trial CA 184-024. Value Health 2014;17 (7):A569.
Not our focus

48. Revicki D, Kotapati S, Van Den Eertwegh AJ, Lorigan P, Linette G, Ottensmeier CH, et al. Health related quality of life (HRQL) outcomes of ipilimumab treatment in patients with previously treated unresectable stage III or iv melanoma (USIII/IV MEL). Ann Oncol 2010;21:viii402-viii403.
Use Revicki 2012 full text instead

49. Revicki D, Kotapati S, Villanueva I. Impact of ipilimumab on the health-related quality of life (HRQL) of patients with previously treated unresectable stage III or IV melanoma. European Journal of Cancer, Supplement 2009;7 (2-3):581.

Not RCT

50. Robert C, Antonio Ascierto P, Maio M, Hernberg M, Schmidt H, Waxman I, et al. A phase III, randomized, double-blind study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus dacarbazine in patients (pts) with previously untreated, unresectable, or metastatic melanoma (MEL). J Clin Oncol 2013;1).
No results

51. Robert C, Flaherty KT, Hersey P, Nathan PD, Garbe C, Milhem MM, et al. METRIC phase III study: Efficacy of trametinib (T), a potent and selective MEK inhibitor (MEKi), in progression-free survival (PFS) and overall survival (OS), compared with chemotherapy (C) in patients (pts) with BRAFV600E/K mutant advanced or metastatic melanoma (MM). J Clin Oncol 2012;1).
Use Flaherty 2012, METRIC full text instead

52. Robert C, Hodi FS, O'Day SJ, Peschel C, Ottensmeier CH, Trefzer U, et al. Re-induction with ipilimumab, GP100 peptide vaccine, or a combination of both in a phase III study of previously-treated patients with advanced melanoma: Update of clinical characteristics of patients. Ann Oncol 2010;21:viii403-viii404.
Not our focus, subanalyses

53. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384(9948):1109-1117.
Dose comparisons

54. Robert C, Schadendorf D, Messina M, Hodi FS, O'Day S, Investigators MDX. Efficacy and Safety of Retreatment with Ipilimumab in Patients with Pretreated Advanced Melanoma Who Progressed after Initially Achieving Disease Control. Clin Cancer Res 2013;19(8):2232-2239.
Subanalyses

55. Robert C, Thomas L, Garbe C, Lebbe C, Baurain JF, Testori A, et al. Phase 3 randomized study of Ipilimumab (IPI) plus dacarbazine (DTIC) vs DTIC alone as first line treatment in patients with unresectable stage III or IV Melanoma. Eur J Cancer 2011;47:S657-s658.
Use Robert 2011 full text instead

56. Schadendorf D, Maio M, Mandala M, Nelson BJ, Goodman GR, Lewis KD. BRIM8: A Phase 3, randomized, double-blind, placebocontrolled study of vemurafenib (VEM) adjuvant therapy in patients with surgically resected, cutaneous BRAFmutant melanoma at high risk for recurrence (nct01667419). Pigment Cell and Melanoma Research 2014;27 (6):1226.
Inappropiate population

57. Schadendorf D, Milhem M, Demidov LV, Rutkowski P, Garbe C, Dummer R, 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;26 (1):154.
Use Schadendorf 2014 full text instead

58. Thomas L, Wolchok JD, Garbe C, Lebbe C, Bondarenko I, Rodrigues K, et al. Safety of ipilimumab in patients (pts) with untreated, advanced melanoma alive beyond 2 years: Results from a phase III study. J Clin

Oncol 2012;30(15 suppl. 1).
Subanalyses

59. Thompson JA. Effect of prior treatment status on the efficacy and safety of ipilimumab monotherapy in treatment-naive and previously treated patients with advanced melanoma [abstract no. 9055]. Journal of Clinical Oncology: ASCO annual meeting proceedings 2008;26(15S part I):496.
Inappropiate endpoints

60. Veenstra DL, Wong W, Reyes C. Budget impact modeling of vemurafenib for treatment of metastatic melanoma. J Manag Care Pharm 2012;18 (2):163.
Not our focus

61. Weber J, Thompson JA, Hamid O, Minor D, Amin A, Ron I, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 2009;15(17):5591-5598.
Inappropiate control

62. Weber JS, Berman D, Siegel J, Minor D, Maraveyas A, Hamid O. Clinical activity of ipilimumab in patients with advanced melanoma and brain metastases. Ann Oncol 2008;19 (S8):viii244.
Inappropiate control

63. Weber JS, Hamid O, Wolchok J, Amin A, Masson E, Goldberg S, et al. Assessment of pharmacokinetic interaction between ipilimumab and chemotherapy in a randomized study. Ann Oncol 2010;21:viii403.
Not our focus, interaction

64. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. The Lancet Oncology 2010;11(2):155-164.
Dose comparison

65. Wolchok JD, Thomas L, Bondarenko IN, O'Day S, Weber JS, Garbe C, et al. Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma. J Clin Oncol 2011;29(18 suppl. 1).
No we use Robert 2011 full text instead

66. Young K, Minchom A, Larkin J. BRIM-1, -2 and -3 trials: Improved survival with vemurafenib in metastatic melanoma patients with a BRAFV600E mutation. Future Oncol 2012;8(5):499-507.
Not RCT

Excluded trials from the ones received from the manufactures, and the reasons for the exclusions

1. Ascierto PA, et al. A phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAF(V600) mutation–positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519). J Transl Med 2015;13(Suppl 1):O4-

O4.
Inappropiate population

2. Ascierto PA, Simeone E, Sileni VC, Vecchio MD, Marchetti P, Cappellini GCA, et al. Sequential treatment with ipilimumab and BRAF inhibitors in patients with metastatic melanoma: Data from the Italian cohort of the ipilimumab expanded access program. Cancer Invest 2014;32(4):144-149.
Not RCT

3. Atkins M, et.al. Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): Data from the KEYNOTE-029 phase 1 study. American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 3009.
Not RCT

4. Brahmer JR, et al. Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J Clin Oncol 2010;28(19):3167-3175.
Not RCT

5. Chmielowski B, et.al. A Phase 3 Open-label Study of Nivolumab (Anti-PD-1; BMS-936558; ONO-4538) vs Investigator's Choice in Advanced Melanoma Patients Progressing Post Anti-CTLA-4 Therapy. American Society of Clinical Oncology 2013;Annual Meeting:Poster.
No results (this we also had from our own search)

6. Cruz-Merino L, et.al. Clinical features of cobimetinib (COBI)–associated serous retinopathy (SR) in BRAFmutated melanoma patients (pts) treated in the coBRIM study. J Clin Oncol 2015;33(Suppl; abstr 9033).
Exclude, do not have specific data for serious AEs

7. Daud A, et.al. Pyrexia in patients (Pts) treated with dabrafenib (D) and trametinib (T) for BRAFV600 mutation-positive metastatic melanoma (MM). Pigment Cell & Melanoma Research. Society for Melanoma Research (SMR) 2013;26:932-1019.
Only sub-analyis of adverse events

8. Daud A, et.al. Updated Clinical Efficacy of the Anti-PD-1 Monoclonal Antibody Pembrolizumab in 411 Patients With Melanoma. Society for Melanoma Research (SMR) 2014:Poster.
Inappropiate comparator

9. Daud A, et.al. Long-term efficacy of pembrolizumab (pembro; MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma (MEL) enrolled in KEYNOTE-001. A. American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 9005.
Dose comparison

10. Dronca RS, et.al. Bim as a predictive T-cell biomarker for response to anti-PD-1 therapy in metastatic melanoma (MM). J Clin Oncol 2015;33(Suppl; abstr 9013).
Not RCT

11. Dummer R, et.al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory melanoma. J Transl Med 2015;13(Suppl 1 (oral presentation)):O5-O5.
Inappropiate population, includes from 15 years

12. Flaherty K, Daud A, Weber JS, Sosman JA, Kim K, Gonzalez R, et al. Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM). J Clin Oncol 2014;1).
We had already included this

13. Gangadhar TC, et.al. Population pharmacokinetic (popPK) model of pembrolizumab (pembro; MK-3475) in patients (pts) treated in KEYNOTE-001 and KEYNOTE-002. American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 3058.
Inappropiate endpoint (pharmacokinetic)

14. Grossman K, et.al. A phase III randomized trial comparing high dose interferon to pembrolizumab in patients with high risk resected melanoma. J Clin Oncol 2015;33(Suppl; abstr TPS9085).
Inappropiate population (≥15 years)

15. Hamid O, et.al. Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma. N Engl J Med 2013;369(2):134-144.
Not RCT

16. Han K, et.al. Population pharmacokinetics and dosing implications for cobimetinib in patients with solid tumors. J Clin Oncol 2015;33(Suppl; abstr 2573).
Not RCT

17. Hauschild A, 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). J Clin Oncol 2013;1).
This with already had included

18. Hersey P, Gowrishankar K. Pembrolizumab joins the anti-PD-1 armamentarium in the treatment of melanoma. Future Oncology 2015;11(1):133-140.
Not RCT

19. Hodi S, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP, et al. Long-term survival of ipilimumab-naive patients with advanced melanoma (MEL) treated with nivolumab (anti-programmed death-1; ANTI-PD-1; BMS-936558; ONO-4538) in a phase i trial. Asia Pac J Clin Oncol 2014;10:177.
Not RCT

20. Johnson DB, et.al. Survivorship in Immune Therapy: Assessing Chronic Immune Toxicities, Health Outcomes, and Functional Status among Long-term Ipilimumab Survivors at a Single Referral Center. Cancer Immunology Research 2015;3(5):6.
Not RCT

21. Joseph R, et.al. Model-based analysis of the relationship between pembrolizumab (MK-3475) exposure and efficacy in patients with advanced or metastatic melanoma. American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 3068.
Not RCT

22. Kibiro M, et.al. Patterns of response to anti-PD1 treatment: Comparison of three radiological response criteria and effect on overall survival (OS) in metastatic melanoma patients (MM). J Clin Oncol 2015;33(Suppl; abstr 9073).

Not RCT

23. Kluger H, et.al. Safety and activity of pembrolizumab in melanoma patients with untreated brain metastases. J Clin Oncol 2015;33(Suppl; abstr 9009).

Not RCT

24. Kluger HM, Sznol M, Callahan MK, Postow MA, Gordon RA, Segal NH, et al. Survival, response duration, and activity by BRAF mutation status in a phase 1 trial of nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab concurrent therapy in advanced melanoma (MEL). Pigment Cell and Melanoma Research 2014;27 (6):1203.

Not RCT

25. Kottschade LA, et.al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. J Clin Oncol 2015;33(Suppl; abstr 9010).

Inappropiate population (≥12 years)

26. Larkin J, et.al. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. Lancet Oncol 2014;15(4):436-444.

Not RCT

27. Lebbe C, et.al. Survival follow-up and ipilimumab retreatment of patients with advanced melanoma who received ipilimumab in prior phase II studies. Ann Oncol 2014;25(11):2277–2284.

No control group

28. Margolin K, et.al. Effectiveness and Safety of First-Line Ipilimumab for Advanced Melanoma: A U.S. Multisite Retrospective Chart Review. International Meeting of the Society for Melanoma Research 2013:Poster.

Not RCT

29. Mathias SD, et.al. Health Care Resource Use of Individuals With Unresectable or Metastatic Melanoma: Preliminary Results From IMAGE Study. Society for Melanoma Research (SMR) 2014:Poster.

Not RCT

30. McDermott D, et.al. Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma. Cancer Treatment Rewies 2014;40:1056–1064.

Not RCT

31. McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol 2013;24(10):2694-2698.

Sub analyses

32. Merck. KEYTRUDA® (pembrolizumab), Merck's Anti-PD-1 Therapy, Demonstrates Superior Survival, Progression Free Survival and Overall Response Rate Compared to Ipilimumab, an Anti-CTLA-4 Therapy, in a Phase 3 Study of Patients with Advanced Melanoma. Merck news release 2015.

Use Robert 2015 instead

33. Middleton M, et.al. Initial Results from IMAGE: A Multinational, Prospective, Observational Study in Patients with Advanced Melanoma. Society for Melanoma Research (SMR) 2013;Annual meeting:Poster.

Not RCT

34. MSD Oncology. Randomized Comparison of Two Dosing Schedules. Cohort B3. European Society for Medical Oncology (ESMO) 2014:Oral presentation (Keynote-001).
No inappropriate intervention/control

35. Munhoz R, et.al. Investigation of intrapatient heterogeneity in the tumor infiltrating T cell repertoire in patients with metastatic melanoma treated with pembrolizumab. J Clin Oncol 2015;33(Suppl; abstr 9075).
Not RCT

36. Patt DA, et.al. A Real-World Observational Study of Patients with Advanced Melanoma Receiving First-line Ipilimumab in a Community Practice Setting. Joural of Cancer Therapy 2014;5:1049-1058.
Not RCT

37. Pavlick AC, et.al. Extended followup results of phase Ib study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in BRAFmutant melanoma. J Clin Oncol 2015;33(Suppl; abstr 9020).
Not RCT

38. Poole RM. Pembrolizumab: First Global Approval. Drugs 2014;74:1973–1981.
Not RCT

39. Porter J, Lee D, Hertel N, Hatswell AJ. Patient reported utilities in first-line advanced or metastatic melanoma: Analysis of trial CA 184-024. Value Health 2014;17 (7):A569.
Not our focus

40. Prieto PA, et.al. CTLA-4 Blockade with Ipilimumab: Long-term Follow-up of 177 Patients with Metastatic Melanoma. Clin Cancer Res 2012:2039-2047.
Not RCT

41. Puzanov I, et.al. Efficacy based on tumor PD-L1 expression in KEYNOTE-002, a randomized comparison of pembrolizumab (pembro; MK-3475) versus chemotherapy in patients (pts) with ipilimumab-refractory (IPI-R) advanced melanoma (MEL). American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 3012.
We use Ribas 2015 full text instead

42. Ribas A, et.al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory melanoma. Society for Melanoma Research (SMR) 2014:Poster.
Use Ribas 2015 full text instead

43. Ribas A, et.al. Efficacy and Safety of the Anti-PD-1 Monoclonal Antibody Pembrolizumab (MK-3475) in 411 Patients With Melanoma. Annual Meeting of American Society Of Clinical Oncology (ASCO) 2014:Poster.
Inappropiate intervention/control

44. Ribas A, et.al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. Lancet Oncol 2014;15(9):954-965.
Not RCT

45. Ribas A, et.al. Phase III study of pembrolizumab (MK-3475) versus ipilimumab in patients with ipilimumab-naive advanced melanoma. Keynote-006. American Association for Cancer Research (AACR) 2015:Poster (Keynote 006).

Use Robert 2015 instead

46. Ribas A, et.al. Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 3001.

Not our focus

47. Ribas A, et.al. A multicenter, open-label trial of talimogene laherparepvec (T-VEC) plus pembrolizumab vs pembrolizumab monotherapy in previously untreated, unresected, stage IIIB-IV melanoma. J Clin Oncol 2015;33(Suppl; abstr TPS9081).

Not RCT

48. Robert C, et.al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. N Engl J Med 2014; 372:320-330.

This we had already included

49. Robert C, et.al. Association of immune-related thyroid disorders with pembrolizumab (pembro, MK-3475) in patients (pts) with advanced melanoma treated in KEYNOTE-001. American Society of Clinical Oncology (ASCO) 2015;Annual Meeting(Abstract 9050).

Inappropiate endpoint

50. Schadendorf D, 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;33:1-7.

Not RCT

51. Schadendorf D, et.al. Patient-reported outcomes (PROs) in KEYNOTE-002, a randomized study of pembrolizumab vs chemotherapy in patients (pts) with ipilimumab-refractory (IPI-R) metastatic melanoma (MEL). American Society of Clinical Oncology (ASCO) 2015;Annual Meeting(Abstract 9040).

We use Ribas 2015 full text instead

52. Sherill B, Wang J, Kotapati S, Chin K. Q-TWiST analysis comparing ipilimumab/dacarbazine vs placebo/dacarbazine for patients with stage III/IV melanoma. Br J Cancer 2013;109:8-13.

Inappropiate endpoint

53. Sosman JA, et.al. An Exploratory Study of the Biologic Effects of Nivolumab (Anti-PD-1; BMS-936558; ONO-4538) Treatment in Patients With Advanced (Unresectable or Metastatic) Melanoma. American Society of Clinical Oncology (ASCO) 2013;Annual Meeting:Poster.

Not RCT

54. Topalian SL, et.al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med 2012;366(26):2443-2454.

Not RCT

55. Topalian SL, et.al. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol 2014;32(10):1020-1031.

Not RCT

56. Tsai K, et.al. Clinical characteristics predictive of response to pembrolizumab in advanced melanoma. J Clin Oncol 2015;33(Suppl; abstr 9031).

Not RCT

57. Weber J, et.al. A Phase 3 Randomized, Open-Label Study of Nivolumab (Anti-PD-1; BMS-936558; ONO-4538) Versus Investigator's Choice Chemotherapy (ICC) in Patients With Advanced Melanoma With Prior Anti-CTLA-4 Therapy. European Society for Medical Oncology (ESMO) 2014:Abstract 7218.

58. Wolchock JD, et.al. Nivolumab plus Ipilimumab in Advanced Melanoma N Engl J Med 2013;369:122-133.
Not RCT

59. Wolchock JD, et.al. Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials. Ann Oncol 2013;24:2174–2180.
Not RCT

60. Wolchok JD, et.al. Atypical patterns of response in patients (pts) with metastatic melanoma treated with pembrolizumab (MK-3475) in KEYNOTE-001. American Society of Clinical Oncology (ASCO) Annual Meeting 2015:Abstract 3000.
Dose comparisons

61. Zaretsky J, et.al. TCR use and cytokine response in PD-1 blockade. J Clin Oncol 2015;33(Suppl; abstr 3027).
Not RCT

Appendix 3. Literature search, Health Technology Assessment agencies

Literature search, HTA agencies

AHRQ - Agency for Healthcare Research and Quality, USA
Results: 1 reference

ASERNIP-S – Australian Safety and Efficacy Register of New Interventional Procedures-Surgical, Australia
Results: No unique references

CADTH - Canadian Agency for Drugs and Technologies in Health
Results: 4 references

IQWIG - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Germany
Results: 3 references

KCE- Belgian Health Care Knowledge Centre, Belgium
Results: 2 references

NICE (National Institute for Health and Care Excellence, United Kingdom)
Results: No unique references

SBU - Statens beredning för medicinsk och social utvärdering, Sweden
Results: No unique references

Appendix 4. Possible relevant ongoing trials

ClinicalTrials.gov
Date: 2015.08.17
Search: drug AND "malignant melanoma"

WHO ICTRP (International Clinical Trials Registry Platform)
Date: 2015.08.17
Search: drug AND "malignant melanoma

NCT02374242. Anti-PD 1 Brain Collaboration for Patients With Melanoma Brain Metastases. 2014.

EUCTR2009-012293-12-NL. BRIM 3: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously untreated Patients with Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF mutation Receiving Vemurafenib (RO5185426) or Dacarbazine. - BRIM 3. 2015.

EUCTR2014-005277-36-ES. Clinical Trial to evaluate the efficacy of vemurafenib in combination with cobimetinib (continuous and intermittent) in BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma. 2015.

NCT01689519. coBRIM: A Phase 3 Study Comparing GDC-0973 (Cobimetinib), a MEK Inhibitor, in Combination With Vemurafenib vs Vemurafenib Alone in Patients With Metastatic Melanoma. 2015.

NCT01597908. Dabrafenib Plus Trametinib vs Vemurafenib Alone in Unresectable or Metastatic BRAF V600E/K Cutaneous Melanoma. 2012.
This is Combi-V study

NCT00324155. Dacarbazine and Ipilimumab vs. Dacarbazine With Placebo in Untreated Unresectable Stage III or IV Melanoma. 2015.
Same NCT as Robert 2011

NCT01940809. Ipilimumab With or Without Dabrafenib, and/or Trametinib in Treating Patients With Melanoma That Is Metastatic or Cannot Be Removed by Surgery. 2015.

NCT02523313. Immunotherapy With Nivolumab or Nivolumab Plus Ipilimumab vs. Double Placebo for Stage IV Melanoma w. NED. 2015.

NCT02519322. Neoadjuvant and Adjuvant Checkpoint Blockade in Patients With Clinical Stage III or Oligometastatic Stage IV Melanoma. 2015.

EUCTR2012-005371-13-BE. Phase 3 Study of Nivolumab or Nivolumab plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma. 2015.

NCT01844505. Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate 067). 2013.

EUCTR2011-002545-35-GB. A randomised phase 2 study of paclitaxel with or without GSK1120212 or pazopanib in advanced wt BRAF melanoma - Paclitaxel, GSK1120212 or pazopanib in Melanoma. PAClitaxel with or without GSK1120212 for treatment of MELanoma (PACMEL)2015.

NCT01584648. A Study Comparing Trametinib and Dabrafenib Combination Therapy to Dabrafenib Monotherapy in Subjects With BRAF-mutant Melanoma. 2012.
Same NCT as Long 2014

NCT01767454. Study of Dabrafenib +/- Trametinib in Combination With Ipilimumab for V600E/K Mutation Positive Metastatic or Unresectable Melanoma. 2013.

NCT01783938. Study of Nivolumab Given Sequentially With Ipilimumab in Subjects With Advanced or Metastatic Melanoma (CheckMate 064). 2013.

NCT01704287. Study of Pembrolizumab (MK-3475) Versus Chemotherapy in Participants With Advanced Melanoma (P08719/KEYNOTE-002). 2012.

EUCTR2011-006087-49-SE. A study to test two investigational drugs, dabrafenib and trametinib, for treating melanoma. 2015.

EUCTR2011-006088-23-SE. A study to test two investigational drugs, dabrafenib and trametinib, in combination together for treating a specific type of melanoma compared to another drug, vemurafenib that is approved for treatingthe same type of melanoma. 2015.

Appendix 5. Trial description, data extraction and Risk of Bias tables for the included trials

In the following tables we used these abbreviations:

OS: overall survival

PFS: Progression free survival

PD: Progressive disease

SAEs: Serious adverse events

HRQL: Health –related quality of life

EORTC QLQ-C30: European Organization for Research and Treatment of cancer Quality of Life Questionnaire

i.v. administration: intravenous administration

IRC: Independent review committee

CT: Computed tomography

MRI: Magnetic resonance imaging

NR: Not reached

IDSMC: Independent data and safety monitoring committee

Trial descriptions: NCT0094653 (MDX010-20) consist of 1) Hodi et al 2010 for OS, PFS and SAES. 2) Revicki et al 2012 for HRQL

Trials: 1) Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Suvival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 2010;363(8):711-23.2) 2) Revicki DA, van den Eertwegh AJ, Lorigan P, Lebbe C, Linette G, Ottensmeier CH, et al. Health re-lated quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. Health and quality of life outcomes 2012;10(66). Both: **NCT00094653,** (MDX010-20)
Design: Randomised, double-blind, phase 3, multicentre in North America, South America, Europe and Africa. No cross over between treatment groups. Analyse cut-off date: not given
Population: 676 patients with unresectable stage III or IV melanoma. Age (years): ≥18, mean 56.2. % male 59.3. *Previous treated* with one or more of dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2. BRAF-status not described
Intervention/comparators: 676 patients randomised 3:1:1 to ipilimumab (3 mg/kg) + gp100 peptide vaccine (n=403) versus ipilimumab +gp100 placebo (n=137) or gp100 + ipilimumab placebo (n=136), all given once every 3 weeks for four treatments, all as i.v. adminstrations. Patients with stable disease for 3 months' after week 12 or a confirmed partial or complete respone were offered additional courses with their assigned treatment regimen if they had disease progression.
Endpoints: *Primary*: OS between ipilimumab+gp100 group vs gp100 alone group. We do not report re-sults from this comparision. *Secondary* included: OS between the two ipilimumab groups and PFS. Both AES and HRQL were pre-defined endpoints. *Definitions of endpoints*: OS: the time from randomization to death from any cause. PFS: the time from randomization to documented disease progression or death. Tumor response determined by investigators only with the use of modified WHO criteria. SAEs as total, Grade 3 and 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse

events, version 3.0. HRQL measured with EORTC QLQ-30 with scores for function and global health status, and symptom scores. Efficacy analyses were performed on the intention-to-treat population. The safety population included all patients who had received any amount of study drug.
Follow-up: All patients should be followed until at least 481 deaths had occurred in the study. Median follow up for overall survival 21.0 and 27.8 months respectively for ipilimumab+gp100 and ipilimumab alone. HRQL: 12 weeks. Monitoring of AEs for at least 70 days after the last dose or until ongoing event resolved or stabilized.
Funding source: Medarex and Bristol-Myers Squibb

Data extraction: NCT0094653 (MDX010-20) consist of 1) Hodi et al 2010 for OS, PFS and AES. 2) Revicki et al 2012 for HRQL

Endpoints	**Intervention Ipilimumab+ gp100** (n=403)	**Control: Ipilimumab alone** (n=137)	**HR, p-values**
Total no of deaths	306	100	nr
Median OS (months)	10.0 (95%CI, 8.5 to 11.5)	10.1 (95%CI, 8.0 to 13.8)	No differences in OS: HR (95% CI) 1.04 (0.83-1.30), p=0.76
Rates of OS at 12 months 18 months 24 months	 43.6% 30.0% 21.6%	 45.6% 33.2% 23.5%	
Median PFS (months)	2.76 (95% CI, 2.73 to 2.79)	2.86 (95% CI, 2.76 to 3.02)	
Rates of PFS at week 12	49.1% (95% CI, 44.1 to 53.9)	57.7% (95% CI, 48.9 to 65.5)	
The reduction in risk of progression was less with ipilimumab+gp100 than with ipilumab alone			HR: 1.25, p=0.04
HRQL, with EORTC QLQ-C30	"no change" or "little change"	"no change" or "little change"	No change during 12 weeks across EORTC QLQ-C30 global health status, function, and symptom subscales.
Any AEs, (number of patients (percent)) **Grade 3** **Grade 4**	 147 (38.7) 26 (6.8)	 49 (37.4) 11 (8.4)	
Deaths related to study drugs	14 deaths related to study drugs, of which 7 were associated with immune-related adverse events		

Risk of Bias: NCT0094653 (MDX010-20) consist of 1) Hodi et al 2010 for OS, PFS and SAEs. 2) Revicki et al 2012 for HRQL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"The Biostatistics group in Medarex will provide a centralized randomization list to Clinical Operations using SAS procedure PROC PLAN" (p 34 in the protocol). No further comments on how this was actually done.
Allocation concealment?	Low	"The Principal Investigator/designee will contact Clinical Operations personnel in Medarex, Inc. to obtain the patient number, which will be stratified by the 3 stratification factors based on the patient's baseline characteristics" (p 33-34 in the protocol).
Blinding of participants and personnel?	Low	The study is double-blind
Blinding of outcome assessments?		
OS	Low	OS will not be influenced by lack of blinding. The site investigator is blinded
PFS	Low	"The IRC will be provided electronic or hard copies of all tumor-imaging data and will be blinded to patient cohort assignments", (p 52 in the protocol).
HRQL	Low	Double-blinded
SAEs	Low	"Because the study is blinded, the Investigator will be required to indicate on the CRF whether the adverse event is attributable to the study medication administered by i.v. infusion (MDX-010 or MDX-010 placebo) or the study medication administered by s.c. injection (melanoma peptide vaccine or melanoma peptide vaccine placebo), or both", (p 52 in the protocol).
Incomplete outcome data?		
OS and PFS	Low	"Efficacy analyses were performed on the intention-to-treat population, which included all patients who had undergone randomization", (p 714 in article).
HRQL	High	.."95% had baseline HRQL assessments and Week 12 assessments were available for 236 (62%) and 85 (65%) of the patients treated with ipilimumab plus gp100 and ipilimumab alone respectively.
SAEs	Low	"The safety population included all patients who had undergone randomization and who had received any amount of study drug", (p 714 in article).
Selective reporting?	Low	Study protocol available, all endpoints were pre-specified, and reported on.
Other sources of bias?	Low	All study sites received funding from Medarex or Bristol-Meyers Squibb
Conclusions	OS, PFS and SAEs: Low risk of bias HRQoL: High risk of bias	

Trial descriptions: NCT00324155 consist of 1) Robert et al 2011 for OS, PFS, SAEs. 2) Maio et al 2012 for 4-years survival rates. 3) Maio et al 2015 for 5-years survival rates 4) Kotapati et al 2011 for HRQoL

Trials:

1) Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med 2011;364(26):2517-2526.

2) Maio M, Bondarenko I, Robert C, Thomas L, Garbe C, Testori A, 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 Pac J Clin Oncol 2012;8:303.

3) Michele Maio, Jean-Jacques Grob, Steinar Aamdal, Igor Bondarenko, Caroline Robert, Luc Thomas, Claus Garbe, Vanna Chiarion-Sileni, Alessandro Testori, Tai-Tsang Chen, Marina Tschaika, and Jedd D. Wolchok. Five-Year Survival Rates for Treatment-Naive Patients With Advanced Melanoma Who Received Ipilimumab Plus Dacarbazine in a Phase III Trial. J Clin Oncol 33:1191-1196. 2015.

4) Kotapati S, Francis S, Sherrill B. Health related quality of life (HRQL) of patients receiving ipilimumab with dacarbazine as first-line treatment for unresectable stage III/IV melanoma. Pigment cell & mela noma research 2011;24(5):1037. All: **NCT00324155** (CA184-024).

Design: Randomised, double-blind, phase 3, multicentre in Europe, Israel, North America. No cross over between treatment groups. Analyse cut-off date: not given for Robert 2011. For Maio 2015: march 2013

Population: 502 patients with unresectable stage III or IV melanoma. Age (years): ≥18, mean 57.5 and 56.4 respectively in intervention (I) and control (C) group. % male 60.8 and 59.1% respectively. Previous *untreated.* Tumors not routinely assessed for BRAF mutation.

Intervention/comparators: 502 randomised 1:1 to ipilimumab (10 mg/kg) + dacarbazine (850 mg/m² body-surface area) (n= 250) or dacrabazine (850 mg/m² body-surface area) + placebo (n= 252), given at weeks 1,4,7 and 10, followed by dacarbazine alone every 3 weeks through week 22 (induction phase), all as i.v. adminstrations At week 24, patients with stable disease or an objective response during induction phase and no dose-limiting toxic effects received ipilimumab or placebo every 12 weeks thereafter (maintenance phase) until progression, toxic effects, or end of study.

Endpoints: Robert 2011: *Primary:* OS. *Secondary*: Included PFS. AEs. Definitions of endpoints: OS: Not further specified. PFS: Radiologic and photographic tumor assessments, based on assessments by IRC. All efficacy end points (except survival) were based on assessments by IRC (blinded). HRQoL: Measured by EORTC-QLQ-C30 at baseline, and week 4, 7, 12 then every 12 weeks until disease progression. AEs as total, Grade 3 and 4 according to the national Cancer Institute's Common Terminology Criteria for Adverse events, version 3.0. Efficacy analyses performed on intention –to-treat (ITT) population. The safety population included all randomized patients who received at least one dose. Maio 2015: Updated Median OS and survival rates up to 5 years.

Patient flow

Stage	Ipilimumab+dacarbazine	Placebo+dacarbazine
Randomised (ITT), analyses for OS, PFS and HRQoL based upon ITT	250	252
Received one or more induction doses, and evaluated for AEs	247	251
Received one or more maintenance doses	43	53
Still on maitenance after 2 years (ipilimumab or placebo ony, no dacarbazine	11	11
Patients alive after 5 years or beyond	40	20

Follow-up: Robert 2011:The target number of events for the primary analysis was 416 deaths, which were reached 37 months after enrolment of the last patients. Monitoring of AEs including 70 days after the last dose. Maio 2015: Median survival follow-up for intervention group: 11.0 months (0.4-71.9);for control group: 8.9 months (0.1-73.2). Minimum 5 years follow-up in all patients for survival.

Funding source: Bristol-Myers Squibb

Data extractions: NCT00324155 consist of 1) Robert et al 2011 for OS, PFS, AEs. 2) Maio et al 2012 for 4-years survival rates. 3) Maio et al 2015 for 5-years survival rates 4) Kotapati et al 2011 for QoL

Endpoints	**Intervention: Ipilimumab +Dacarbazine** (n=250)	**Control: Placebo+ Dacarbazine** (n=252)	**HR, p-values**
Total no of deaths, 37 months after last patients en-rolled (Robert 2011) After 60 months (Maio	196	218	HR (95% CI) 0.72 (0.59-0.87), p<0.001
Median overall survival (months)	From Robert 2011: 11.2 (95% CI, 9.4 to 13.6) Updated from Maio 2015: 11.2 (95% CI, 9.5 to 13.8)	From Robert 2011 9.1 (95% CI, 7.8 to 10.5) Updated from Maio 2015: 9.1 (95% CI, 7.8 to 10.5)	HR (95% C) 0.69 (0.57-0.84)
Rates of OS (%) at 12 months	Robert 2011: 47.3 (41.0-53.6), Maio 2015: 47.6 (41.2-53.7)	Robert 2011: 36.3 (30.4-42.4), Maio 2015: 36.4 (30.4 to 42.4)	
24 months	Robert 2011: 28.5 (22.9-34.2), Maio 2015: 28.9 (23.3-34.7),	Robert 2011: 17.9 (13.3-22.8), Maio 2015: 17.8 (13.3-22.8),	
36 months	Robert 2011: 20.8 (15.7-26.1), Maio 2015: 21,3 (16.3-26.6)	Robert 2011: 12.2 (8.2-16.5), Maio 2015: 12.1 (8.4-16.5)	
48 months, from Maio 2012 and Maio 2015	19.1 (14.4-24.3)	9.7 (6.4-13.7)	
60 months, only from Maio 2015	18.2 (13.6-23.4)	8.8 (5.7-12.8)	P=0.002
Rates of PFS at week 12, only Rob-ert 2011	57.7% (95% CI, 48.9 to 65.5)	49.1% (95% CI, 44.1 to 53.9))	
Disease of pro-gression-no of events, only Robert 2011	203/250	223/252	HR: 0.76 (0.63-0.93), p=0.006
There was a 24% **reduction in the risk of progression** in the ipilimumab-dacarbazine group as compared with the dacarbazine group			HR: 0.76;p=0.006
HRQoL	No difference between groups. “Longitudinal analyses using repeated measures modelling did not detect		GHS P=0.19

	statistically significant differences between treatment groups for any HRQL scales or symptom scores"		
Any AEs , (number of patients (per-cent)) **Grade 3** **Grade 4**	 99 (40.1) 40 (16.2)	 45 (17.9) 24 (9.6)	
Deaths related to study drugs	None	1	

Risk of Bias: NCT00324155 consist of 1) Robert et al 2011 for OS, PFS, AEs. 2) Maio et al 2012 for 4-years survival rates. 3) Maio et al 2015 for 5-years survival rates 4) Kotapati et al 2011 for QoL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	Restricted randomization within strata, as decribed in the protocol (p 68):"The site will call an interactive voice response system (IVRS) to obtain the patient number". "..all eligible patients will be randomized to one of the two arms in a 1:1 ratio". "The randomization procedure will dynamically minimize the imbalance between treatment arms within the levels of each of the following stratification factors:.."
Allocation concealment?	Low	"The site will call an interactive voice response system (IVRS) to obtain the patient number", (p 68 in the protocol)
Blinding of participants and personnel?	Low	The study is double -blind
Blinding of outcome assessments? OS PFS HRQoL SAEs	 Low Low Low Low	 OS will not be influenced by lack of blinding. The site investigator is blinded "All imaging from this trial (radiographic and photographic) will be reviewed in a blinded and sequential fashion by an IRC to uniformly assess response" (p 50 in protocol). The study is double -blind The study is double -blind
Incomplete outcome data? OS, PFS HRQoL SAEs	 Low Low Low	 "Efficacy analyses were performed on the intention- to –treat population", p 2520 in Robert 2011. "Health-related quality of life (HRQoL) will be assessed for all randomized patients", p 63 in protocol. "The safety analysis included all patients who underwent randomization and received at least one

		dose of the assigned study drug (247 and 251 patients respectively in intervention and control group)," p. 2521 in Robert 2011.
Selective reporting?	Low	Study protocol available, all endpoints were pre-specified and reported on.
Other sources of bias?	Low	The study was supported by Bristol-Meyers Squibb
Conclusion: Overall for all endpoints	Low risk of bias	

Trial description: NCT0050102 (MDX010-08), Hersh et al 2011

Study: Hersh EM, O'Day SJ, Powderly J, Khan KD, Pavlick AC, Cranmer LD, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs 2011;29(3):489-498.**NCT00050102**

Design: A randomised, open-label, phase II, multicentre in USA. *Crossover allowed*: patients who progressed on monotherapy could cross over and receive combination therapy. The crossover patients were analysed according to the treatment group to which they were originally randomised, i.e., ipilimumab monotherapy. Enrollment started in September of 2002 and ended in August of 2004. Analyse cut-off date: not given

Population: 76 patients with unresectable, metastatic melanoma. Age (years): ≥18, median 61.0, range 25-82. % male 65.3. *Chemotherapy-näive.* BRAF-status not described

Intervention/comparators: 76 patients randomised to ipilimumab (3 mg/kg) every 4 weeks for four doses, either alone (n=40) or in combination with dacarbazine (250 mg/m²) (n=36) for five consecutive days every 3 weeks (maximum 6 cycles). Patients who progressed on monotherapy could cross over and receive combination therapy.

Endpoints: *Primary*: Adverse events. *Secondary*: None relevant. OS data was collected as part of a follow-up study. *Definitions of endpoints*: AEs: Severity graded using Common Toxicity Criteria version 2.0, where severe events were defined as those ≥grade 3. The safety population 74 of the 76 randomised. OS were analyzed based upon 64 patients.

Patient flow

Stage	Ipilimumab	Ipilumumab + dacarbazine
Randomised (ITT)	40	36
Safety population	39	35
OS population	32	32
Per protocol population	37	35
Patients that crossover from ipilimumab to ipilimumab+ dacarbazine: 13		

Follow-up: Median follow-up for OS was 20.9 and 16.4 months respectively for ipilimumab plus dacarbazine and ipilimumab alone.

Funding source: Writing and editorial support funded by Bristol-Myers Squibb Co.

Data extraction: NCT0050102 (MDX010-08), Hersh et al 2011 for AEs and OS

Endpoints	**Intervention: Ipilimumab + dacarbazine** (n=36)	**Control: Ipilimumab** (n=40)	**HR, p-values**
Median OS (months)	Ipilimumab + dacarbazine (n=32) 14.3 (95% CI, 10.2-18.8)	Ipilimumab (n=32) 11.4 (95% CI, 6.1 to 15.6)	

Rates of OS at 12 months 24 months 36 months	 62% 24% 20%	 45% 21% 9%	
Any SAEs, (number of patients (percent)) **Grade 3/4**	8/35 (22.9)	5/39 (12.8)	
Deaths related to study drugs	1 patients died, consider possible related to both treatments	1 patients died, consider related to treatment	

Risk of Bias: NCT0050102 (MDX010-08), Hersh et al 2011

Entry/Domain	Judgement	Description
Random sequence generation?	Low	Says that randomized. Does not explained how. Cannot find protocol. We decided that we assume that they have done this in a proper way, article from 2011.
Allocation concealment?	Low	This is an open-label study. But even if participants and investigators will know the assignment, we assume that this will have no impact on the endpoints; ie SAEs (hospitalization) and OS.
Blinding of participants and personnel?	Low	Same comments as above
Blinding of outcome assessments?	Low	Same comments as above
Incomplete outcome data? OS SAEs	 High Low	 OS analyses were not based upon ITT population (Figure 2).
Selective reporting? OS SAEs	 High Low	 OS was not predefined This was predefined (primary objective)
Other sources of bias? OS and SAEs	High	The patients were allowed to cross to over to the combination group after progression. The study was funded by Bristol-Myers Squibb Co
Conclusion: Overall for both endpoints	High risk of bias	

Trial description: NCT not given. Weber et al 2013

Study: Weber J, Hamid O, Amin A, O'Day S, Masson E, Goldberg SM, et al. Randomised phase I pharmacokinetic study of ipilimumab with or without one of two different chemotherapy regimens in patients with untreated advanced melanoma. Cancer Immun 2013;13:7
Design: Randomised, phase I, multicentre in USA. Not blinded. No cross over between treatment groups. Analyse cut-off date: not given.
Population: 59 patients with advanced melanoma. Age (years): Median 56. % male 64. Previous *untreated.* BRAF mutation: No information
Intervention/comparators: 59 patients randomised 1:1:1 to ipilimumab alone (10 mg/kg) (n=20), or ipilimumab +dacarbazine (850 mg/m² body-surface area) (n= 19), or ipilimumab + paclitaxel 175 mg/m² and carboplatin [AUC=6] , all as i.v. adminstrations. Ipilimumab given every 3 weeks for 4 doses, i.e. up to 12 weeks as induction. Chemotherapy every 3 weeks continued up to week 24. From week 24, patients without dose-limiting toxicities were eligible to receive maintenance ipilimumab every 12 weeks until disease progressed or toxicity requiring discontinuation.
Endpoints: *Primary:* Not our focus. *Secondary*: Safety. Definitions of endpoints: Es population = ITT population.
Follow-up: Until disease progressed or to toxicity that requiring discontinuation
Funding source: Bristol-Myers Squibb

Data extraction: NCT not given. Weber et al 2013, for AEs

Endpoints	**Intervention:** Ipilimumab + dacarbazine (n=19)	**Control:** Ipilimumab (n=20)	**Control**: ipilimumab + paclitaxel 175 mg/m² and carboplatin (n= 20)	**HR, p-values**
Any AEs, (number of patients (percent)) **Grade 3-4**	14 (74)	10 (50)	15 (75)	
Deaths related to study drugs	None	none		

Risk of Bias: NCT not given. Weber et al 2013

Entry/Domain	**Judgement**	**Description**
Random sequence generation?	Low	Says that randomized. Does not explained how. Cannot find protocol. We decided that we assume that they have done this in a proper way, article from 2013.
Allocation concealment?	Low	This is an open-label study. But even if participants and investigators will know the assignment, we assume that this will have no impact on the outcome, ie SAEs (hospitalization).

Blinding of participants and personnel?	Low	Same comments as above
Blinding of outcome assessments?	Low	Same comments as above
Incomplete outcome data?	Low	AEs analysis on all patients
Selective reporting?	Low	All outcomes were prespecified and reported upon
Other sources of bias?	Low	The study was sponsered by Bristol-Myers Squibb
Conclusion, for the outcome SAEs	Low risk of bias	

Trial *description:* NCT01866319 (KEYNOTE-006) consist of 1) Robert et al 2015 for PFS, OS, AEs.

Trial: Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. Published on April 19, 2015, at NEJM.org

Design: This is a randomised, open-label, phase 3 multicentre study in Europe, Israel, Australia and North America. The first interim analysis, had a data cutoff of September 2014. The second interim in March 2015. After the second interim the DSMC recommended that patients with disease progression in the ipilimumab group could crossover to the pembrolizumab group. However, all data presented here are from the first interim analysis, except those for OS, which are from the second interim analysis, i.e. in this study *no patients crossed over.*

Population: 834 patients with unresectable stage IIIC or IV melanoma and had received no more than one previous systemic therapy for advanced disease (P*revious treated/nontreated)*. Known *BRAF V600 mutations status was required.* Age (years): ≥18, median (range): 61 (18-89), 63 (22-89) and 62 (18-88) respectively for pembrolizumab every 2 weeks, pembrolizumab every 3 weeks or ipilimumab. % male 57.7, 62.8 and 58.3 respectively. % previous treated with immunotherapy: 2.9, 2.5 and 4.3 respectively.

Intervention/comparators: 834 patients randomised 1:1: 1 to pembrolizumab (10 mg/kg) either every 2 weeks or every 3 weeks or four cycles of ipilimumab (3 mg/kg) every 3 weeks. Patients were stratified according toline of therapy (first vs second), and PD-L1 (positive vs negative).

Endpoints: *Primary:* PFS and OS. *Secondary*: included safety. *Definitions of endpoints*: PFS: the time from randomization to documented disease progression or death of any cause. OS: the time from randomization to death of any cause Safety: were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Efficacy analyses performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug.

Patient flow

Stage	**Intervention: Pembrolizumab every 2 weeks**	**Intervention: Pembrolizumab every 3 weeks**	**Control: Ipilimumab**
Randomised (ITT), included in efficacy analyses	279	277	278
Patients in the AEs analysis	278	277	256

Follow-up: For PFS: Until the time of the prespecified number of PFS events (First interim, September 2014). OS: At the time of data cutoff for the second interim analysis (March 2015), driven by a minimum follow-up of 12 months for all patients. *The median duration of follow-up at the time was of data cutoff*

was 7.9 months (range,6.1-11.5) . AEs: Mean duration of exposure was 164 days, 151 days and 50 days respectively for those receiving pembrolizumab every 2 weeks, pembrolizumab every 3 weeks or ipilimumab.
Funding source: Merck Sharp & Dohme

Data extraction: NCT01866319 (KEYNOTE-006) consist of 1) Robert et al 2015 for PFS, OS, AEs.

Endpoints	**Intervention: Pembrolizumab every 2 weeks** (n=279)	**Intervention: Pembrolizumab every 3 weeks** (n=277)	**Control: Ipilimumab** (n=278)	**HR, p-values**
PFS rates (months) At 6 months (as of September 2014)	47.3	46.4	26.5	HR for PFS: - every 2 weeks vs ipilimumab: 0.58 (95% CI, 0.46-0.72); P<0.001 -every 3 weeks vs ipilimumab: 0.58 (95% CI, 0.47-0.72); P<0.001
Median PFS (months), as of September 2014	5.5 (95% CI, 3.4-6.9)	4.1 (95% CI, 2.9-6.9)	2.8 (95% CI, 2.8-2.99)	
Total no of deaths n (**%)** at minimum 12 months, as of March 2015	85	92	112	HR for death: - every 2 weeks vs ipilimumab: 0.63 (95% CI, 0.47-0.83); P<0.0005 -every 3 weeks vs ipilimumab: 0.69 (95% CI, 0.52-0.90); P=0.0036
Median OS (months) at March 2015	Not reached	Not reached	Not reached	
Rates of OS (%) At 12 months (as of March 2015)	74.1	68.4	58.2	
Any AEs , (number of patients (percent)) at March **Grade 3 -5**	37 (13.3)	28 (10.1)	51 (19.9)	
Deaths related to study drugs (number)	None reported	None reported	1	

Risk of Bias: NCT01866319 (KEYNOTE-006) consist of 1) Robert et al 2015 for PFS, OS, AEs.

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"This study will utilize IVRS/IXRS for central randomization during the study". "IVRS will be used for randomizing patients in a 1:1:1 ratio.." "Randomization ..will be stratified..", (P 65-66 in protocol)
Allocation concealment?	Low	"..the patient will be randomly assigned a unique allocation number via IVRS/IXRS," (p 66 in protocol).
Blinding of participants and personnel?	Low	This is an open-labeled study, so the participants and investigators know the treatment. We, however, assume that this will not influence the assessments OS, PFS ("..the independent radiologist(s) will perform the central imaging review without knowledge of treatment assignments") p 92 protocol); or SAEs (hospitalization).
Blinding of outcome assessments?	Low	As above, and in addition: "Although this study is being conducted as an open-label study, in order to ensure data integrity, the analysis and reporting team will be blinded to the treatment assignments", p 92 in protocol
Incomplete outcome data?	Low	All patients accounted for
Selective reporting?	Low	All outcomes were prespecified and reported upon
Other sources of bias?	Low	The study was funded by Merck Sharp & Dohme
Conclusions	Low risk of bias for all endpoints, ie: OS, PFS, SAEs	

Trial descriptions: NCT017004287 (KEYNOTE-002) consist of Ribas et al 2015 for PFS, HRQoL, SAEs.

Trial: Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. The Lancet Oncology 2015;16(8):908-918.
Design: This is a randomised, open-label, phase 2 multicentre study in USA and Europe. Data cutoff date: May 2014. *Crossover allowed*: Patients in the chemotherapy group with documented and verified disease progression at or after week 12 could cross over to receive pembrolizumab after a washout period of at least 28 days from the last dose of chemotherapy; patients who crossed over were randomly assigned to one of the two pembrolizumab doses. Randomization was stratified by BRAFV600 status.
Population: 540 patients with unresectable stage III or IV melanoma who were *previous treated* (had confirmed progressive disease within 24 weeks after two or more ipilimumab doses and, if BRAF V600 mutant-positive, previous treatment with a BRAF or MEK inhibitor or both, Age (years): ≥18, median (range): 62 (15-87), 60 (27-89) and 63 (27-87) respectively for pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg and chemotherapy . % male 58, 60, and 64 respectively.
Intervention/comparators: 540 patients randomised 1:1: 1 to pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg given intravenously every 3 weeks or investigator-cgoice chemotherapy (paclitaxel+ carboplatin, paclitaxel, carboplatin, dacarbazine or oral temozolomide).
Endpoints: *Primary:* At the second interim analysis was PFS. At final analysis: OS (not reported here). *Secondary*: Safety. : Prespecified exploratory endpoints: Health related quality of life. *Definitions of endpoints* PFS: the time from randomization to first documented disease progression per RECIST by independt central review, or death from any cause, whichever occurred first. PFS was also assessed by investigator review. OS: the time from randomization to death of any cause. HRQoL: measured by EORTC QLQ-C30. Safety: was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Efficacy analyses performed on intention –to-treat

(ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug.

Patient flow

Stage	Intervention: Pembrolizumab 2 mg/kg	Intervention: Pembrolizumab 10 mg/kg	Control: Chemotherapy
Randomised (ITT), included in efficacy analyses	180	181	179
Patients in the HRQoL analysis	176	177	167
Patients in the SAEs analysis	178	179	171
Patients that have crossed over to pembrolizumab treatment	As of the data cutoff date: 86 of the 179 patients in the chemotherapy group crossed over to pembrolizumab		

Follow-up: For PFS: Median follow-up: 10 months (IQR 8-12)

Funding source: Merck Sharp & Dohme

Data extraction: NCT017004287 (KEYNOTE-002) consist of Ribas et al 2015 for PFS, HRQoL, SAEs.

Endpoints	Intervention: Pembrolizumab 2 mg/kg * (n=180)	Intervention: Pembrolizumab 10 mg/kg * (n=181)	Control: Chemotherapy (n=179)	HR, p-values
Poroportion progression free (%) after 9 months (investigator assessed**)** as of May 2014	32 (25-40)	36 (29-44)	10 (6-15)	HR for PFS: - for 2 mg/kg versus chemotherapy: 0.49 (95% CI, 0.38-0.62); P<0.0001, in favour of pembrolizumab - for 10 mg/kg versus chemotherapy: 0.41 (95% CI, 0.32--0.52); P<0.0001, in favour of pembrolizumab
HRQoL, The least squares mean change from baseline to week 12 in the EORTC QLQ-C30 global health status and quality –of-life score	-2.60 (95%CI -6.15 to 0.96)	-2.55 8-5.99 to 0.89)	-9.13 (-12.86 to -5.39)	Favour pembrolizumab. A significant difference in the least squares mean change, in favour of pembrolizumab (for both 2 and 10 mg/kg) as compared to chemotherapy. For the 2 mg group versus the chemotherapy group: 6.53 (95%CI 1.53 to 11.53) For the 10 mg/kg group versus the chemotherapy group: 6.57 (1.65 to 11.50)

Any AEs , (number of patients (percent)) at March **Grade 3/4**	19 (10.7)	25 (14.0)	45 (26.3)	
Deaths related to study drugs (number)	There were no treatment related deaths			

**We analyzed 2 mg and 10 mg as one group*

Risk of Bias: NCT017004287 (KEYNOTE-002) consist of Ribas et al 2015 for PFS, HRQoL, SAEs.

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"A centralized interactive voice-response system with or without web functionality was used to allocate patients to treatment"
Allocation concealment?	Low	This is an open-label study: "Individual treatment assignment between pembrolizumab and chemotherapy was open label; investigators and patients were masked to assignment to pembrolizumab dose". But even if participants and investigators will know the assignment, we assume that this will have no impact on the endpoints, PFS and SAEs (hospitalization). For the HRQoL this will have impact
Blinding of participants and personnel?	Low	See above
Blinding of outcome assessments?	Low for PFS and SAEs High for HRQoL	"A non-Merck unmasked statistician generated interim analysis reports for external data monitoring committee review for the fi rst and second interim analyses". The investigator and patients are also unblinded. Our assessment: No impact for PFS and SAEs. Can influence the HRQoL
Incomplete outcome data?	Low	All patients accounted for
Selective reporting?	Low	All outcomes were prespecified and reported upon
Other sources of bias?	Low	The patients were allowed to cross to over to the combination group after progression. The study was funded by Merck Sharp & Dohme
Conclusions	Low risk of bias for PFS and SAEs High risk of bias for HRQoL	

Trial descriptions: NCT01721772 (CheckMate 066) consist of 1) Robert et al 2015 for PFS, OS at 1 year, SAEs; 2) Long et al 2015 for QoL

Trials:

1) Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372(4):311-319.
2) Long GV, Atkinson V, Ascierto PA, Robert C, Hassel JC, Rutkowski P, et al. Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): results of a phase III study (CheckMate 066). J Clin Oncol 33, 2015 (suppl; abstr 9027)

Design: This is a randomised, double-blind, phase 3 multicentre study in Europe, Israel, Australia, Canada and South America. *Clinical* d*ata cut off*: June 24, 2014. Amendment in June, 10 2014 : allowed patients in the dacarbazine group to receive nivolumab. This had no implications for the results reported in this study, ie for the reported results: *no crossover.*
Final database locked: August 2015.

Population: 418 patients with unresectable, *previous untreated* stage III or stage IV melanoma *without* a BRAF mutation (ie patients of the wild type). Age (years): ≥18, median (range): 64 (18-86) and 66 (26-87) respectively for nivolumab and dacarbazine. % male 57.6 and 60.1 respectively.

Intervention/comparators: 418 patients randomised 1:1 to receive intravenously either nivolumab 3 mg/kg every 2 weeks + dacarbozine matched placebo every 3 weeks, or dacarbazine 1000 mg/m^2 every 3 weeks + a nivolumab- matched placebo every 2 weeks. Randomization was stratified according to tumor PD-L1 status.

Endpoints: 1) Robert 2015: *Primary:* OS. *Secondary:* Investigator assessed PFS. *Exploratory objective:* Safety. 2) Long 2015: QoL, defined in protocol as a secondary endpoint. *Definitions of endpoints*: PFS and OS not further defined. Safety: were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.2) Long: QoL was assessed by (EORTC_QLQ)-C30 and EuroQoL EQ-5D at baseline and at treatment cycles Q6W.
Efficacy analyses performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug.

Patient flow

Stage	**Intervention: Nivolumab**	**Control: Dacarbazine**
Randomised (ITT), included in efficacy analyses, including HRQoL	210	208
Patients in the AEs analysis	206	205

Follow-up: Robert 2015 and Long 2015: All patients were followed for up to 16.7 months.

Funding source: Bristol-Myers Squibb

Data extraction: NCT01721772 (CheckMate 066) consist of 1) Robert et al 2015 for PFS, OS at 1 year, AEs; 2) Long et al 2015 for QoL

Endpoints	**Intervention: Nivolumab** (n=210)	**Control: Dacarbazine** (n=208)	**HR, p-values**
Median OS (months) at June 2014	Not reached	10.8 (95% CI, 9.3-12.1)	
Rates of OS (%) At 12 months	72.9 (95% CI, 65.5-78.9)	42.1 (95% CI, 33.0-50.9)	HR for death: 0.42 (99.79% CI, 0.25-0.73); P<0.001
Total no of deaths n (**%)** at June 2014	50	96	
Median PFS (months), June 2014	5.1 (95% CI, 3.5-10.8)	2.2 (95% CI, 2.1-2.4)	HR for disease progression or death: 0.43 (95% CI, 0.34-0.56); P<0.001
HRQoL, EORTC Global Health EQ-5D visual analog scale scores:	No results, due to lack of dacarbazine data after baseline		
Any AEs, (number of patients (percent)) **Grade 3 or 4** at June 2014	70 (34)	78 (38)	
Deaths related to study drugs Aug 2013 Jan 2015	Not reported	Not reported	

Risk of Bias: NCT01721772 (CheckMate 066) consist of 1) Robert et al 2015 for PFS, OS at 1 year, AEs; 2) Long et al 2015 for QoL

Entry/Domain	**Judgement**	**Description**
Random sequence generation?	Low	"Subjects will be randomized 1:1 and stratified .." (p 27 in protocol)
Allocation concealment?	Low	"Subject is enrolled using the Interactive Voice Response System (IVRS)", s 29 in protocol
Blinding of participants and personnel?	Low	The study is double blinded
Blinding of outcome assessments?	Low	As above, and PFS by CT or MRI
Incomplete outcome data?	Low	No missing outcome data

Selective reporting?	Low	All endpoints pfredined and reported upon. SAEs was a exploratory objective
Other sources of bias?	Low	The study was funded by Bristol-Myers Squibb
Conclusion	For all endpoints, ie OS, PFS, HRQoL and SAEs low risk of bias	

Trial description: NCT01721746 (CheckMate 037), Weber et al 2015 for OS, PFS, SAEs.

Trial: Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015:10

Design: This is a randomised, open-label, phase 3 multicentre study in USA, Canada and Europe. *No crossover* of patients between treatment groups. Analyse cut-off dates: At the time of the first planned assessment of objective responses. The randomisation was stratified by tumour PD-L1 status and BRAF status.

Population: 405 patients with unresectable stage IIIC or stage IV metastatic melanoma. Patients with *BRAF wild-type tumours* must have had progression after anti-CTLA-4 treatment, such as ipilimumab, and patients with a $BRAF^{V600}$ mutation-positive tumour mutation must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor. Age (years): ≥18, median (range): 59 (23-88) and 62 (29-85) respectively for nivolumab and investigators choice chemotherapy (ICC). % male 65 and 64 respectively.

Intervention/comparators: 405 patients randomised 2:1 to either nivolumab 3 mg/kg every 2 weeks or ICC (either dacarbazine 1000 mg/m^2 every 3 weeks, or carboplatin area under the curve 6+ paclitaxel 175 mg/ m^2 every 3 weeks) by intravenous infusion.

Endpoints: *Primary:* None of our interest. *Secondary*: A descriptive comparison of PFS between groups, OS, HRQoL. Safety was not pre-defined. PFS assessed by investigator according to RECIST, version 1.1 ; and confirmed central radiologists with CT or MRI. *Definitions of endpoints*: OS, PFS, not further defined. Safety: were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Efficacy analyses performed on the intention –to-treat (ITT) objective response analysis population (ie, all 182 patients who had been randomised at the point of the first planned assessment of objective responses). The safety analyses were performed in all patients who received at least one dose of study drug.

Patient flow

Stage	**Intervention: Nivolumab**	**Control: ICC**
Randomised (ITT), included in efficacy analyses done on the objective response analysis population	ITT: 272 Objective response analysis population:122	ITT: 133 Objective response analysis population:60
Patients in the AEs analysis	268	102

Follow-up: Patients received nivolumab for a median of 5.3 months (95% CI, 3.3-6.5), and 2.0 months (95% CI, 1.6-2.9) for chemotherapy. AEs: until 100 days after discontinuation of study treatment.

Funding source: Bristol-Myers Squibb

Data extraction: NCT01721746 (CheckMate 037), Weber et al 2015 for PFS, SAEs

Endpoints	Intervention: Nivolumab (n=272)	Control: ICC (n=133)	HR, p-values
OS	No data	No data	
Median PFS, months	4.67 (95% CI, 2.33-6.51)	4.24 (95% CI, 2.14-6.34)	HR: 0.82 (99.99% CI, 0.32-2.05), a descriptive comparison
Rates of PFS (%) 6 months	48 (95% CI, 38-56)	34 (95% CI, 18-51PFS)	
HRQoL	No data	No data	
Any AEs, (number of patients (percent)) **Grade 3-4**	24 (9%)	32 (31)	
Deaths related to study drugs	none	none	

Risk of Bias: NCT01721746 (CheckMate 037), Weber et al 2015 for PFS, SAEs.

Entry/Domain	Judgement	Description
Random sequence generation?	Low	Restricted randomized (2:1) with an interactive voice system. The randomization was stratified with permuted blocks within each stratum (p 3 in Weber 2015).
Allocation concealment?	Unclear	
Blinding of participants and personnel?	Low	The study was open-label, ie the treatment was not blinded for the investigator and patients. We, however, mean that this will not influence the assessments of PFS (those doing tumour assessments were masked to treatment assignment, p 1 in Weber 2015).); or SAEs (hospitalization).
Blinding of outcome assessments?	Low	As above
Incomplete outcome data? PFS SAEs	Low	All patients accounted for
Selective reporting? PFS SAEs	Low Uncertain	Was predfined and reported upon. Safety was not predefined
Other sources of bias?	Low	The study was funded by Bristol-Myers Squibb
Conclusion	Low for both PFS and SAEs	

Trial descriptions: NCT01927419 (CheckMate 069) consist of 1) Postow et al 2015 for OS, PFS and SAEs; 2) Abernethy et al 2015 for QoL

Trials:

1) Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N ENGL J MED 2015 May 21;372(21):2006-17. doi: 10.1056/NEJMoa1414428. Epub 2015 Apr 20
2) Abernethy AP, Postow MA, Chesney JA, Grossmann KF, Fiona Taylor F, Coon C, et al. Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): results of a phase II study (CheckMate 069). J Clin Oncol 33, 2015 (suppl; abstr 9029)

Design: This is a randomised, double-blind, phase 2 multicentre study USA and Europe. After progression the patients in the ipilimumab group had the option of receiving nivolumab at a dose of 3 mg/kg, ie, *crossover allowed.* Clinical database lock for the results reported in this study: January 2015. The randomisation was stratified by BRAF mutation status.

Population: 142 patients with unresectable, *previously untreated* stage III or IV melanoma. Patients should have a known BRAF V600 mutation status (both positive and wild included). Age (years): ≥18, median (range): 64 (27-87) and 67 (31-80) respectively for nivolumab + ipilimumab. % male 66 and 68 respectively.

Intervention/comparators: 142 patients randomised 2:1 to both nivolumab and ipilimumab (combination group) or ipilimumab alone (ipilimumab monotherapy group). In the combination group, nivolumab was administred intravenously at a dose of 1 mg/kg, once every 3 weeks for four doses. Thirty minutes after the completion of each nivolumab infusion, patients received 3 mg ipilimumab/kg.After the fourth dose of both agents, ipilimumab was discontinued, and thereafter (maintenance phase), nivolumab was administred as a single agent , 3 mg/kg once every 2 weeks. In the ipilimumab-monotherapy group the same dosing schedule was used, except that nivolumab was replaced with placebo.

Endpoints:1) Postow 2015: *Primary:* None of our interest. *Secondary*: included investigator assessed PFS in patients with *BRAF* wild-type tumors, PFS in patients with *BRAF* V600 mutation –positive tumors and safety *Exploratory objectives:* OS and safety. 2) Abernethy 2015: QoL. *Definitions of endpoints*: PFS: No further definition. HRQoL was assessed by (EORTC-QLQ-C30 and EuroQoL EQ-5D at baseline and every 6 week for the first 6 months. Safety: was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Efficacy analyses performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug.

Patient flow

Stage	**Intervention: Nivolumab+ ipilimumab**	**Control: Ipilimumab**
All randomised patients (ITT), included in efficacy analyses, including HRQoL	95	47
Randomised patients with *BRAF* wild-type tumors	72	37
Randomised patients with *BRAF* BRAF V600 mutation	23	10
Patients in the AEs analysis	94	46

Follow-up:

1. Postow 2015:Treatment was continued as long as clinical benefit (as defined by investigator) was observed or until unacceptable side effects occurred. *The minimum follow-up period* was 11 months after randomisation.
2. Abernethy 2015: 6 months

Funding source: Bristol-Meyers Squibb

Data extraction: NCT01927419 (CheckMate 069) consist of 1) Postow et al 2015 for PFS and AEs; 2) Abernethy et al 2015 for QoL

Endpoints	**Intervention: Nivolumab+ ipilimumab** (n=95)	**Control: Ipilimumab** (n=47)	**HR, p-values**
Median PFS (months), at January 2015:			HR for disease progression or death:
- in the population with *BRAF* wild-type tumors	Not reached	4.4 (95% CI,2.8-5.7)	0.40 (95% CI, 023-0.68); P<0.001
-in the population with *BRAF* mutation-positive tumors	8.5 (95% CI, 2.8-not estimable)	2.7 (95% CI, 1.0-5.4)	0.38 (95% CI, 0.15-1.00)
No of deaths, n (%)	25 (27)	17 (37)	
HRQoL, EORTC QLQ-C30, mean global health scores			Niivolimumab + ipilimumab and ipilimumab alone maintained QoL to a similar level
At baseline	76.9	80.9	
At week 7	69.2	74.5	
At week 13	78.5	72.2	
EQ-5D Mean utility index scores			
At baseline	0.861	0.847	
At week 7	0.788	0.789	
At week 13	0.894	0.834	
Any AEs, (number of patients (percent)) **Grade 3 or 4**	51 (54)	11 (24)	
Deaths related to study drugs	3	none	

Risk of Bias: NCT01927419 (CheckMate 069) consist of 1) Postow et al 2015 for PFS and AEs; 2) Abernethy et al 2015 for QoL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	Restricted randomization (2:1). Randomization stratified.
Allocation concealment?	Low	
Blinding of participants and personnel?	Low	Double-blinded
Blinding of outcome assessments?	Low	Double-blinded. Tumor assessed by blinded investigator.
Incomplete outcome data?	Low	
Selective reporting?	Low	All predefined and reported upon
Other sources of bias? PFS OS QoL SAEs	 Low High High High	The study was funded by Bristol-Meyers Squibb. Patients in the ipilimumab group was allowed to receive nivolumab after progression.
Conclusion	PFS: Low risk of bias OS, QoL and SAEs: High risk of bias	

Trial description: NCT01844505 (CheckMate 067) consist of Larkin et al 2015 for OS, PFS and SAEs

Trial: Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373(1):23-34.
Design: This is a randomised, double-blind, phase 3 multicentre study USA, Europe and Australia.. *No crossover* of patients between treatment groups. The database lock: February 17, 2015. The randomisation was stratified by BRAF mutation status.
Population: 945 patients with *previously untreated unresectable,* stage III or IV melanoma. Patients should have a known BRAF V600 mutation status. Age (years): ≥18, mean (range): 59(25-90), 59 (18-88) and 61 (18-89) respectively for nivolumab, nivolumab + ipilimumab, and ipilimumab. % male 63.9, 65.6 and 64.1 respectively.
Intervention/comparators: 945 patients randomised !:1:1 to receive one of the following: 3 mg nivolumab/kg every 2 weeks ; 1 mg nivolumab/kg every 3 weeks + 3 mg ipilimumab /kg every 3 weeks for 4 doses, followed by 3 mg of nivolumab/kg every 2 weeks for cycle 3 and beyond; or 3 mg ipilimumab /kg every 3 weeks for 4 doses. Both nivolumab and ipilimumab were administred intravenously. Patients could be treated after progression, provided that they had a clinical benefit and did not have substantial adverse effects.
Endpoints: *Primary:* Progression free survival and overall survival were coprimary endpoints. The results for PFS were presented in the publication, and the OS results was presented in the Appendix, S1. *Secondary*: SAEs. *Definitions of endpoints*: PFS: The time between the date of randomization and the date of documented progression or death, whichever occurred first. Patients treated after progression were considered to have had progressive disease at the time of the initial progression event, as assessed by the investigator, regardless of subsequent tumor responses. Safety: was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Efficacy analyses

performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug.
Patient flow **Stage** / **Intervention: Nivolumab+ ipilimumab** / **Control: Ipilimumab** / **Control: Nivolumab** All randomised patients (ITT), included in the PFS and OS efficacy analyses: 314 / 315 / 316 Patients in the AEs analysis: 313 / 311 / 313
Follow-up: A median follow-up ranging from 12.2 to 12.5 months across the three treatment groups for PFS and OS. Safety assessments were made continuously during the treatment phase and up to 100 days after the last dose of study drug.
Funding source: Bristol-Meyers Squibb

Data extraction: NCT01844505 (CheckMate 067) consist of Larkin et al 2015 for OS, PFS and SAEs

Endpoints	**Intervention: Nivolumab+ ipilimumab** (n=314)	**Control: Ipilimumab** (n=315)	**Control: Nivolumab** (n=316)	**HR, p-values**
Median PFS (months), at February 2015	11.5 (95% CI, 8.9- 16.7)	2.9 (95% CI, 2.8-3.4)	6.9 (95% CI, 4.3 -9.5)	HR for disease progression free survival for: nivolumab + ipililumab versus ipilimumab: 0.42 (99.5 % CI, 0.31-0.57); P<0.001; in favour of the combination group; and for nivolumab versus ipili-lumab : 0.57 (99.5 % CI, 0.43-0.76); P<0.001; in favour of the nivolumab group
No of deaths, n (%)	86 (27.5)	114 (36.7)	85 (27.2)	
Any AEs, (number of patients (percent)) **Grade 3 or 4**	215 (68.7)	173 (55.6)	136 (43.5)	
Deaths related to study drugs	Not reported	Not reported		

Risk of Bias: NCT01844505 (CheckMate 067) consist of Larkin et al 2015 for OS, PFS and SAEs

Entry/Domain	Judgement	Description
Random sequence generation?	Low	The subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain tthe subject number", page 47 in Protocol.
Allocation concealment?	Low	"Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS, ", page 47 in Protocol.
Blinding of participants and personnel?	Low	The study is double-blind
Blinding of outcome assessments?	Low	Double-blinded. Tumor assessed by blinded investigator
Incomplete outcome data?	Low	All patients accounted for
Selective reporting?	Low	All predefined and reported upon, (OS reorted on in the Appendix)
Other sources of bias? PFS OS QoL SAEs	Low	Funding was provided by Bristol-Meyers Squibb
Conclusion	Low for OS, PFS, SAEs	

Trial descriptions: NCT01227889 consist of: 1) Hauschild et al 2012 (BREAK-3) for PFS, OS, SAEs; 2) Hauschild et al 2013, ASCO for updates of PFS and OS; 3) Hauschild et al 2014, ESMO, for updates of OS and SAEs; 4) Grob et al 2014, SMR, for updates OS and SAEs; 5) Grob et al 2014 for QoL

Trials:

1) Hauschild A, Grob J-J, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380(9839):358-365;

2) Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. An update on BREAK-3, a phase III, randomised trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). J Clin Oncol 2013;1);

3) Hauschild et al. An update on overall survival (OS) and follow-on therapies in BREAK-3, a Phase III, randomised trial: dabrafenib (D) vs. dacarbazine (DTIC) in patients (pts) with BRAF V600E mutation-positive metastatic melanoma (MM). Annals of Oncology (2014) 25 (suppl_4): iv374-iv393. 10.1093/anonc/mdu344;

4) Grob et al. A Landmark Analysis of 3-year Overall Survival (OS) and Follow-On Therapies in BREAK-3, a Phase III, Randomised Trial: Dabrafenib vs. Dacarbazine (DTIC) in Patients (pts) with BRAF V600E Mutation-Positive Metastatic Melanoma. Poster vist på SMR 2014;
5) Grob JJ, Amonkar MM, Martin-Algarra S, Demidov LV, Goodman V, Grotzinger K, 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;25(7):1428-1436. All NCT01227889

Design: Randomised, open-phase, phase 3, controlled, multicentre in Europe, Russia, Australia, Canada. Patients in the dacarbazine group were allowed to *cross over* to receive dabrafenib after progression. Analyse cut-off date: 1) for Hauschild 2012: Dec 19, 2011; 2) for Hauschild 2013: June 2012 for PFS and December 2012 for OS

Population: 250 patients with unresectable stage III or IV melanoma, *$BRAF^{V600E}$ mutation-positive*. Age (years): ≥18, median (range): 53.0 (22-93) and 50.0 (21-82) respectively in intervention (I) and control (C) group. % male 60 and 59 respectively. Previous *untreated* other than with inter-leukin 2.

Intervention/comparators: 250 patients randomised 3:1 to dabrafenib (150 mg twice daily, orally) (n=187) or dacarbazine (1000 mg/m² i.v. every 3 weeks) (n= 63). Treatment continued until disease progression, death, study treatment discontinuation, or withdrawal.

Endpoints: *Primary:* PFS as assessed by the individual investigator. *Secondary*: Included PFS assessed by an IRC. OS, QoL (described in Grob 2014), safety. Definitions of endpoints: PFS: the time from randomization to the earliest date of radiographic or photographic disease progression or death due to any cause. QoL measured with EORTC-QLQ-C30 at baseline and week 6 and 12. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Efficacy analyses performed on intention –to-treat (ITT) population. The safety population included all randomised patients who received at least one dose.

Patient flow

Stage	**Dabrafenib**	**Dacarbazine**
Randomised (ITT), used in efficacy analyses, included QoL analyses	187	63
Included in the safety analyses	187	59
Included in QoL analyses	Completed baseline assessments: at least 90% of ITT. Completed assessments at week 6 and week 12: at least 80%	At least 90% At least 80%
Number of patients that had crossed over from dacarbazine to dabrafenib: in Hauschild 2012: Dec 2011: 24 in Grob 2014: through Jun 2012: 35 in Hauschild 2013, Dec 2012: 36 in Hauschild 2014, Jan 2014: 37 in Grob 2014, Aug 2014: 37		
Still on randomised treatment by data cut off: in Hauschild 2012: Dec 2011 in Hauschild 2013, Dec 2012 in Hauschild 2014, Jan 2014 in Grob 2014, Aug 2014	 107 Not given 24 (13%) 22 (12%)	 14 Not given 0 (0%) 0 (0%)

Follow-up:

Data cut off date/study	**Median follow-up (months) fo dabrafenib**	**Median follow-up (months) for dacarbazine**
Dec 2011, primary analysis for PFS and OS/Hauschild 2012	5	Not given

Update Jun 2012 for PFS /Hauschild 2013, ASCO	10.5	9.9
Update Dec 2012 for OS/Hauschild 2013, ASCO	15.2	12.7
Update Jan 2014 for OS, AEs/Hauschild 2014, ESMO	18.6	12.8
Update Aug 2014 for OS, SAEs/Grob 2014	18.7	13.6

SAEs assessed while patients were on study and for 28 days afterwards (Hauschild 2012). Assessed Aug 2014 (after 3 yrs) in Grob 2014.
QoL data were collected through 25 June 2012 (from Dec 2010).

Funding source: GlaxoSmithKline

Data extractions: NCT01227889 consist of: 1) Hauschild et al 2012 (BREAK-3) for PFS, OS, AEs; 2) Hauschild et al 2013, ASCO for updates of PFS and OS; 3) Hauschild et al 2014, ESMO, for updates of OS and AEs; 4) Grob et al 2014, SMR, for updates OS and AEs; 5) Grob et al 2014 for QoL

Endpoints/data cut off/median follow-up (months)	**Intervention: Dabrafenib** (n=187)	**Control: Dacarbazine** (n=63)	**HR, p-values**
Total no of deaths (%)/ Dec 2011/5 months	21 (11%)	9 (14%)	Overall survival HR: 0.61 (95% CI, 0.25-1.48), in favour of dabrafenib
Updates Dec 2012/15.2 and 12.7 months follow-up respectively for dabrafenib and dacarbazine	78 (42%)	28 (44%)	0.76 (95% CI, 0.48-1.21), in favour of dabrafenib
Updates Jan 2014/18.6 and 12.8 months follow-up respectively for dabrafenib and dacarbazine	115 (61%)	39 (62%)	0.77 (95% CI, 0.52-1.13), in favour of dabrafenib, but not statistically significant
Median OS (months) /Dec 2012/ medium follow-up not known	18.2 (16.6, NR)	15.6 (12.7, NR)	
Updates Jan 2014/18.6 and 12.8 months follow-up respectively for dabrafenib and dacarbazine	20.0 (16.8-24.4)	15.6 (12.7-21.2)	
Updates Aug 2014/18.7 and 13.6 months follow-up respectively for dabrafenib and dacarbazine	20.1 (16.7-24.4)	15.6 (11.9-21.2)	
Rates of OS (%) at **1 year/**data cut-off: Dec 2012	70 (62.4-75.8)	63 (48.9-74.1)	
2 years/data cut-off: Jan 2014	45 (37.3-51.9)	32 (20.3-45.0)	
3 years /data cut-off: Aug 2014	31 (23.9-37.7)	28 (16.9-40.8)	HR: 0.81 (95% CI, 0.56-1.18), in favour of dabrafenib, but not statistically significant
Median PFS (months), as *measured by individual in-*			

vestigators (primary end-point)/ Dec 2011/4.9 months Updates Jun 2012/10.2 months	5.1 6.9	2.7 2.7	HR: 0.30 (95% CI, 0.18 -0.51), p<0.0001 HR: 0.37 (95% CI, 0.23-0.57)
Median PFS (months), as *measured by independent review* (secondary end-point)/ Dec 2011/4.9 months	6.7	2.9	HR: 0.35 (95% CI, 0.20 -0.61), p<0.0001
HRQL, with EORTC QLQ-C30	In favour of dabrafenib. "Clinically, meaningful changes were observed at week 6 and 12 for two of five functional and six of eight symptoms dimensions. Although the remaining dimensions (except role function and pain) did not meet the minimum clinically important differences (MCIDs), the mean favored dabrafenib".		
Any AEs Grade 4 (number of patients (percent))/Dec 2011 **Any SAEs** (number of patients (percent))/Jan 2014 and Aug 2014	No figures for any AEs Grade 3 and 4 60/187 (32)	No figures for any AEs Grade 3 and 4 14/59 (24)	
Deaths related to study drugs/Dec 2011	Not reported	Not reported	

Risk of Bias: NCT01227889 consist of: 1) Hauschild et al 2012 (BREAK-3) for PFS, OS, AEs; 2) Hauschild et al 2013, ASCO for updates of PFS and OS; 3) Hauschild et al 2014, ESMO, for updates of OS and AEs; 4) Grob et al 2014, SMR, for updates OS and AEs; 5) Grob et al 2014 for QoL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	Restricted (3:1), stratified randomization by a computerized system: "A centrally located, computerised, interactive, voice activated response system controlled assignment of patient treatment". "Eligible patients were randomly assigned (ratio 3:1) to receive either oral dabrafenib or intravenous dacarbazine". "We stratified patients according to American Joint Committee on Cancer stage (unresectable III+IVM1a+IVM1b *vs* IVM1c", (p 359in-Hauschild 2012).
Allocation concealment?	Low	This is an open-label study. But even if participants and investigators will know the assignment, we assume that

		this will have no impact on the endpoints, ie SAEs (hospitalization).” .. a masked independent review committee (IRC) reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarbazine to dabrafenib”.
Blinding of participants and personnel? OS PFS HRQoL SAEs	 Low Low High Low	 An open study will have no impact on assessment of OS. “Although investigators were aware of treatment group when assessing progression-free survival, a masked independent review committee (IRC) reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarba zine to dabrafenib”, (p 359 in Hauschild 2012). The EORTC QLQ-C30 was used, this is a self-reporting instrument, hence the patients could be biased. Even if participants and investigators will know the assignment, we assume that this will have no impact on the outcome SAEs (hospitalization).
Blinding of outcome assessments?	Low	See the comments above
Incomplete outcome data?	Low	All patients accounted for
Selective reporting? OS, PFS, HRQoL and SAEs	 Low	 All endpoints were predefined, and all were reported on
Other sources of bias? PFS OS, SAEs, QoL	 Low High	Patients in the dacarbazine group were allowed to cross over to dabrafenib after progression was confirmed by independent review. This will influence the results for all endpoints, except PFS . Funding was provided by GlaxoSmithKline
Conclusions:	PFS: Low risk of bias OS, HRQoL and SAEs: High risk of bias	

Trial description: NCT01006980 (BRIM-3) consist of 1) Chapman et al 2011 for PFS, OS, SAEs; 2) McArthur et al 2011 for updated OS (additional 3 months); 3) Hauschild et al 2011 for updated OS (additional 3 months); 4) Chapman 2012, updated OS (12 months); McArthur et al 2014 for OS, PFS, SAEs

Trials:

1) Chapman PB, Hauschild A, Robert C,Haanen JB, Ascierto P, Larkin J, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med 2011;364(26):2507-2516.
2) McArthur G, Hauschild A, Robert C, Haanen JB, Ascierto P, Lee RJ, et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: Updated survival results from a phase III randomised, open-label, multicentre trial. Eur J Cancer 2011;47:14.
3) Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. An update on BREAK-3, a phase III, randomised trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). J Clin Oncol 2013;1).
4) Chapman PB, Hauschild A, Robert C, Larkin JMG, Haanen J, Ribas A, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomised, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. J Clin Oncol 2012;30(15 suppl. 1).
5) McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, 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. The Lancet Oncology 2014;15(3):323-332.

Design: Randomised, open-label (from protocol) phase 3, multicentre in 12 countries worldwide. No cross over between treatment groups.

Analyse cut-off date:

1) Chapman 2011: December 2010 (this is the interim analysis present in this study).
2) McArthur 2011: March 2011
3) Hauschild 2011: March 2011
4) Chapman 2012: November 2011
5) McArthur 2014: February 2012

Patient cross over or not:

1) Chapman 2011: No cross over of patients.

A protocol amendment of January 2011 recommended patients in dacarbazine group to cross over to vemurafenib. This means that the follow-up trials will included patients that have crossed over:

2) McArthur 2011; 3) Hauschild 2011; 4) Chapman 2012 and 5) McArthur 2014 all included patients that had crossed over.

Population: 675 patients with unresectable, *previously untreated* stage III C or IV melanoma that tested *positive for the BRAF V600E mutation*. Age (years): ≥18, median (range): 56 (21-86) and 52 (17-86) respectively in intervention (I) and control (C) group. % male 59 and 54 respectively.

Intervention/comparators: 675 patients randomised 1:1 to vemurafenib (960 mg twice daily orally) (n=337) or dacarbazine (1000 mg/m² i.v. every 3 weeks) (n= 338). These patients included 20 with non-V600E mutations.

Treatment was discontinued on disease progression unless continued treatment was in the best interest of the patient in the judgement of the investigator and the sponsor (Chapman 2011).

An amendment of January 2011 recommended that patients in the dacarbazine group was *allowed to cross* over to vemurafenib, this will apply for the trials 2) McArthur 2011; 3) Hauschild 2011; 4) Chapman 2012; and 5) McArthur 2014.

Endpoints:

1) Chapman 2011: *Coprimary:* Rates of OS and PFS. *Secondary*: Included AEs. *Definitions of endpoints*: Survival: the time from randomization to death from any cause. PFS: the time from randomization to documented disease progression or death. Tumor responses were determined by

investigators according to RECIST, version 1.1. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

2) McArthur 2011: Updated analysis of OS with an additional 3 months follow-up. Survival data were censored at time of crossover for the 50 patients who had crossed over to vemurafenib after releasing of results in January 2011.
3) Hauschild 2011: Updated analysis of OS with an additional 3 months follow-up. Survival data were censored at time of crossover for the 50 patients who had crossed over to vemurafenib after releasing of results in January 2011.
4) Chapman 2012: Updated OS, 12 months. OS data for dacarbazine patients that crossed to vemurafenib were censored at the time of cross over.
5) McArthur 2014: OS, PFS, AEs. OS and PFS data were censored at crossover. They however also give analysis without censoring at crossover. We will use the data without censoring in our network analyses.

Efficacy analyses performed on intention –to-treat (ITT) population. The safety population included all patients who received a study drug and who had undergone at least one assessment during the study.

Patient flow

Stage	**Vemurafenib**	**Dacarbazine**
Randomised (ITT), included in efficacy analyses	337	338
Patients evaluated for OS in Chapman 2011	336	336
Patients evaluated for OS with censoring at crossover in McArthur 2014	337	338
Patients evaluated for OS without censoring at crossover in McArthur 2014	337	338
Patients evaluated for PFS in Chapman	275	274
Patients evaluated for PFS with censoring at crossover in McArthur 2014	337	338
Patients evaluated for PFS without censoring at crossover in McArthur 2014	337	338
Patients evaluated for AEs in Chapman 2011	336	282
Patients evaluated for AEs in McArthur 2014	337	287
Number of patients that have crossed over from dacarbazine to vemurafenib at data cut off for: Chapman 2011: none McArthur 2011: 50 Hauschild 2011: 50 Chapman 2012: 81 McArthur 2014: 83		

Follow-up:

Median follow-up:

1) Chapman 2011 (the interim analysis): 3.8 and 2.3 months for the patients in the vemurafenib group and the dacarbazine group respectively.
2) McArthur 2011: 6.1 months (range<1-13.9) and 4.46 months (range<1-11.7) in the vemurafenib group and the dacarbazine group respectively.
3) Hauschild 2011: 6.2 months
4) Chapman 2012: 10.5 months (range 0.4-18.1) and 8.4 months (range<1-18.3) in the vemurafenib group and the dacarbazine group respectively
5) McArthur 2014: 12.5 months (IQR 7.7-16.0) and 9.5 months (IQR3.1-14.7) in the vemurafenib group and the dacarbazine group respectively

AEs monitoring continued for up to 28 days after the last dose of study drug or until any ongoing events resolved or stabilized (Chapman 2011).

Funding source: Hoffmann-La Roche

NCT01006980 (BRIM-3) consist of 1) Chapman et al 2011 for PFS, OS, AEs; 2) McArthur et al 2011 for updated OS (additional 3 months); 3) Hauschild et al 2011 for updated OS (additional 3 months); 4) Chapman 2012, updated OS (12 months); McArthur et al 2014 for OS, PFS, AEs

Endpoints	**Intervention: Vemurafenib** (n=337)	**Control: Dacarbazine** (n=338)	**HR, p-values**
Median OS months			
Dec 2010, no crossover	Not reached	Not reached	
March 2011, censored at time of crossover	Has not been reached (95% CI, 9.59-NR)	7.89 (95% CI, 7.26-9.63)	
November 2011, censored at time of crossover	13.2 (95% CI, 12.0-15.0)	9.6 (95% CI, 7.9-11.8)	
February 2012, with censoring at time of crossover	13.6 (95% CI, 12.0-15.2)	9.7 (95% CI, 7.9-12.8)	
February 2012, without censoring at time of crossover	13.6 (95% CI, 12.0-15.2)	10.3 (95% CI, 9.1-12.8)	
OS (%) at			
6 months (Chapman 2011), no crossover	84 (95% CI, 78 -89)	64 (95% CI, 56-73)	Overall survival HR: 0.37 (95% CI, 0.26-0.55); P<0.001 in favour of vemurafenib
6 months (McArthur 2011; Hauschild 2011), censored at time of crossover	83	63	0.44 (95% CI, 0.33-0.59); favouring vemurafenib
6 months (McArthur 2014), with censoring at time of crossover	84 (80-88)	66 (61-72)	
6 months (McArthur 2014), without censoring at time of crossover	84 (80-88)	67 (62-72)	
	55	43	HR for death:

12 months (Chapman 2012), censored at time of crossover 12 months (McArthur 2014), with censoring at time of crossover 12 months (McArthur 2014), without censoring at time of crossover 18 months (McArthur 2014), without censoring at time of crossover	56 (95% CI, 50-61) 56 (95% CI, 50-61) 39 (95% CI, 33-45)	44 (95% CI, 38 -51) 46 (95% CI, 40-51) 34 (95% CI, 29-40)	0.62 (95% CI, 0.49-0.77); favouring vemurafenib HR for death: 0.70 (95% CI, 0.57-0.87); p=0.0008 HR for death: 0.76 (95% CI, 0.63-0.93); p=0.0068
Median PFS (months), December 2010 , no crossover February 2012, with censoring at time of crossover February 2012, without censoring at time of crossover	5.3 6.9 (95% CI, 6.1-7.0)	1.6 1.6 (95% CI,1.6-2.1)	HR for tumor progression: 0.26 (95% CI, 0.20-0.33); P<0.001 in favour of vemurafenib HR: 0.38 (95% CI, 0.32-0.46); P<0.0001 in favour of vemurafenib; Log-rank test: P<0.0001 Log-rank test: P<0.0001
PFS (%), at 18 months (McArthur 2014), without censoring for crossover	14 (95% CI,10-19)	6 (3-9)	
Any AEs, (number of patients (percent)) Chapman 2011 **Grade 3 or 4** McArthur 2014 (Grade 4 or worse)	Not reported 29 (8)	Not reported 32 (11)	

Deaths related to study drugs	Not reported in any of the trials	Not reported in any of the trials	

Risk of Bias: NCT01006980 (BRIM-3) consist of 1) Chapman et al 2011 for PFS, OS, AEs; 2) McArthur et al 2011 for updated OS (additional 3 months); 3) Hauschild et al 2011 for updated OS (additional 3 months); 4) Chapman 2012, updated OS (12 months); McArthur et al 2014 for OS, PFS, AEs

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"Randomization to the treatment groups will be done in a 1:1 Ratio", (p 4 in protocol).The randomization was stratified with respect to cancer stage, geographic region and serum lactate dehydrogenase.
Allocation concealment?	Low	This is an open-label study. But even if participants and investigators will know the assignment, we assume that this will have no impact on the endpoints: OS; PFS (measured by CT, SAEs (hospitalization).
Blinding of participants and personnel?	Low	See above
Blinding of outcome assessments?	Low	See above
Incomplete outcome data? OS, at 6 months PFS, analyzed in Dec 2010 OS and PFS, analyzed after Dec 2010 *with* censoring for cross over OS and PFS, analyzed after Dec 2010 *without* censoring for cross over AEs (only data after Dec 2010), and without censoring	 Low Low Low Low Low	
Selective reporting?	Low	All endpoints predefined in protocol, and all reported for
Other sources of bias?		There was no cross over in the Chapman 2011 study. However, a protocol amendment of January 2011 recommended patients in dacarbazine group to cross over to vemurafenib. This means that all the follow-up trials will included patients that had crossed over. Further, they have analysed all endpoints, except for those in Chapman 2011, "with censoring at time of crossover" and "without

		censoring at time of crossover". This means that those that are censored do not have any cross over problem, whereas the results from data without censoring will be bias. However, in our network analyses we will use the results from the analyses without censoring, since this is what all the other trials included in our HTA have used. The study was funded by Hoffmann-La Roche-Genetech
OS, at 6 months PFS, analyzed in Dec 2010	Low	
OS and PFS, analyzed after Dec 2010 *with* censoring for cross over	Low	
PFS, analyzed after Dec 2010 *without* censoring for cross over	Low	
OS analyzed after Dec 2010 *without* censoring for cross over	High	
AEs (only data after Dec 2010), and without censoring	High	
Conclusion:	OS and AEs analyzed after Dec 2010 *without* censoring for cross over: High risk of bias. For the other endpoints: Low risk of bias	

Trial descriptions: NCT01072175 (BRF113220 study) consist of 1) Flaherty et al 2012, part C of the study, PFS, OS (12 months) and SAEs; 2) Flahert et al ASCO abstract 2014, 18 months updates of OS; 3) Daud et al ASCO 2015, updated OS

Trials:

1) Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations. N Engl J Med 2012;367(18):1694-1703.

NCT01072175;

2) Flaherty K, Daud A, Weber JS, Sosman JA, Kim K, Gonzalez R, et al. Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM). J Clin Oncol 2014;1).
3) Daud A, et al. Updated overall survival (OS) results for BRF113220, a phase I–II study of dabrafenib alone versus combined dabrafenib and trametinib in patients with BRAF V600 metastatic melanoma (MM). J Clin Oncol I (Meeting Abstracts) 2015;33(15):Suppl 9036.

Design: We include the results from Part C of the study, this is a randomised, open –label, phase 2, multicentre study in North America and Australia. Patients with disease progression while receiving dabrafenib *could cross over* to receive combination therapy (150/2). Analyse cut-off dates: 1) For Flaherty 2012: May 2012; for Flaherty 2014: January 2014: 3) Daud 2015: January 2015

Population: 162 patients with metastatic melanoma *with either BRAF V600E or BRAF V600K mutations. Both previously untreated/treated.* Age (years): ≥18, median (range): 50 (18-82) and 49 (23-85) and 58 (27-79) respectively in intervention (I) and the control (C) groups (150/1 and 150/2 respectively). % male 54, 56 and 63 respectively.

Intervention/comparators: 162 patients randomised 1:1: to oral dabrafenib (150 mg twice daily) +once daily trametinib, at a dose of either 1 mg (combination 150/1 or 2 mg (combination 150/2), or dabrafenib monotherapy (150 mg twice daily). The study went on until the prespecified rate of progression events required for final analysis in part C (70% across the three study groups) was reached (May 2012).

Endpoints: 1) Flaherty 2012: *Primary:* PFS, safety. *Secondary*: Included OS at 12 months. 2) Flaherty 2014: Update of OS at 18 months. *Definitions of endpoints*: Not defined. PFS was assessed both by investigator and by IRC. 3) Daud 2015, updated OS

Efficacy analyses performed on intention –to-treat (ITT) population. The safety population was not defined.

Patient flow

Stage	**Intervention: Dabrafenib + trametinib 1 mg (150/1)**	**Intervention: Dabrafenib + trametinib 2 mg (150/2)**	**Control: Dabrafenib monotherapy**
Randomised (ITT), included in efficacy analyses	54	54	54
Patients evaluated for PFS	54	54	54
Patients evaluated for OS	54	54	54
Patients evaluated for AEs	54	55	53
Patients that crossed over: 1) Flaherty 2012:80% of the patients in the monotherapy group crossed over to the 150/2 group at the time of progression. 2) Flaherty 2014: 83% cross over at time of analysis 3) Daud 2015:			

Follow-up:

1) Flaherty 2012: At the time of the prespecified efficacy analysis (May 2012) the median follow-up for the patients in part C was 14.1 months (range, 10.8-17.6).
2) Flaherty 2012: Median follow-up: 24 months.

Funding source: GlaxoSmithKline

Data extractions: NCT01072175 (BRF113220 study) consist of 1) Flaherty et al 2012, *part C of the study* for PFS, OS (12 months) and AEs; 2) Flahert et al ASCO abstract 2014, 18 months updates of OS; 3) Daud et al ASCO 2015, updated OS

Endpoints	**Intervention: Dabrafenib + trametinib 1 mg (150/1)** (n=54)	**Intervention: Dabrafenib + Trametinib 2 mg (150/2)** (n=54))	**Control: Dabrafenib monotherapy** (n=54)	**HR, p-values**
Median PFS (months), as measured by investigator	9.2 (6.4-11.0)	9.4 (8.6-16.7)	5.8 (4.6-7.4)	HR for progression or death: 0.56 (95% CI, 0.37-0.87); P=0.006; and 0.39 (95% CI, 0.25-0.62); P<0.001 in favour of the 150/1 and 150/2 groups respectively.

Median PFS (months), as measured by IRC	Was less pronounced			HR: 0.55 (95% CI, 0.33-0.93); P=0.02
PFS (%) at 12 months	26 (15-39)	41 (27-54)	9 (3-20	P<0.001 for the comparison 150/2 vs monotherapy
Total no of deaths n (**%)** at 12 months 18 months 36 months	 Not reported 27 (50) Not reported	 11 (21) 25 (46) 36 (67)	 16 (30) 31 (57) 41 (76)	
Median OS (months) at 12 months 18 months 36 months	 Not reached 18.7 (13.7- NR) Not reported	 Not reached 23.8 (17.5- NR) 25.0 (17.5-36.5)	 Not reached 20.2 (14.5-25.9) 20.2 (14.5-27.1)	 HRs: 0.96 (95% CI, 0.57-1.60), P=0.87 and 0.73 (95% CI, 0.43-1.24), P=0.24 in favour of combination treatment respectively for 150/1 and 150/2 0.77 (0.49-1.21)
Rates of OS (%) at 12 months 18 months 24 months 36 months	 69 51 Not reported Not reported	 80 63 51 38	 70 56 44 31	
Any AEs, number of patients (percent)) **Grade3 or 4** at 12 months at 18 months	 26 (48) Not reported	 32 (58) Not reported	 24 (43) Not reported	
Deaths related to study drugs at 12 months at 18 months	 None Not reported	 none not reported		

Risk of Bias: NCT01072175 (BRF113220 study) consist of 1) Flaherty et al 2012, part C of the study for PFS, OS (12 months) and AEs; 2) Flahert et al ASCO abstract 2014, 18 months updates of OS

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"Subjects will be assigned to study treatment in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software", p 31 in protocol.
Allocation concealment?	Low	As above
Blinding of participants and personnel?	Low	This is an open-label study. But even if participants and investigators will know the assignment, we assume that this will have no impact on the endpoints: OS; PFS (size ≥10 mm by MRI or CT, less than 10 mm measured by physical examination), p 89 in protocol. The PFS was measured both by investigator and by an IRC; and on SAEs (hospitalization).
Blinding of outcome assessments?	Low	As above
Incomplete outcome data? OS PFS SAEs	 Low Low Low	All patients accounted for
Selective reporting?		All endpoints predefined in protocol, (p 123), and all were reported upon
Other sources of bias? OS PFS SAEs	 High Low High	Patients who had disease progression while receiving dabrafenib monotherapy could cross over to receive combination 150/2", p 1695 in Flaherty 2012. This will introduce a risk of bias for all endpoints measured after progression, ie. For OS and SAEs. The study was supported by GlaxoSmithKline
Conclusions	OS: High risk of bias PFS: Low risk of bias SAEs: High risk of bias	

Trial descriptions: NCT01584648 (Combi-D study) consist of 1) Long et al 2014 for PFS, interim OS, SAEs; 2) Long et al 2015 for Final OS, updated PFS, SAEs; 3) Schadendorf 2015 abstract

Trials:

1) Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. N Engl J Med 2014;371(20):1877-1888;

2) Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, 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;386(9992):444-451.

3) Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, 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;51(7):833-840.

Design: This is a randomised, double-blind, phase 3 multicentre study in North America, Australia, Europe and Russia. Subjects were *not permitted to crossover* to combination therapy until after the Final OS analysis. Analyse cut-off dates: 1) Long 2014: August 2013; 2) Long 2015: January 2015; 3) Schadendorf 2015: Not given.

Population: 423 patients with unresectable stage IIIC or stage IV metastatic melanoma *with BRAF V600E or BRAF V600K mutations. Previously untreated with systemic anticancer therapy.* Age (years): ≥18, median (range): 55.0 (22-89) and 56.5 (22-86) respectively for dabrafenib plus trametinib and for dabrafenib alone. % male 53 and 54 respectively.

Intervention/comparators: 423 patients randomised 1:1: to either a combination of oral dabrafenib (150 mg twice daily, and oral trametinib (2 mg once daily) or dabrafenib (150 mg twice daily) + placebo. Patients were stratified according to BRAF genotype.

Endpoints:

1) Long 2014: *Primary:* PFS. *Secondary*: OS, safety.

2) Long 2015 Final OS, updated PFS and AEs

3) Schadendorf 2015:QoL. *Definitions of endpoints*: PFS: the time from randomization until disease progression or death of any cause, assessed by investigator according to RECIST (Respons Evaluation Criteria in Solid Tumors), version 1.1. OS: the time from randomization to death of any cause. Safety: was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. HRQoL was assessed by (EORTC-QLQ)-C30 at baseline, weeks 8, 16, 24, 40 and up to progression. Efficacy analyses performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug. The HRQoL questainnaire completion rates were >95% at baseline, >85% to week 40 and >70% at disease progression.

Patient flow

Stage	**Intervention: Dabrafenib + trametinib**	**Control: Dabrafenib + placebo**
Randomised (ITT) included in efficacy analyses	211	212
Patients in the AEs analysis	209	211
Still on randomised treatment by data cut off of Jan 2015, n (%)	64 (30)	35 (17)

Follow-up:

1) Long 2014: Until the time of the prespecified number of disease progressions or deaths (whichever came first)) had occurred (August 2013). *The median follow-up time was 9 months* (range, 0-16). A prespecified interim analysis of OS was planned at the time of the analysis of PFS. A final OS analysis will be conducted when 70% of the randomised patients have died or been lost to follow up. AEs Throughout the study until 30 days after the discontinuation of study treatment.
2) Long 2015/Updates 2015: Median follow-up, months (range): 20 (0-30) and 16 (0-32) respectively in dabrafenib+ trametinib and dabrafenib group.

Funding source: GlaxoSmithKline

Data extraction: NCT01584648 (Combi-D study) consist of 1) Long et al 2014 for PFS, interim OS, safety; 2) Long et al 2015; for Final OS, updated PFS and AES. 3) Schadendorf 2015 for HRQoL

Endpoints	**Intervention: Dabrafenib + trametinib** (n=211)	**Control: Dabrafenib + placebo** (n=212)	**HR, p-values**
Median PFS (months), August 2013 January 2015	 9.3 11.0 (8.0-13.9)	 8.8 8.8 (5.9-9.3)	HR for disease progression or death: 0.75 (95% CI, 0.57-0.99); P=0.03 0.67 (95% CI, 0.53-0.84); P=0.0004 Both in favour of the dabrafenib-trametinib group
Total no of deaths n (**%)** at August 2013 January 2015	 40 (19) 99 (47)	 55 (26) 123 (58)	HR for death: 0.63 (95% CI, 0.42-0.94); P=0.02 0.71 (95% CI, 0.55-0.92); P=0.0107
Median OS (months) at August 2013 January 2015	 Not reached 25.1 ((95% CI, 19.2-not reached)	 Not reached 18.7 (15.2-23.7)	
Rates of OS (%) At 6 months At Final OS analysis, % (95% CI) 1 year 2 years	 93 74 (67-79) 51 (44-58)	 85 68 (61-74) 42 (35-49)	
HRQoL, overall	In favour of the combination treatment. "Dabrafenib + trametinib provides better preservation of HRQoL and pain improvements versus dabrafenib monotherapy. For nausea, vomiting, diarrhoea, dyspnoea and constipation scores trended in favour of dabrafenib monotherapy".		
Any AEs, (number of patients (percent)) **Grade 3,** at Aug 2013, Jan 2015	 66 (32) 66 (32)	 72 (34) 63 (30)	
Deaths related to study drugs Aug 2013 Jan 2015	 0 0	 0 1	

Risk of Bias: NCT01584648 (Combi-D study) consist of 1) Long et al 2014 for PFS, interim OS, safety; 2) Long et al 2015; for Final OS, updated PFS and AES. 3) Schadendorf 2015 for HRQoL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"Randomization will be done centrally using a randomization schedule generated by the GSK Biostatistical Department, which will assign subjects in a 1:1 ratio", (p 33 in protocol)
Allocation concealment?	Low	"Upon completion of all the required screening assessments, eligible subjects will be registered into the Registration and Medication Ordering System (RAMOS), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff. RAMOS allows study sites to register and randomize subjects, and also records stratification information." (Neither GSK, the site, nor the subject will know the treatment assignment," (p 33 in protocol).
Blinding of participants and personnel?	Low	"Study treatment will be double-blinded. Neither GSK, the site, nor the subject will know the treatment assignment. Every effort must be made to maintain the blind until the final PFS analysis is performed",(p 33 in protocol).
Blinding of outcome assessments?	Low	Cannot find that described specifict. But assume low risk of bias for OS; and for PFS ("tumor assessments size ≥10 mm with MRI or CT, when the scan slice thickness is <5 mm",(p 104 in projectplan; as well as for SAEs (hospitalization required).
Incomplete outcome data? OS PFS QoL SAEs	 Low Low Low Low	All patients accounted for
Selective reporting?	Low	All endpoints predefined in protocol, (p 27 and 28), and all were reported on
Other sources of bias?	Low	The study was funded by GlaxoSmithKline
Conclusion overall for all endpoints:	Low risk of bias	

Trial descriptions: NCT01689519 (CoBRIM) consist of 1) Larkin et al 2014 for PFS, interim OS, safety; 2) Larkin et al 2015, ASCO for update of PFS; 3) Dréno et al 2015 ASCO for QoL

Trials:

1) Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. N Engl J Med 2014;371(20):1867-1876.

2) Larkin JMG, Yan Y, McArthur GA, Ascierto PA, Liszkay G, Maio M, et al. Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced *BRAF*mutated melanoma. J Clin Oncol 33, 2015 (suppl; abstr 9006).
3) Dréno B, Bartley K, Ascierto PA, Atkinson V, Liszkay G, Maio M, et al. Quality- of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). J Clin Oncol 33, 2015 (suppl; abstr 9021).

Design: This is a randomised, double-blind, phase 3 multicentre study in |USA, Canada, Australia, New Zealand, Europe, Russia, Turkey, and Isreal. Contunuation of the study treatment or *crossover after disease progression was not permitted*. Analyse cut-off dates: 1) Larkin 2014: May 2014; 2) Larkin 2015: January 2015, 3) Dréno 2015: not reported.

Population: 495 patients with unresectable, locally advanced stage IIIC or IV melanoma *with a BRAF V600 mutations. Previously untreated.* Age (years): ≥18, median (range): 56 (23-88) and 55 (25-85) respectively for vemurafenib + cobimetinib and for vemurafenib + placebo. % male 59 and 56 respectively.

Intervention/comparators: 495 patients randomised 1:1: to receive vemurafenib orally (960 mg twice daily) + cobimetinib (60 mg once daily for 21 days, followed by 7 days off) (combination group) or vemurafenib + placebo (control group). The study treatment continued until patients withdrew consent, unacceptable AEs, or disease progression occurred. Continuation of the study treatment *or crossover after disease progression was not permitted.*

Endpoints: 1) Larkin 2014: *Primary:* PFS as assessed by the investigator. *Secondary*: included OS, PFS assessed by IRC, safety.2) Larkin 2015: Update of PFS; 3) Dréno 2015: QoL.
Definitions of endpoints: PFS: as the time between the date of randomization and the date of the first documented event of disease progression or death, whichever occurred first according to the assessment of the investigator according to RECIST criteria. QoL: assessed by EORTC-QLQ-C30 at baseline and up to 224 days (8 cycles). Safety: graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
Efficacy analyses performed on intention –to-treat (ITT) population. Safety was analyzed according to the study treatment received.

Patient flow

Stage	**Intervention: Vemurafenib+ cobimetinib**	**Control: Vemurafenib+ placebo**
Randomised (ITT), included in efficacy analyses, including HRQoL	247	248
Patients in the AEs analysis*	254	239

*****Eight patients assigned to the control group received investigational cobimetinib as a result of dispensing errors.

Follow-up:
1) Larkin 2014: Until the time of the prespecified number of progression events (206) events) was reached (May 2014). *The median follow-up time was 7.3 9 months* (*range, 0.5-16.5).* Two interim analyses of OS were planned: the first at the time of the final analysis of PFS, and the second interim analysis of OS when 256 deaths have occurred. The final after 385 deaths are
2) recorded.
3) Larkin 2015: *The median follow-up time was about 14 months.*
3) Dréno 2015: Until patient withdrawal or end of study.

Funding source: F. Hoffmann-La Roche/Genentech

Data extraction: NCT01689519 (CoBRIM) consist of 1) Larkin et al 2014 for PFS, interim OS, safety; 2) Larkin et al 2015, ASCO for update of PFS; 3) Dréno et al 2015 ASCO for QoL

Endpoints	**Intervention: Vemurafenib+ cobimetinib** (n=247)	**Control: Vemurafenib+ placebo** (n=248)	**HR, p-values**
Median PFS (months), May 2014, according to investigator assessment	9.9 (95% CI, 9.0-NR)	6.2 (95% CI, 5.6-7.4)	HR for death or disease progression: 0.51 (95% CI, 0.39-0.68); P<0.001
May 2014, according to IRC	11.3 (95% CI, 8.5-NR)	6.0 (95% CI, 5.6-7.5)	0.60 (95% CI, 0.45-0.79);P<0.001
January 2015, according to investigator	12.3 (95% CI, 9.5-13.4)	7.2 (95% CI, 5.6-7.5)	HR: 0.58 (95% CI, 0.46-0.72), P not given
Total no of deaths n (**%)** at May 2014	34	51	
Median OS (months) at May 2014	Not reached	Not reached	
Rates of OS (%) At 9 months, interim (May 2014), at this time had not crossed the prespecified HR boundary for significance	81 (95% CI, 75-87)	73 (95% CI, 65-80)	HR for death: 0.65 (95% CI, 0.42-1.00); P=0.046
HRQoL, assessed with EORTC-QLQ-C30 up to C8D1 (each C=28 days)	Similar QOL in the two groups		
Any AEs, (number of patients (percent)) at May 2014			
Grade 3	125 (49)	117 (49)	
Grade 4	34 (13)	22 (9)	

Deaths related to study drugs May 2014	Not reported	not reported	

Risk of Bias: NCT01689519 (CoBRIM) consist of 1) Larkin et al 2014 for PFS, interim OS, safety; 2) Larkin et al 2015, ASCO for update of PFS; 3) Dréno et al 2015 ASCO for QoL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"A stratified, permuted, block randomization scheme will be used to obtain approximately a 1:1 ratio between the 2 treatment groups", (p 85 in protocol).
Allocation concealment?	Low	"After written informed consent has been obtained and eligibility has been established, each patient will be assigned an identification number and be randomized to 1 of the 2 treatment arms through use of an IxRS" (interactive response system). "Patients and investigators will remain blinded to treatment assignment unless unblinding is recommended by the DSMB," (p 85 in protocol).
Blinding of participants and personnel?	Low	"The investigator, patient, and Sponsor will be blinded to treatment assignment", (p 85 in protocol).
Blinding of outcome assessments?	Low	"The process for independent review of tumor evaluations will be outlined in a separate study manual. Tumor assessments with CT or MRI scans".. "All scans will be collected for independent review",(p 88 in protocol). The investigator, patient, and Sponsor will be blinded to treatment assignment", (p 82 in protocol)
Incomplete outcome data?	Low	All patients accounted for
Selective reporting?	Low	All endpoints predefined, and reported upon, p 69 in protocol
Other sources of bias?	Low	The study was funded by F. Hoffmann-La Roche/Genentech
Conclusion	Low risk of bias for all endpoints	

Trial descriptions: NCT01597908 (Combi-V study) consist of 1) Robert et al 2015 for OS, PFS, SAEs; and 2) Grob et al 2015 for HRQoL

Trials:

1) Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. N Engl J Med 2015;372(1):30-39.
2) Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol 2015;16(13):1389-1398.

Design: This is a randomised, open-label, phase 3 multicentre study in Europe, Australia and North-America. *Crossover was prohibited* until the IDSMC recommended stopping the study early for efficacy. Analyse cut-off date: June 2014. Then a protocol amendment was issued that allowed for crossover to the combination-therapy group for patients assigned to the vemurafenib group, *but no patient had crossed over* as of the effective data freezing date of June 27, 2014.

Population: 704 patients with unresectable stage IIIC or IV melanoma *with BRAF V600E or BRAF V600K mutations. Previously untreated .* Age (years): ≥18, median (range): 55 (18-91) and 54 (18-88) respectively for dabrafenib plus trametinib and for vemurafenib alone. % male 59 and 51 respectively.

Intervention/comparators: 704 patients randomised 1:1: to either a combination of dabrafenib (150 mg orally twice daily) + trametinib (2 mg orally once daily) (n=352) or vemurafenib (960 mg orally twice daily) (n=352). Patients were stratified for BRAF mutation status.

Endpoints: *Primary:* OS. *Secondary*: included PFS and safety. *Definitions of endpoints*: OS: the time from randomization until death from any cause. PFS: the time from randomization until the earliest date of disease progression or death due to any cause. Assessed by investigator, and confirmed with a scan at least 4 weeks after. AEs: were graded by the investigator, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. HRQoL was assessed by EORTC QLQ-C30, EQ-5D, and FACT-M.
Efficacy analyses performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug.

Patient flow

Stage	**Intervention: Dabrafenib + trametinib**	**Control: Vemurafenib**
Randomised (ITT), included in efficacy analyses (OS, PFS, HRQoL)	352	352
Patients in the AEs analysis	350	349

Follow-up: At the time when the prespecified stopping boundary (P<0.0214) for OS was crossed.
The median follow-up durations were 11 months and 10 months, and the median exposure durations were 10 and 6 months in the combination-therapy group and the vemurafenib group, respectively.
AEs: Until 30 days after the discontinuation of study treatment.
HRQoL: to week 48 and at disease progression.

Funding source: GlaxoSmithKline

Data extraction: NCT01597908 (Combi-V study) consist of 1) Robert et al 2015 for OS, PFS, SAEs; and 2) Grob et al 2015 for HRQoL

Endpoints	**Intervention: Dabrafenib + trametinib** (n=352)	**Control: Vemurafenib** (n=352)	**HR, p-values**
Median PFS (months), June 2014 assessed by investigator	11.4	7.3	HR for progression or death: 0.56 (95% CI, 046-0.69); P<0.001
Median OS (months) at June 2014	Not reached	17.2	HR for death: 0.69 (0.95% CI, 0.53-0.89); P=0.005
Rates of OS (%) at 12 months	72 (95% CI, 67-77)	65 (95% CI, 59-70)	
HRQoL assessed by: EORTC-QLQ-C30 and EuroQoL EQ-5D and FACT-M, During study and at disease progression. In this table we report at 48 weeks (latest) and at progression	Favour the combination group for all the three instruments. Differences in mean scores between treatment groups: EORTC-QLQ-C30 -at 48 weeks: 7.57 (3.56 to 11.57) -at disease progression: 7.57 (3.44 to 11.70) EuroQoL EQ-5D -at 48 weeks: 9.08 (4.96 to 13.20) -at disease progression: 10.51 (6.79 to 14.23) FACT-M -at 48 weeks: 3.00 (1.52 to 4.48) -at disease progression:3.68 (2.39 to 4.96)		
Any AEs Grade 3 or 4 (number of patients (percent)) at June 2014	182 (52)	220 (63)	
Deaths related to study drugs	Non related to study drug	Non related to study drug	

Risk of Bias: NCT01597908 (Combi-V study) consist of 1) Robert et al 2015 for OS, PFS, SAEs; and 2) Grob et al 2015 for HRQoL

Entry/Domain	**Judgement**	**Description**
Random sequence generation?	Low	"randomized 1:1.. and stratified" (p 15 in protocol)
Allocation concealment?	Low	"Subjects will be assigned to study treatment in accordance with the randomization schedule". An interactive voice response system (IVRS) is used, p 34 in protocol

Blinding of participants and personnel?	Low	This is an open-labeled study, so the participants and investigators know the treatment. We, however, assume that this will not influence the assessments OS, PFS (scans with CT or MRI by investigator and by central review) or SAEs (hospitlaization). It will however have impact on HRQoL
Blinding of outcome assessments?	Low for OS, PFS, and SAEs. High for HRQoL	As above
Incomplete outcome data?	Low	All patients accounted for
Selective reporting?	Low	All reported endpoints predefined in protocol
Other sources of bias?	Low	The study was funded by GlaxoSmithKline
Conclusion	Low for the endpoints; ie OS, PFS and SAEs. High for HRQoL	

Trial descriptions: NCT01245062 (METRIC study), consist of 1) Flaherty et al 2012 for PFS; OS at 6 months, SAEs; 2) Schadendorf et al 2013, updated OS; 3) Schadendorf et al 2014 for QoL

Trials: 1) Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. N Engl J Med 2012;367(2):107-114. 2) Schadendorf D, Flaherty KT, Hersey P, Nathan P, Garbe C, Milhem MM, et. Overall survival (OS) update on METRIC (NCT01245062), a randomised phase 3 study to assess efficacy of trametinib (T) compared with chemotherapy (C) in patients (pts) with BRAFV600E/K mutation_positive (+) advanced or metastatic melanoma (MM). Poster Presented at the SMR 2013 Congress *3)* Schadendorf D, Amonkar MM, Milhem M, Grotzinger K, Demidov LV, Rutkowski P , 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;25(3):700-706.
Design: This is a randomised, open-label phase 3 multicentre study in North America, Europe, Australia and Russia. Patients in the chemotherapy group were *allowed to cross over* to receive trametinib after disease progression had been confirmed by an independent review. Data cut-off: 1) Flaherty 2012: October 2011; 2) Schadendorf 2013: May 2013; 2) Schadendorf 2014: October 2011. Protocol Amendment of February 2012: *immediate crossover to trametinib should be permitted.*
Population: 322 patients with unresectable stage IIIC or IV cutaneous melanoma *with BRAF V600E or BRAF V600K mutations*. *Both previously treated* (with chemotherapy or immunotherapy (mainly interferon)) *and previously untreated*. Should not have been treated with BRAF and MEK ihibitors and ipilimumab. Age (years): ≥18, median (range): 55 (23-85) and 54 (21-77) respectively for trametinib and chemotherapy. % male 56 and 49 respectively. Patients with stable brain metastases were allowed to enroll. 322 patients were in the ITT population. The primary efficacy population included patients with the V600E BRAF mutation who did not have brain metastases at baseline.
Intervention/comparators: 322 patients randomised in a 2:1:ratio to oral trametinib (2 mg once daily) or intravenous Patients were stratified according to previous chemotherapy for advanced disease. Treatment continued until disease progression, death, or withdrawal from the study.

Endpoints: 1) Flaherty 2012: *Primary:* PFS. *Secondary*: included OS and safety. 2) Schadendorf 2013: Updated OS (12 and 24 months) 3) Schadendorf 2014: QoL. *Definitions of endpoints*: PFS: the time from randomization to the first documented radiologic progression or death on the basis of the investigators assessment. OS: *Not further defined.* HRQoL was assessed by (EORTC-QLQ)-C30 at baseline, week 6 and 12, this included cross over. Safety:were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Efficacy analyses performed on intention –to-treat (ITT) population. The safety analyses were performed in all patients who received at least one dose of study drug. QoL analyses were performed on the primary efficacy population.

Patient flow

Stage	**Intervention: Trametinib**	**Control: Chemotherapy (dacarbazine or paclitaxel)**
Randomised (ITT), included in efficacy analyses	214	108
The primary efficacy population (patients with V600E BRAF mutation without brain metastases at baseline	178	95
Patients in the QoL analysis equal the primary efficacy population	178	95
Patients in the AEs analysis	211	99
Patients that crossed over from chemotherapy to trametinib: 1) Flaherty 2012: 51 2) Schadendorf 2013:70 3) Schadendorf 2014: 51		

Follow-up:

1) Flaherty 2012: The prepecified number of progression-free survival events was reached in October 2011. *The* median follow-up time was not described. SAEs: Throughout the study until 30 days after the discontinuation of study treatment.
2) Schadendorf 2013: The median follow-up time was 14.7 and 8.7 months respectively in the trametinib and chemotherapy arm
3) Schadendorf 2014: Until the data cut-off used for analyses of the primary end point, October 2011.

Funding source: GlaxoSmithKline

Data extraction: NCT01245062 (METRIC study), consist of 1) Flaherty et al 2012 for PFS; OS at 6 months, SAEs; 2) Schadendorf et al 2015, updated OS; 3) Schadendorf et al 2014 for QoL

Endpoints	**Intervention: Trametinib** (n=214)	**Control: Chemotherapy (dacarbazine or paclitaxel)** (n=108)	**HR, p-values**

Median PFS (months), October 2011, *ITT population*, -assessed by investigator -assessed by IRC *Primary efficacy population*(patients with V600E BRAF mutation without brain metastases at baseline)	4.8	1.5	HR for disease progression: 0.45 (95% CI, 0.33-0.63); P<0.001 0.42 (95% CI, 0.29-0.59); P<0.001 Similar results
Total no of deaths n (**%),** *ITT population* -October 2011 -May 2013 *Primary efficacy population* -May 2013	 35 (16) 137 (64) 109 (61)	 29 (27) 67 (62) 61 (64)	HR for death: 0.54 (95% CI, 0.32-0.92); P=0.01 0.78 (95% CI, 0.57-1.06); P=0.09 0.72 (95% CI, 0.52-1.01); P=0.04
Median overall survival (months), *ITTpopulation* -October 2011 -May 2013 *Primary efficacy population* -May 2013	 Not reached 15.6 16.1	 Not reached 11.3 11.1	
Rates of OS (%), 6 months in: *-ITT population:* *-Primary efficacy population* 12 months in: *-ITT population:* *-Primary efficacy population* 24 months in: *-ITT population:*	81 61 (54-67) 63 (55-70) 31 (25-38) 34 (27-41)	67 50 (39-59) 50 (39-59) 29 (20-38) 28 819-38)	Identical results

-Primary efficacy population			
HRQoL, Global health status scores (measured by EORTC QLQ-C30) in the *Primary efficacy population* Adjusted mean (SE) change from baseline to 12 weeks	n=104 1.2 (1.7)	n=32 -4.6 (3.0)	Favour trametinib "Trametinib was associated with less functional impairment, smaller declines in health status, and less exacerbation of symptoms versus chemotherapy"
Any AEs Grade 4 (number of patients (percent)) at October 2011	Not reported	Not reported	
Deaths related to study drugs October 2011	Not reported	Not reported	

Risk of Bias: NCT01245062 (METRIC study), consist of 1) Flaherty et al 2012 for PFS; OS at 6 months, AEs; 2) Schadendorf et al 2015, updated OS; 3) Schadendorf et al 2014 for QoL

Entry/Domain	Judgement	Description
Random sequence generation?	Low	"Subjects will be centrally randomized using a randomization schedule generated by the GSK Biostatistical Department, which will assign subjects in a 2:1 ratio ..",.p 26 in protocol
Allocation concealment?	Low	"Once a randomization number has been assigned it must not be re-assigned even in cases of errors", p 26 in protocol.
Blinding of participants and personnel? OS, PFS, SAEs HRQoL	Low High	However, this is an open-labeled study, so the participants and investigators know the treatment. We, however, assume that this will not influence the assessments OS, PFS (scans with CT or MRI, p.50 in protocol) and by central review) or SAEs (hospitlaization). Self-reported (with the EORTC QLQ-C30)

Blinding of outcome assessments? OS, PFS, SAEs HRQoL	Low High	 As above
Incomplete outcome data? OS, PFS, SAEs HRQoL	 Low High	 No missing outcome data Was done on the primary efficacy population (ie not the ITT population)
Selective reporting?	Low	All endpoints predefined in protocol, (p 15-16), and all were reported on. HRQoL was an exploratory objective
Other sources of bias? PFS OS, HRQoL, SAEs	 Low High	"Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review" (p 109 in Flaherty 2012).. This will introduce a risk of bias for all endpoints measured after progression, ie. for OS, HRQoL and SAEs. The study was supported by GlaxoSmithKline
Conclusions	PFS: Low risk of bias OS, HRQoL and SAEs: High risk of bias	

Appendix 6 Evidences from the pairwise comparisons based upon RevMan analyses

Hazard ratios (95% CI) *for overall survival (OS), progression free survival (PFS) and relative risk (95% CI) for SAEs for the pairwise comparisons based upon REVMan Analyses*

Study	**Intervention**	**Comparator**	**Overall survival** p-value, in favour of	**Progression free survival** p-value, in favour of	**Any serious adverse events, , Grade 3 and 4 and above** p-value, in favour of
Hodi 2010, NCT00094653	Ipilimumab +gp100	Ipilimumab alone	1.04 (0.83 to 1.30), p=0.73	1.25 (1.01 to 1.55) P=0.04, favours ipi	0.98 (0.79 to 1.22) P=0.86
Robert 2011/NCT 00324155	Ipilimumab+ dacarbazine	Dacarbazine + placebo	0.72 (0.59 to 0.88), P=0.001, favours combination treatment	0.76 (0.63 to 0.92) P=0.004, favours combination treatment	2.05 (1.63 to 2.57) P<0.00001, favours dacarbazine
Maio 2015, 5 years update of OS to the NCT 00324155 study	Ipilimumab + dacarbazine	Dacarbazine + placebo	0.69 (0.57 to 0.84), P=0.0001, favours combination treatment	-	-
Hersh 2011, NCT00050102 and Weber 2013, NCT not given	Ipilimumab + dacarbazine	Ipilimumab	Not estimable	Not estimable	1.53 (0.97 to 2.42)* P=0.07, favour ipilimumab
Weber 2013, NCT not given	Ipilimumab +paclitaxel and carboplatin	Ipilimumab	Not estimable	Not estimable	1.50 (0.90 to 2.49), P=0.12, ns (favours ipilimumab)
Weber 2013, NCT not given	Ipilimumab +paclitaxel and carboplatin	Ipilimumab+ dacarbazine	Not estimable	Not estimable	1.02 (0.70 to 1.47), P=0.93
Robert 2015/CheckMate 066, NCT01721772 for overall survival.	Nivolumab	Dacarbazine	0.42 (0.30 to 0.59), P<0.00001,	0.57 (0.31 to 1.08)**,	0.51 (0.17 to 1.58)**, P=0.24

For PFS and serious adverse events: Robert 2015/CheckMate 066, NCT01721772 and Weber 2015/CheckMate 037, NCT01721746			favours nivolumab	P=0.08, ns (favours nivolumab)	
Weber 2015/CheckMate 037, NCT01721746	Nivolumab	Chemotherapy (unspecified)	Not estimable	0.82 (0.51 to1.31), P=0.41	0.29 (0.18 to 0.46), P<0.00001, favours nivolumab
Postow 2015/CheckMate069, NCT 01927419 and Larkin 2015 CheckMate067, NCT01844505	Ipilimumab + nivolumab	Ipilimumab	0.75 [0.60, 0.92]***, P=0.006, favours combination treatment	0.41 ([0.32, 0.53)***, P<0.00001, favours combination treatment	1.58 (0.86, 2.89)***, P=0.14
Larkin 2015/CheckMate067, NCT01844505	Ipilimumab + nivolumab	Nivolumab	RR: 1.01 (0.78 to 1.30), P=0.97	Not estimable	1.58 (1.36 to1.83), P P<0.00001, favours nivolumab
	Nivolumab	Ipilimumab	RR: 0.74 (0.59 to 0.94), P=0.01, favours nivolumab	0.57 (0.43 to 0.76), P<0.0001, favours nivolumab	0.78 (0.67 to 0.92), P=0.003, favours nivolumab
Robert 2015/Keynote 006, NCT01866319	Pembrolizumab	Ipilimumab	0.66 (0.54 to 0.81), P<0.0001, favours pembrolizumab	0.58 (0.50 to 0.67), P<0.00001, favours pembrolizumab	0.59 (0.42 to 0.82), P=0.002, favours pembrolizumab
Ribas 2015/KEYNOTE-002, NCT01704287	Pembrolizumab	Investigator-choice chemotherapy	Not estimable	0.45 (0.38 to 0.53), P P<0.00001, favours pembrolizumab	0.47 (0.32 to 0.68) P<0.0001, favours pembrolizumab
Hauschild 2014, BREAK-3, NCT01227889 for overall survival, Hauschild 2013 for progression free survival and Grob	Dabrafenib	Dacarbazine	0.77 (0.52 to 1.14), P=0.19	0.37 (0.23 to 0.60), P P<0.0001, favours dabrafenib	1.35 (0.82 to 2.24), P=0.24

2014 for serious adverse events					
Grob 2014, 36 months update of BREAK-3	Dabrafenib	Dacarbazine	0.81 (0.56 to 1.17), P=0.26	-	-
McArthur 2014, 18 months update of BRIM-3, NCT01006980	Vemurafenib	Dacarbazine	0.76 (0.63 to 0.92), P=0.004, favours vemurafenib	0.38 (0.32 to 0.45), P P<0.00001, favours vemurafenib	0.77 (0.48 to 1.24), P=0.29
Meta-analysis of Flaherty 2014, NCT01072175) and Long 2015, NCT01584648 for overall suvival; and Flaherty 2012 and Long 2015 for progression free survival and serious adverse events	Dabrafenib+ trametinib	Dabrafenib	0.75 (0.61 to 0.92)****, P=0.007, favours combination treatment	0.58 (0.41 to 0.81)*****, P=0.002	1.12 (0.90 to 1.40)*****, P=0.31
Daud 2015 36 months update of NCT01072175	Dabrafenib+ trametinib	Dabrafenib	0.72 (0.58 to 0.90)******, P=0.004, favours combination treatment	-	-
Larkin 2014, CoBRIM/, NCT01689519	Vemurafenib+ cobimetinib	Vemurafenib	0.65 (0.42 to 1.01), P=0.05 (favours combination treatment)	0.58 (0.46 to 0.73), P<0.00001, favours combination treatment	1.08 (0.93 to 1.24), P=0.32
Robert 2015, Combi-V, NCT01597908	Dabrafenib+ trametinib	Vemurafenib	0.69 (0.53 to 0.90), P=0.006, favours combination treatment	0.56 (0.46 to 0.68), P<0.00001, favours combination treatment	0.82 (0.73 to 0.94), P=0.003 favours combination treatment
Schadendorf 2013 for OS and Flaherty 2012 / METRIC, NCT01245062for PFS	Trametinib	Dacarbazine or paclitaxel	0.78 (0.57 to 1.07, P=0.12 (favours trametenib)	0.45 (0.33 to 0.61), P<0.00001, favours trametinib	Not estimable

*Meta-analysis of two studies Hersh 2011 and Weber 2013
**Meta-analysis of two studies Robert 2015/CheckMate 066 and Weber 2015/CheckMate 037, NCT01721746
*** Meta-analysis of two studies Postow 2015/CheckMate 069 and Larkin 2015/CheckMate067
****Meta-analysis of two studies Flaherty 2014 and Long 2015
***** Meta-analysis of two studies Flaherty 2012 and Long 2015
****** Meta-analysis of two studies Daud 2015 and Long 2015

Appendix 7. Tables of results from network meta-analyses

Table 7.1 Overall Survival from NMA (HR (95% Credible Interval))

	Dacarbazine	Ipilimumab	Dabrafenib	Vemurafenib	Pembrolizumab	Nivolumab	Nivolumab+ Ipilimumab	Vemurafenib+ cobimetinib	Dabrafenib+ trametenib	Ipilimumab+ Dacarbazine	Ipilimumab+ gp100
Dacarbazine	1										
Ipilimumab	0.69 (0.44-1.26)										
Dabrafenib	0.73 (0.49-1.10)	1.06 (0.51-1.90)									
Vemurafenib	0.77 (0.54-1.10)	1.12 (0.55-1.92)	1.05 (0.70-1.59)								
Pembroli-zumab	0.46 (0.26-0.99)	0.66 (0.45-1.00)	0.62 (0.31-1.49)	0.59 (0.31-1.39)							
Nivolumab	0.45 (0.30-0.71)	0.65 (0.42-0.91)	0.61 (0.35-1.14)	0.58 (0.35-1.04)	0.99 (0.52-1.61)						
Nivolumab+ Ipilimumab	0.48 (0.28-0.90)	0.69 (0.47-0.97)	0.65 (0.34-1.38)	0.61 (0.34-1.28)	1.04 (0.58-1.74)	1.05 (0.72-1.65)					
Vemura-fenib+cobi-metinib	0.50 (0.26-0.96)	0.72 (0.29-1.54)	0.68 (0.34-1.36)	0.65 (0.37-1.13)	1.10 (0.39-2.54)	1.11 (0.50-2.36)	1.06 (0.42-2.36)				
Dabrafenib+ trametenib	0.55 (0.37-0.84)	0.79 (0.39-1.43)	0.74 (0.56-1.02)	0.71 (0.49-1.04)	1.20 (0.50-2.39)	1.21 (0.66-2.13)	1.15 (0.55-2.17)	1.09 (0.57-2.12)			
Ipilimumab+ Dacarbazine	0.70 (0.47-0.99)	1.01 (0.53-1.62)	0.95 (0.54-1.61)	0.90 (0.53-1.46)	1.53 (0.69-2.73)	1.55 (0.89-2.47)	1.47 (0.75-2.51)	1.39 (0.66-2.84)	1.28 (0.72-2.14)		
Ipilimumab+ gp100	0.72 (0.40-1.55)	1.04 (0.69-1.60)	0.98 (0.49-2.37)	0.93 (0.48-2.19)	1.57 (0.89-2.77)	1.60 (0.96-3.05)	1.52 (0.91-2.69)	1.43 (0.61-4.03)	1.32 (0.65-3.13)	1.03 (0.57-2.27)	
Trametinib	0.78 (0.49-1.22)	1.13 (0.52-2.09)	1.06 (0.57-1.94)	1.01 (0.56-1.77)	1.71 (0.68-3.46)	1.73 (0.89-3.12)	1.64 (0.74-3.18)	1.55 (0.70-3.40)	1.03 (0.57-2.27)	1.12 (0.63-2.03)	1.08 (0.44-2.23)

Note: First row denotes treatments and first row denotes comparators. When reading from left to right. A ratio of less than 1 indicates a favour toward treatment, and a ratio of greater than 1 indicates a favour toward comparator.

Table 7.2 Progression Free Survival from NMA (HR (95% Credible Interval))

	Dacarbazine	Dabrafenib	Vemurafenib	Trametinib	Nivolumab	Vemurafenib + cobimetinib	Dabrafenib + trametenib	Ipilimumab + Dacarbazine	Ipilimumab	Pembrolizumab	Nivolumab+ Ipilimumab
Dacarbazine	1										
Dabrafenib	0.37 (0.22-0.63)										
Vemurafenib	0.38 (0.24-0.62)	1.04 (0.61-1.84)									
Trametinib	0.45 (0.25-0.82)	1.23 (0.55-2.70)	1.18 (0.55-2.47)								
Nivolumab	0.50 (0.36-0.82)	1.38 (0.76-2.89)	1.32 (0.76-2.59)	1.12 (0.59-2.48)							
Vemura-fenib+cobimeti-nib	0.22 (0.11-0.48)	0.60 (0.28-1.34)	0.58 (0.33-1.03)	0.49 (0.20-1.30)	0.44 (0.18-0.95)						
Dabra-fenib+trame-tenib	0.21 (0.12-0.37)	0.58 (0.39-0.85)	0.56 (0.34-0.88)	0.47 (0.21-1.06)	0.42 (0.20-0.77)	0.96 (0.45-1.95)					
Ipilimumab+Da-carbazine	0.76 (0.45-1.33)	2.08 (0.97-4.54)	2.00 (0.96-4.03)	1.69 (0.76-3.86)	1.51 (0.72-2.74)	3.43 (1.35-8.33)	3.56 (1.67-7.94)				
Ipilimumab	0.84 (0.54-1.52)	2.31 (1.15-5.19)	2.21 (1.16-4.65)	1.88 (0.92-4.42)	1.68 (1.03-2.63)	3.81 (1.56-9.70)	3.95 (1.99-9.06)	1.11 (0.55-2.55)			
Pembrolizumab	0.47 (0.30-0.76)	1.28 (0.63-2.62)	1.23 (0.63-2.38)	1.04 (0.50-2.30)	0.93 (0.51-1.48)	2.12 (0.87-5.01)	2.20 (1.07-4.66)	0.62 (0.30-1.30)	0.56 (0.32-0.86)		
Nivolumab+ Ipi-limumab	0.35 (0.21-0.66)	0.96 (0.45-2.22)	0.92 (0.44-2.05)	0.79 (0.36-1.90)	0.70 (0.40-1.14)	1.59 (0.63-4.19)	1.65 (0.77-3.90)	0.46 (0.22-1.08)	0.42 (0.27-0.63)	0.75 (0.42-1.42)	
Ipi-limumab+gp100	1.05 (0.53-2.40)	2.88 (1.20-7.71)	2.76 (1.19-6.98)	2.34 (0.94-6.51)	2.09 (0.99-4.20)	4.75 (1.69-14.15)	4.93 (2.05-13.35)	1.38 (0.56-3.75)	0.75 (0.42-1.42)	2.24 (1.12-4.86)	2.99 (1.49-6.11)

Note: First row denotes treatments and first row denotes comparators. When reading from left to right. A ratio of less than 1 indicates a favour toward treatment, and a ratio of greater than 1 indicates a favour toward comparator.

Table 7.3 Serious Adverse Events from NMA (HR (95% Credible Interval))

	Dacarbazine	Ipilimumab	Dabrafenib	Vemurafenib	Pembrolizumab	Nivolumab	Nivolumab+ Ipi-limumab	Vemurafenib+ cobimetinib	Dabrafenib+ trametenib	Ipilimumab+ Dacarbazine	Ipi-limumab+gp100
Dacarbazine	1										
Ipilimumab	0.87 (0.36-2.08)										
Dabrafenib	1.03 (0.38-2.95)	1.19 (0.31-4.74)									
Vemurafenib	1.02 (0.36-2.84)	1.18 (0.30-4.54)	0.99 (0.32-2.89)								
Pembrolizumab	0.49 (0.19-1.27)	0.57 (0.22-1.46)	0.48 (0.12-1.92)	0.48 (0.12-1.99)							
Nivolumab	0.61 (0.29-1.26)	0.71 (0.30-1.64)	0.60 (0.16-2.05)	0.60 (0.17-2.14)	1.25 (0.42-3.60)						
Nivolumab+ Ipi-limumab	1.28 (0.46-3.88)	1.48 (0.67-3.48)	1.24 (0.28-5.64)	1.26 (0.29-5.85)	2.61 (0.81-8.92)	2.08 (0.82-5.92)					
Vemurafenib+ cobimetinib	1.10 (0.23-5.08)	1.27 (0.21-7.44)	1.07 (0.21-5.03)	1.08 (0.34-3.37)	2.23 (0.36-13.62)	1.79 (0.33-9.90)	0.86 (0.12-5.43)				
Dabrafenib+ trametenib	1.03 (0.34-3.20)	1.20 (0.29-5.02)	1.00 (0.46-2.16)	1.01 (0.39-2.79)	2.10 (0.49-9.21)	1.69 (0.45-6.59)	0.81 (0.17-3.70)	0.94 (0.21-4.38)			
Ipilimumab+ Da-carbazine	1.51 (0.58-3.57)	1.74 (0.72-3.86)	1.46 (0.34-5.44)	1.47 (0.36-5.70)	3.06 (0.95-9.05)	2.45 (0.86-6.58)	1.17 (0.35-3.36)	1.37 (0.22-7.81)	1.46 (0.32-5.84)		
Ipilimumab+ gp100	0.85 (0.20-3.64)	0.98 (0.31-3.13)	0.82 (0.14-4.86)	0.83 (0.14-5.05)	1.72 (0.39-7.72)	1.38 (0.33-6.02)	0.66 (0.16-2.67)	0.77 (0.09-6.62)	0.82 (0.13-5.14)	0.56 (0.14-2.49)	
Ipilimumab+ paclitaxel/ car-boplatin	1.41 (0.37-5.10)	1.63 (0.50-4.99)	1.37 (0.24-6.88)	1.38 (0.25-7.25)	2.87 (0.66-11.47)	2.29 (0.58-8.83)	1.10 (0.26-4.12)	1.29 (0.17-9.52)	0.56 (0.14-2.49)	0.94 (0.31-2.93)	1.67 (0.31-8.19)

Note: First row denotes treatments and first row denotes comparators. When reading from left to right. A ratio of less than 1 indicates a favour toward treatment, and a ratio of greater than 1 indicates a favour toward comparator.

Appendix 8. Summary of Findings Tables from the network meta-analyses

Ipilimumab+gp100 compared to ipilimumab for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Ipilimumab+gp100

Comparison: Ipilimumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 1.04** (0.69 to 1.60)	**540 (1 RCT)** [1]	⊕⊕⊕◯ **MODERATE** [2]
Progression free survival (investigator assessed)	**HR 0.75** (0.42 to 1.42)	**540 (1 RCT)** [1]	⊕⊕⊕◯ **MODERATE** [2]
Serious adverse events	**RR 0.98** (0.31 to 3.13)	**540 (1 RCT)** [1]	⊕⊕◯◯ **LOW** [2,3]

1. **Hodi 2010**
2. **The 95% CI overlaps no effect, wide CI**
3. **Few events**

Ipilimumab+dacarbazine compared to dacarbazine for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Ipilimumab+dacarbazine

Comparison: Dacarbazine

Outcomes	Relative effect (95% CI)	№ of parti-cipants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.72** (0.59 to 0.88)	502 (1 RCT) [1]	⊕⊕⊕⊕ HIGH
Overall survival (latest available data)	**HR 0.69** (0.57 to 0.84)	502 (1 RCT) [2]	⊕⊕⊕⊕ HIGH
Progression free survival	**HR 0.76** (0.45 to 1.33)	502 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [4]
Serious adverse events	**RR 2.05** (0.61 to 6.77)	498 (1 RCT) [1]	⊕⊕◯◯ LOW [3,4]

1. Robert 2011
2. Maio 2015
3. Few events
4. The 95% CI overlaps no effect, wide CI

Ipilimumab+dacarbazine compared to ipilimumab for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Ipilimumab+dacarbazine

Comparison: Ipilimumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 0.91** (0.00 to 880.10)	(1 RCT) [1]	⊕◯◯◯ VERY LOW [2][3][4]
Progression free survival	not pooled	(0 RCTs)	
Serious adverse events	**RR 1.30** (0.47 to 3.49)	113 (2 RCTs) [5]	⊕◯◯◯ VERY LOW [2][3][4]

1. Hersh 2011
2. Patients were allowed to cross over from the control to the intervention group
3. The 95% CI overlaps no effect, wide CI
4. Few events
5. Hersh 2011; Weber 2013

Ipilimumab+paclitaxel and carboplatin compared to ipilimumab for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Ipilimumab+paclitaxel and carboplatin

Comparison: Ipilimumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	not pooled	(0 studies)	
Progression free survival	not pooled	(0 RCTs)	
Serious adverse events	**RR 1.5** (0.4 to 5.1)	40 (1 RCT) [1]	⊕⊕◯◯ LOW [2]

1. Weber 2013
2. There are very few events, and CI include both benefit and harm

Ipilimumab+ paclitaxel and carboplatin compared to ipilimumab + dacarbazine for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Ipilimumab+paclitaxel and carboplatin

Comparison: Ipilimumab+ dacarbazine

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	not pooled	(0 studies)	
Progression free survival	not pooled	(0 RCTs)	
Serious adverse events	**RR 1.2** (0.3 to 4.3)	39 (1 RCT) [1]	⊕⊕◯◯ LOW [2]

1. Weber 2013
2. There are very few events, and CI include both benefit and harm

Pembrolizumab compared to Ipilimumab for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Pembrolizumab

Comparison: Ipilimumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 0.66** (0.45 to 1.00)	834 (1 RCT) [1]	⊕⊕⊕⊕ HIGH
Progression free survival (investigator assessed)	**HR 0.58** (0.50 to 0.67)	834 (1 RCT)	⊕⊕⊕⊕ HIGH
Serious adverse events	**RR 0.60** (0.15 to 2.38)	811 (1 RCT) [1]	⊕⊕◯◯ LOW [2][3]

1. Robert 2015 (KEYNOTE-006)
2. The 95% CI overlaps no effect, wide CI
3. Few events

Pembrolizumab compared to dacarbazine for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Pembrolizumab

Comparison: Dacarbazine

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	Not measured		
Progression free survival (investigator assessed)	HR 0.45 (0.38 to 0.53)	(1 RCT) [1]	⊕⊕⊕⊕ HIGH

Serious adverse events	**RR 0.46** (0.12 to 1.88	(1 RCT) [1]	⊕⊕◯◯ LOW [2,3]

1. Ribas 2015
2. Patients were allowed to cross
3. Few events

Nivolumab compared to dacarbazine for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Nivolumab

Comparison: dacarbazine

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 0.42** (0.30 to 0.59)	418 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Progression free survival (investigator assessed)	**HR 0.49** (0.40 to 0.60)	600 (2 RCTs) [3]	⊕⊕⊕◯ MODERATE [4]
Serious adverse events	**RR 0.53** (0.20 to 1.30)	781 (2 RCTs) [3]	⊕◯◯◯ VERY LOW [2,4,5]

1. Robert 2015 (CheckMate 066)
2. Few events
3. Robert 2015 (CheckMate 066); Weber 2015)
4. I-square>75%
5. The 95% CI overlaps no effect, wide CI

Nivolumab + ipilimumab compared to ipilimumab for inoperable or metastatic malignant melanoma pati

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Nivolumab + ipilimumab

Comparison: Ipilimumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 0.75** (0.60 to 0.92)	142 (2 RCTs) [1][2]	⊕⊕◯◯ LOW [3][4]
Progression free survival (investigator assessed)	**HR 0.42** (0.31 to 0.57)	142 (2 RCTs) [1][2]	⊕⊕⊕◯ MODERATE [4]
Serious adverse events	**RR 1.6** (0.7 to 3.7)	140 (2 RCTs) [1][2]	⊕◯◯◯ VERY LOW [3][4][5]

1. Postow 2015
2. Larkin 2015/CheckMate 067
3. Patients in the ipilumumab group was allowed to receive nivolumab after progression (Postow 2015)
4. Few events
5. The 95% CI overlaps no effect, wide CI

Nivolumab + ipilimumab compared to nivolumab for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Nivolumab+ipilimumab

Comparison: Nivolumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 1.01** (0.78 to 1.30)	(1 RCT) [1]	⊕⊕◯◯ LOW [2]
Progression free survival (investigator assessed)	**HR 0.74** (0.00 to 79.61)	(1 RCT) [1]	⊕⊕◯◯ LOW [2]
Serious adverse events	**RR 1.38** (0.33 to 5.71)	(1 RCT) [1]	⊕⊕⊕◯ MODERATE [3]

1. Larkin 2015/CheckMate 067
2. Few events and wide CI
3. The 95% CI overlaps no effect, wide CI

Nivolumab compared to Ipilimumab inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Nivolumab

Comparison: Ipilimumab

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival	**HR 0.74** (0.59 to 0.94)	(1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]

Progression free survival	**HR 0.57** (0.43 to 0.76)	(1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Serious adverse events	**RR 0.78** (0.22 to 2.72)	(1 RCT) [1]	⊕⊕⊕◯ MODERATE [3]

1. Larkin 2015/CheckMate 067
2. Few events
3. The 95% CI overlaps no effect, wide CI

Dabrafenib compared to Dacarbazine for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Dabrafenib

Comparison: Dacarbazine

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.77** (0.52 to 1.14)	250 (1 RCT) [1]	⊕⊕◯◯ LOW [2,3]
Overall survival (latest available data)	**HR 0.81** (0.56 to 1.17)	250 (1 RCT) [4]	⊕◯◯◯ VERY LOW [2,5]
Progression free survival (investigator assessed)	**HR 0.37** (0.23 to 0.60)	250 (1 RCT) [6]	⊕⊕⊕◯ MODERATE [3]
Progression free survival (assessed by IRC)	**HR 0.35** (0.20 to 0.61)	250 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [3]

Serious adverse events	**RR 1.37** (0.38 to 5.04)	246 (1 RCT) [4]	⊕◯◯◯ VERY LOW [2] [5]

1. Hauschild 2014
2. Patients were allowed to cross over from comparator group to intervention group
3. Few events
4. Grob 2014
5. There are very few events, and CI include both benefit and harm
6. Hauschild 2013

Vemurafenib compared to dacarbazine for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Vemurafenib

Comparison: Dacarbazine

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.76** (0.63 to 0.92)	675 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Progression free survival (investigator assessed)	**HR 0.38** (0.32 to 0.45)	675 (1 RCT) [1]	⊕⊕⊕⊕ HIGH
Serious adverse events	**RR 0.77** (0.21 to 2.75)	624 (1 RCT) [1]	⊕◯◯◯ VERY LOW [2] [3]

1. McArthur 2014
2. The patients were allowed to cross over from the comparator group to the intervention group
3. There are few events, and CI include both benefit and harm

Dabrafenib + trametinib compared to dabrafenib for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Dabrafenib + trametinib

Comparison: Dabrafenib

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.79** (0.61 to 0.92)	585 (2 RCTs) [1]	⊕⊕⊕◯ MODERATE [2]
Overall survival (latest available data)	**HR 0.72** (0.58 to 0.90)	531 (2 RCTs) [3]	⊕⊕⊕◯ MODERATE [2]
Progression free survival (investigator assessed)	**HR 0.60** (0.50 to 0.73)	162 (2 RCTs) [4]	⊕⊕⊕◯ MODERATE [5]
Serious adverse events	**RR 1.13** (0.47 to 2.71)	582 (2 RCTs) [4]	⊕◯◯◯ VERY LOW [2 5 7]

1. Flaherty 2014 and Long 2015
2. Patients were allowed to cross over from control group to intervention group in the Flaherty study
3. Daud 2015 and Long 2015
4. Flaherty 2012 and Long 2015
5. Few events

6. Flaherty 2012
7. The 95% CI overlaps no effect, wide CI

Vemurafenib + cobimetinib compared to vemurafenib for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Vemurafenib + cobimetinib

Comparison: Vemurafenib

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.65** (0.37 to 1.13)	495 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Progression free survival (investigator assessed)	**HR 0.58** (0.33 to 1.03)	495 (1 RCT) [3]	⊕⊕⊕◯ MODERATE [2]
Serious adverse events	**RR 1.08** (0.34 to 3.37)	493 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [4]

1. Larkin 2014
2. Few events
3. Larkin 2015
4. The 95% CI overlaps no effect, wide CI

Dabrafenib + trametinib compared to vemurafenib for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Dabrafenib + trametinib

Comparison: Vemurafenib

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.69** (0.53 to 0.90)	704 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Progression free survival (investigator assessed)	**HR 0.56** (0.46 to 0.68)	704 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Serious adverse events	**RR 0.82** (0.24 to 2.76)	699 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [3]

1. Robert 2015 (Combi-V)
2. Few events
3. The 95% CI overlaps no effect, wide CI

Trametinib compared to chemotherapy (unspecified) for inoperable or metastatic malignant melanoma patients

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older

Intervention: Trametinib

Comparision: Chemotherapy (unspecified)

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Overall survival (first report measuring 2 years survival)	**HR 0.78** (0.49 to 1.22)	322 (1 RCT) [1]	⊕⊕◯◯ LOW [2,3]
Progression free survival (investigator assessed)	**HR 0.45** (0.25 to 0.82)	322 (1 RCT) [4]	⊕⊕⊕◯ MODERATE [3]
Serious adverse events	not pooled	(0 studies)	

1. Schadendorf 2013
2. Patients were allowed to cross over from control group to intervention group
3. Few events
4. Flaherty 2012

Appendix 9. Hazard ratios for overall survival from first report measuring 2 years survival, and latest available data

Table Appendix 9: Hazard ratios (95% CI) and p-values for overall survival (OS) measured from first report measuring 2 years survival, and latest available data

Trials (comparisons)	Follow-up time for OS (months)	
	First report measuring 2 years survival	Latest available survival data
Robert 2011 and Maio 2015 (Ipilimumab + dacarbazine vs dacarbazine)	0.72 (0.59 to 0.88); p=0.001 in favour of combination treatment (Robert 2011, 37 months after last patients enrolled)	0.69 (0.57 to 0.84); p=0.0001 in favour of of combination treatment (Maio 2015, 5-years data)
Hauschild 2014 and Grob 2014 (BREAK-3) (dabrafenib vs dacarbazine)	0.77 (0.52 to 1.14); p=0.19 (Hauschild 2014)	0.81 (0.56 to 1.17); p=0.26 (Grob 2014, 3 years data)
Flaherty 2014/Long 2014, and Daud 2015/Long 2015, both as meta-analyses) (dabrafenib+ trametinib vs dabrafenib)	0.75 (0.61 to 0.92); p=0.007 in favour of combination treatment (Flaherty 2014/Long 2014)	0.72 80.58 to 0.90); p=0.004 in favour of combination treatment (Daud 2015/Long 2015, 3 years data

Appendix 10. Health related quality of life from the included trials

Appendix Table 10: Health related quality of life results from the included trials

Study/ (mother study)	HRQL Instrument	Measured at baseline and up to	Intervention/ HRQL results	Comparison/ HRQLresults	Results
Revicki 2012/ (Hodi 2010)	EORTC QLQ-30	week 12	Ipilimumab+ gp100/ "no change" or "little change"	Ipilimumab monotherapy/ "no change" or "little change"	No change during 12 weeks across EORTC QLQ-C30 global health status, function, and symptom subscales. No SD or CI presented
Kotapati 2011/ (Robert 2011)	EORTC-QLQ-C30	To disease progression	Ipilimumab+ dacarbazine	Dacarbazine+ placebo	No difference between groups. "Longitudinal analyses using repeated measures modelling did not detect statistically significant differences between treatment groups for any HRQL scales or symptom scores;(GHS P=0.19)" No SD or CI presented

Long 2015/ (Robert 2015 (CheckMate 066))	EORTC-QLQ-C30 and EuroQoL EQ-5D	At treatment cycles Q6W	Nivolumab:	Dacarbazine:	No results, due to lack of dacarbazine data after baseline
Abernethy 2015/ (Postow 2015 CheckMate 069))	EORTC-QLQ-C30 and EuroQoL EQ-5D	For the first 6 months, included cross over	Nivolumab+ ipilimumab: **HRQoL, EORTC QLQ-C30,** mean global health scores At baseline: 76.9 At week 7: 69.2 At week 13: 78.5 **EQ-5D** Mean utility index scores At baseline: 0.861 At week 7: 0.788 At week 13: 0.894	Ipilimumab 80.9 74.5 72.2 0.847 0.789 0.834	Niivolimumab + ipilimumab and ipilimumab alone maintained QoL to a similar level. No SD or CI presented
Grob 2014/ (Hauschild 2012 (BREAK-3))	EORTC-QLQ-C30	week 12, includes cross over patients	Dabrafenib	Dacarbazine	In favour of dabrafenib. "Clinically, meaningful changes were observed at week 6 and 12 for two of five functional and six of eight symptoms dimensions. Although the remaining dimensions (except role function and pain) did not meet the minimum clinically important differences (MCIDs), the mean favored dabrafenib". CI presented
Schadendorf 2015/ (Long 2014 (Combi-D))	EORTC-QLQ-C30	To disease progression. Results at 8, 16 and 24 weeks	Dabrafenib + trametinib	Dabrafenib + Placebo	In favour of the combination treatment. "Dabrafenib + trametinib provides better preservation of HRQoL and pain improvements versus dabrafenib monotherapy. For nausea, vomiting, diarrhoea, dyspnoea and constipation scores trended in favour of dabrafenib monotherapy".

					No SD or CI presented
Dréno 2015/ (Larkin 2014 (CoBrim))	EORTC-QLQ-C30	Up to 224 days (8 cycles)	Vemurafenib+ cobimetinib	Vemurafenib+ placebo	Similar QOL in the two groups No SD or CI presented
Grob 2015/(Robert 2015 (Combi-V))	EORTC-QLQ-C30 and EuroQoL EQ-5D and FACT-M	During study and at disease progression. In this table we report at 48 weeks (latest) and at progression	Dabrafenib + trametinib Mean scores measured at Baseline 48 weeks Disease progression	Vemuarafenib Mean scores measured at Baseline 48 weeks Disease progression	Favour the combination group for all the three instruments. Differences in mean scores between treatment groups: EORTC-QLQ-C30 48 weeks: 7.57 (3.56 to 11.57) Disease progression: 7.57 (3.44 to 11.70) EuroQoL EQ-5D 48 weeks: 9.08 (4.96 to 13.20) Disease progression: 10.51 (6.79 to 14.23) FACT-M 48 weeks: 3.00 (1.52 to 4.48) Disease progression:3.68 (2.39 to 4.96)
Schadendorf 2014/ (Flaherty 2012 (METRIC))	EORTC-QLQ-C30	Up to week 12, this included cross over	Trametinib : Global health status scores in the Primary efficacy population Adjusted mean (SE) change from baseline to 12 weeks: 1.2 (1.7)	Chemotherapy (dacarbazine or paclitaxel): Adjusted mean (SE) change from baseline to 12 weeks: -4.6 (3.0)	Favour trametinib "Trametinib was associated with less functional impairment, smaller declines in health status, and less exacerbation of symptoms versus chemotherapy" CI presented
Ribas 2015/ Ribas 2015 (KEYNOTE-002))	EORTC-QLQ-C30.	Up to week 12	Pembrolizumab 2 or 10 mg/kg: The least squares mean change from baseline to week 12 in the EORTC QLQ-C30 global health status and quality – of-life score was for: Pembrolizumab 2 mg/kg:	Chemotherapy	Favour pembrolizumab. A significant difference in the least squares mean change, in favour of pembrolizumab (for both 2 and 10 mg/kg) as compared to chemotherapy. For the 2 mg group versus the chemotherapy group: 6.53 (95%CI 1.53 to 11.53) For the 10 mg/kg group versus the chemotherapy group: 6.57 (1.65 to 11.50).

			-2.60 (95%CI -6.15 to 0.96) 10 mg/kg: -2.55 8-5.99 to 0.89)	-9.13 (-12.86 to -5.39)	

EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life
EuroQoL EQ-5D: European Quality of Life-5 Dimensions
FACT-M: Melanoma Subscale of the Functional Assessment of Cancer Therapy-Melanoma

Appendix 11. Survival among patients receiving dacarbazine

From our information, dacarbazine was the most common treatment for unoperable and/or unresectable malign melanoma in Norway until 2012. Therefore, we wanted to compare the overall survival from the randomized controlled trial we used as input for the meta-analysis and economic model, with data from the Cancer Registry of Norway. The comparison shows that in terms of overall survival, the data we included in the network meta-analysis, as well as in the economic model, seems to match the survival of Norwegian stage IV patients better than stage III.

We calculated the overall survival for the Norwegian malignant melanoma patients by multiplying the average relative survival data from the Cancer Registry of Norway (2009 to 2013)[1], with the general population mortality for the same age and calendar year. The purple and green lines in **Feil! Fant ikke referansekilden.** represents the reported 1,2,3 and 4 year overall survival for patients of both genders with stage III and IV with unresectable and/or metastatic malign melanoma, respectively.

In the decision model, whe used the randomized controlled trial data from NCT00324155 (See trial description pp.23 in the appendix for Robert 2011/Maio

[1] Data received from the Cancer Registry of Norway spring 2015. The Norwegian Knowledge Centre for the Health Services are responsible for the correct use of the data.

2015), represented by the blue curve for 1,2,3 and 4 years (non-parametric Kaplan-Meier).

The orange curve is the estimated overall survival from our economic model, with survival estimated from the log-logistic cumulative density function, fitted from patient-level data from NCT00324155 (Robert 2011/Maio 2015). Some differences between the purple and blue curve are to be expected due to different estimation methods, but with both curves somewhat below the survival of the Norwegian stage IV patients reported by the Norwegian Cancer Registry.

There are some differences between the randomized controlled trial data and the data from the Cancer Registry of Norway. We have not attempted to control for any of these differences. The study population in NCT00324155 had a mean age of 57,5 and 56,4 for unresectable stage III and IV melanoma, respectively. Stage III had 60,8% and stage IV, 59,1% men. The share of the study population in NCT00324155, for stage IV malignant melanoma were 57 % and 55 %. For the time period 2009-2013, the mean age at diagnosis for C43 (ICD 10) malignant melanoma in Norway was about 61 years for women and 64 years for men (62,5 both sexes). Of the incidence for the time period 2009-2013, 50,7% were women and 49,3% men. For both sexes, the proportion diagnosed at stage III were 54%, and at stage IV 46%.

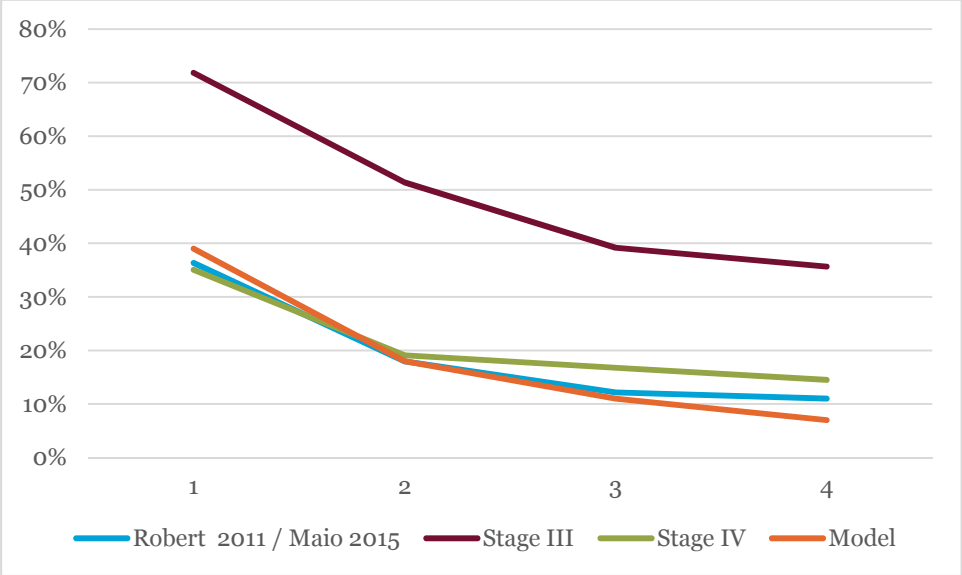

Figure 1. Survival curves for malignant melanoma patients.

Appendix 12. Estimation of the transition probabilities

The decision model we use corresponds to the generic case of a three-state illness to death model with no recovery, for instance illustrated by Jackson[2] and Welton[3] in the form of a transition probability matrix. The transition probability matrix have a solution for each transition probability. However, we did not have individual-level event history data on transitions for such accurate estimation of the transition probabilities.

Another option is to estimate the transition probabilities from aggregate data, and we used the cumulative density functions for overall survival and progressive-free-survival as the starting point to approximate the transition probabilities.

We estimated the transition probabilities from the formulae suggested in Briggs[4] pp.53 for a simple discrete-time Markov-model with two states, alive and dead, for the transition from alive to dead:

$$tp(t_u) = 1 - \frac{\mathrm{S(t)}}{\mathrm{S(t-u)}}$$

t_u denotes time measured in integers for the cycle-length u.
$tp(t_u)$ is the discrete transition probability between time-points t-u

S(t) can be substituted with the complement of the survivor function, which is one minus the cumulative density function, S(t)= 1- F(t).

$$tp(t_u) = 1 - \frac{1-\mathrm{F(t)}}{1-\mathrm{F(t-u)}}$$

We used the above formulae to calculate the baseline transition from alive to dead in the model, both from progression free survival (PFS) and progressed disease (PD), as we assume the same mortality regardless of progression status. The formulae is summarized below, where the subscript for F denotes the cumulative density function for overall survival (OS).

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[2] Christopher H. Jackson (2011). Multi-State Models for Panel Data: The msm Package for R. Journal of Statistical Software, 38(8), 1-29. URL http://www.jstatsoft.org/v38/i08/.
[3] Welton et al. 2012. Evidence Synthesis for Decision Making in Healthcare. John Wiley & Sons. Chapter 10.
[4] Briggs 2006. Decision modelling for health economic evaluation. Oxford University Press. Page 53.

$$p(PFS/PD \rightarrow dead) = 1 - \frac{1 - \mathrm{F}_{OS}(\mathrm{t})}{1 - \mathrm{F}_{OS}(\mathrm{t-u})}$$

The theoretically best approach to estimate the transition probability from PFS to PD (1 to 2) is one minus the probability of death minus the probability of staying in PFS. But we could not estimate the transition probability this way because the OS and PFS functions sometimes return values so that the sum of the probabilities exceed one. This discrepancy with the basic properties of probabilities is related to the separate estimation of survival functions for two partially overlapping events, where the transitions from PFS to dead are included as events in both survival functions.

We instead calculated the transitions to death (PFS→death and PD →death) and to progressed disease (PFS→PD) in two steps, so that the probability of transition from PFS to PD is the conditional probability:

$$p(PFS \rightarrow PD|Survival) = \frac{p(\{PFS \rightarrow \mathrm{PD}\} \cap \{PFS \rightarrow \text{ not dead}\})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})} = \frac{p(\{PFS \rightarrow \mathrm{PD}\})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= \frac{1 - p(PFS/PD \rightarrow \text{dead}) - p(PFS \rightarrow \mathrm{PFS})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= \frac{p(PFS/PD \rightarrow \text{not dead}) - p(PFS \rightarrow \mathrm{PFS})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= 1 - \frac{p(PFS \rightarrow \mathrm{PFS})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= 1 - \frac{\frac{\mathrm{S}_{PFS}(\mathrm{t})}{\mathrm{S}_{PFS}(\mathrm{t-u})}}{\frac{\mathrm{S}_{OS}(\mathrm{t})}{\mathrm{S}_{OS}(\mathrm{t-u})}} = 1 - \left(\frac{\mathrm{S}_{PFS}(\mathrm{t}) * \mathrm{S}_{OS}(\mathrm{t-u})}{\mathrm{S}_{PFS}(\mathrm{t-u}) * \mathrm{S}_{OS}(\mathrm{t})}\right)$$

The transition probability $p(PFS \rightarrow PD|Survival)$, is one minus the ratio of the probability of staying in the PFS state over the probability of not dying. It should be noted that $p(PFS \rightarrow PD|Survival) + p(PFS \rightarrow PFS|Survival)$ occasionally returns values that results in probabilities exceeding 1, but with small deviations. This is handled in the decision model by normalizing the probabilitites for $p(PFS \rightarrow PD|Survival)$ and $p(PFS \rightarrow PFS|Survival)$, which is 1- $p(PFS \rightarrow PFS|Survival)$.

Briggs[5] shows that $tp(t_u)$ can be rewritten so that a hazard ratio α can be correctly applied to the hazard rate, not the probability.

[5] Briggs 2006. Decision modelling for health economic evaluation. Oxford University Press. Page 53.

$tp(t_u) = 1 - exp^{\alpha\{H(t-u)-H(t)\}}$
$tp(t_u) = 1 - exp^{\{H(t-u)-H(t)\}^{\alpha}}$

The cumulative hazard function H(t) can be expressed as
$H(t) = -\ln(S(t) = -\ln\big(1 - F(t)\big)$.

Substituting $H(t)$ for $- ln(1 - F(t))$ in $tp(t_u)$ gives

$$tp(t_u) = 1 - (\frac{1 - \mathrm{F(t)}}{1 - \mathrm{F(t-u)}})^{\alpha}$$

We adjust the baseline transition probabilities according to recommendation by applying the hazard ratio to the power of the ratio.

Appendix 13. Calculation of costs

Drug costs

We used the publicly available maximum pharmacy retail price (PRP) per package (AUP) as of October 2015 for dabrafenib, vemurafenib, trametinib, dabrafenib+trametinib, ipilimumab, nivolumab and pembrolizumab. Cobimetinib does not have marketing authorization in Norway and consequently no PRP. For dacarbazine we used the publicly available LIS-price of NOK 1,853 per package. In the base case model, we assumed that cobimetinib would have the same PRP as trametinib, however running a scenario (see scenario analyses chapter in the report) for a tentative price received from the producer. Table 1 shows an overview.

The calculations were done with respect to a monthly cycle length (30,42 days) and an average weight of the patients of 80 kg. For dacarbazine, we assumed an average skin area of 1.7 square meters.

Table 1. Overview of the price information per package we have used in the model

Active ingredient	Trade name	Trade number	Max. PRP per package	Cost per month of treatment at maximum price and full dosage
Vemurafenib	**Zelboraf, 240 mg**	438759	21,845	94,930
Vemurafenib +cobimetinib				196,051
Dabrafenib	**Tafinlar, 75 mg**	459037	90,732	92,002
Dabrafenib +trametinib				193,123
Ipilimumab	**Yervoy, 5 mg/ml**	199940	176,396	846,700*
Dacarbazine	**Dacarbazine Lipomed**	208422	1,853	1,259**
Nivolumab	**Opdivo 10 mg/ml**	579240	16,578	86,452
Pembrolizumab	**Keytruda, 50 mg**	529787	20,043	92,909
Trametinib	**Mekinist 2 mg**	116808	99,725	101,121

**Estimated from the package price paid by Norwegian hospitals which is NOK 1,020*

***The full cost of 4 doses over 3 months.*

Dosages are according to the Norwegian summary of product charachteristics (SPC) for the following drugs in monotherapy or combination therapy, with marketing authorization:

- Dacarbazine
- Ipilimumab
- Nivolumab
- Pembrolizumab
- Dabrafenib
- Dabrafenib+trametinib
- Vemurafenib
- Trametinib

Cobimetinib is only included in the analysis in combination with vemurafenib, and did not have marketing authorization at the time of writing. If information about drug dosages were not available from the SPC, we used the dosages specified in the studies we included in the systematic review. The following drugs did not have dosages specified for combination therapy in the SPC at the time of writing:

- Vemurafenib+cobimetinib
- Nivolumab+ipilimumab
- Ipilimumab+dacarbazine

Information on the dosages used in the price per model cycle calculations are provided in

Table 2.

Table 2 Dosages

Active ingredient	Information about dosages
Dabrafenib	2x75 mg, twice a day, 300 mg/day.
Dabrafenib +trametinib	Dosages as stated for each drug alone.
Ipilimumab	4 doses in the course of 3 months, 3 mg/kg and an average weight of 80 kg/patient.
Ipilimumab +Dacarbazine	Dosages as stated for each drug alone.
Dacarbazine	200 mg/m^2 /day for 5 days, every 3 weeks. We have assumed an average skin area of 1.7 m^2.
Vemurafenib +Cobimetinib	Vemurafenib, same as monotherapy. Cobimetinib: No information regarding dosage used (drug costs estimated from assumption).
Nivolumab	3 mg/kg, every 2 weeks.
Nivolumab +Ipilimumab	Nivolumab, 1 mg/kg, every 2 weeks. Ipilimumab: 4 doses in the course of 3 months, 3 mg/kg and an average weight of 80 kg.
Pembrolizumab	2 mg/kg, every 3 weeks.
Trametinib	2 mg/ once daily.
Vemurafenib	4x240 mg, twice a day. 1920 mg/daily

Monitoring costs

We show in the following tables a detailed break-down of the monitoring costs for each treatment arm.

Table 3. Monitoring costs during treatment. Ipilimumab, ipilimumab+dacarbazine and pembrolizumab treatment arms.

Resource	Num-ber/Share	Price/DRG	Cost
Outpatient visit specialist (Dermathologist/oncolo-gist)	1.33	1,034	1,379
Blood count	1.33	114	152
CT scan	0.11	1,443	159
Ultrasound	0.11	1,042	115
Bone scintigraphy	0.11	2,097	231

PET	0.03	15,027	501
MR	0.11	1,980	218
Total cost per model cycle			**2,753**

Table 4. Monitoring costs during treatment. Nivolumab, nivolumab+ipilimumab treatment arm.

Resource	Number/Share	Price/DRG	Cost
Outpatient visit specialist (Dermathologist/oncologist)	2	1,034	2,068
Blood count	2	114	228
CT scan	0.11	1,443	159
Ultrasound	0.11	1,042	115
Bone scintigraphy	0.11	2,097	231
PET	0.03	15,027	501
MR	0.11	1,980	218
Total cost per model cycle			**3,519**

Table 5. Monitoring costs during treatment. Dabrafenib, dabrafenib+trametinib, vemurafenib, vemurafenib+trametinib, trametinib and cobimetinib treatment arms.

Resource	Number/Share	Price/DRG	Cost
Outpatient visit specialist (Dermathologist/oncologist)	1.67	1,034	1,723
Blood count	1.33	114	152
CT scan	0.17	1,443	241
Ultrasound	0.17	1,042	174
Bone scintigraphy	0.17	2,097	350
PET	0.03	15,027	501
MR	0.17	1,980	330
Total cost per model cycle			**3,470**

Table 6. Monitoring costs during treatment. Dacarbazine treatment arm.

Resource	Number/Share	Price/DRG	Cost
Outpatient visit specialist (Dermathologist/oncologist)	1.33	1,034	1,379

Blood count	1.33	114	152
CT scan	0.08	1,443	120
Ultrasound	0.08	1,042	87
Bone scintigraphy	0.08	2,097	175
PET	0.03	15,027	501
MR	0.08	1,980	165
Total cost per model cycle			**2,578**

Table 7. Monitoring costs after disease progression. All treatment arms.

Resource	Number/Share	Price/DRG	Cost
Surgery	0.03	90,346	3,012
Palliative treatment (at a hospital palliative center)	0.13	27,365	3,649
Palliative treatment (day care)	0.13	5,473	730
Radiotherapy	0.08	52,284	4,357
Total cost			**11,747**

Unit costs

We based all aforementioned costs on the following unit costs we retrieved from several sources, as shown in the tables below.

One DRG-point value in 2015 is valued at NOK 41,462. For diagnostic services (Røntgen, CT, MR, PET, UL), the total cost is calculated by dividing the reimbursement from the State (currently at 40%), in order to take into account that the grant finances 60% of the cost.

The outpatient costs based on tariffs were multiplied by 2 in order to account for the fact that the tariff on average covers about 50% of the costs of the providers.

Table 8. Outpatient unit costs

Resource	Tariff (takst)	Public reimbursement	Value used (public reimbursement x2)	Source
Visit to GP	2ad	2	**286**	

Visit to specialist and full examination	3ad+4b1	493	**1034**	Normaltariffen - fastleger 2015-2016
Biopsy	100	109	**218**	
Blood test	1e	7	**114**	

Table 9. Unit costs at hospital.

Resource	Takst/DRG/Kode	DRG-weight	100% refund	Source
Visit to oncologist	909c	0.03	1244	
Palliative treatment (at a hospital palliative center)	Z51.50	1	27,365	ISF regelverk. 2015, IS-2230
Palliative treatment (day care)	959W	0	5,473	
In-patient treatment of AEs caused by medicine treatment	453b	1	20,814	
External radiotherapy (all cancers)	850A + 851J	0.061 & 25*0.048	52,284	
Skin tumor resection	269	2	90,346	
Patient copayment - Diagnostics (per session)	899a	-	227	Helsedirektoratet https://lovdata.no/dokument/SF/forskrift/2003-06-27-959
Røntgen	RG1	-	643	
Røntgen	RG2	-	723	
Røntgen	RG3	-	1,990	
Computer Tomografi CT1	CT1	-	1,125	
Computer Tomografi CT2	CT2	-	1,415	
Computer Tomografi CT3	CT3	-	2,385	
MR 1	MR1	-	1,485	
MR 2	MR2	-	1,565	
MR 3	MR3	-	3,330	
Ultralyd 1	UL1	-	663	
Ultralyd 2	UL2	-	730	
Ultralyd 3	UL3	-	868	
PET 1 (Prosedyrekode SY0AL)	PET 1	-	14,968	
Nukleærmedisin 1	NM 1	-	1,480	
Nukleærmedisin 2	NM 2	-	1,885	
Nukleærmedisin 3	NM 3	-	2,453	
Nukleærmedisin 4	NM 4	-	2,705	
Nukleærmedisin 5	NM 5	-	3,333	

Appendix 14. HRQoL in the CUA analysis

Clinical trials generally record health related quality of life using disease-specific instruments. Such instruments have the advantage of being more sensitive to changes in patients' health related quality of life on disease-relevant dimensions, for relatively small sample sizes, but at the expense of comparability across disease areas.

We chose not to use mapping algorithms on disease specific instruments and searched the literature for relevant values elicited from patients not previously treated, preferably from multi-attribute instruments such as the SF-6D or EQ-5D.

We searched Embase, Medline and PsychINFO with the following search strategy (Table 10), resulting in 228 references reviewed for title and abstract.

Table 10 Search strategy for health related quality of life

Resource
(eq5d or eq-5d or euroqol or euro qol or euroqol-eq-5d or eq-5d-euroqol or eq-5d-3L or eq-5d-5L).tw
(quality adjusted life or quality-adjust-life).tw
(qaly* or qald* or qale* or qtime* or qali*).tw
(health related quality of life hql or hqol or h qol or hrqol).tw
(Sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw
(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).tw
(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw
(hui or hui 2 or hui 3 or hui2 or hui3 or hui-2 or hui-3).tw
(EORTC QLQ-C30 or QLQ-C30 or EORTC-8D).tw
(FACT-General or FACT-G or FACT-Melanoma or FACT-M).tw
(tto or time trade off or time tradeoff or standard gamble or SG).tw
or/1-11
exp Melanoma/ or melanoma.tw
12 and 13

Table 11 shows the HRQoL weights we identified from the literature and considered using in the decision model. The list includes values identified from hand searching published economic evaluations.

The SF-6D data had been mapped from SF-36, and were from previously treated patients. The standard-gamble (SG) is a direct elicitation method and the data from Beusterien (2009), are from non-patients elicited with the use of vignettes that describes hypothetical health states. Such values can vary according to the respondents willingness to take hypothetical risks and by the fact that different people will have different perceptions of how it will be like to be in a given hypothetical health state.

Since the SG and EQ-5D weighs differs both with regards to the absolute values of the PFS and PD states and the % reduction in HRQoL from PFS to PD, and we therefore chose to run a scenario analysis with the SG weights to see the impact of the results.

Table 11. Overview of HRQoL weights

Source	MAU instrument	QALY-weights		%-reduction from PFS to PD
		Progression-free survival	Progressed disease	
Beusterien et al. (non-treatment specific)	Standard gamble (SG)	0,8	0,52	35 %
Vemurafenib application to NICE (Vemurafenib) [6]	Based on SG	0,806	0,59	27 %
Vemurafenib application to NICE (Dacarbazine) [7]	Based on SG	0,767	0,59	23 %

[6] National Institute for Health and Care Excellence (NICE). 2012. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. Rockwille MD. Agency for Healthcare Research and Quality. URL: http://www.guideline.gov/content.aspx?id=39273&search=health+technology+assessment+and+metastatic+melanoma

[7] National Institute for Health and Care Excellence (NICE). 2012. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. Rockwille MD. Agency for Healthcare Research and Quality. URL: http://www.guideline.gov/content.aspx?id=39273&search=health+technology+assessment+and+metastatic+melanoma

Ipilimumab application to Norwegian Medicines Agency[8]	SF36/SF-6D	0,64	0,62	3 %
Combi-V (Vemurafenib) ([9])	EQ-5D	0,715	0,665	7 %
Keynote 006 (Pembrolizumab)[10]	EQ-5D	0,80	0,70	13 %

Appendix 15 Model parameters and distributions

Type	Name	Param 1	Param 2
Beta	Distr_uPD_perorale_mono	0.665	0.10*0.665
Beta	Distr_uPFS_perorale_mono	0.715	0.10*0.715
Gamma	Distrib_Administration_cost_per_infusion	((1312)^2)/((1312/2)^2)	(1312)/((1312/2)^2)
Gamma	Distrib_Dispensing_Costs_Cobimetinib_and_vemurafenib	((416)^2)/((416/2)^2)	(416)/((416/2)^2)
Gamma	Distrib_Dispensing_Costs_Dabrafenib	((416)^2)/((416/2)^2)	(416)/((416/2)^2)
Gamma	Distrib_Dispensing_Costs_Dabrafenib_and_trametinib	((416)^2)/((416/2)^2)	(416)/((416/2)^2)
Gamma	Distrib_Dispensing_Costs_Trametinib	((208)^2)/((208/2)^2)	(208)/((208/2)^2)
Gamma	Distrib_Dispensing_Costs_Vemurafenib	((416)^2)/((416/2)^2)	(416)/((416/2)^2)
Gamma	Distrib_AEs_treatment_cost	((20814)^2)/((20814/2)^2)	(20814)/((20814/2)^2)
Gamma	Distrib_Gen_testing_cost	((4089.4)^2)/((4089.4/2)^2)	(4089.4)/((4089.4/2)^2)
Gamma	Distrib_Monit_Costs_PFS_Ipi_and_Dacar_Pembrolizumab_Ipilim	(((3033))^2)/(((3033/2))^2)	((3033))/(((3033/2))^2)
Gamma	Distrib_Monit_Costs_PFS_Nivolumab_Nivolumab_and_ipilimumab	((3938)^2)/(((3938/2))^2)	(3938)/(((3938/2))^2)
Gamma	Distrib_Monit_Costs_PFS_Dabra_Dabra_and_tramet_Vemur_and_cobimetinib_Vemur_Trametinib_and_cobimetinib	(((3820))^2)/(((3820/2))^2)	((3820))/(((3820/2))^2)

[8] Norwegian Medicines Agency 2012. Ipilimumab for treatment of advanced malignant melanoma in adults. www.legemiddelverket.no%2FBlaa_resept_og_pris%2FHelseoekonomiske%2520rapporter%2FDocuments%2F2012-2011%2FYervoy_malignt melanom_2012.pdf&usg=AFQjCNFtkvHTGa4wWEBVmhIGGVLCIZJ2Ug

[9] Jean-Jacques Grob, et al. 2015. Health-related quality of life in treatment naïve patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma: results of the randomized phase 3 COMBI-v study comparing the combination of dabrafenib and trametinib with vemurafenib. Lancet Oncol 2015;16:1389-98

[10] Underlag for beslut i landstingen, Keytruda (pembrolizumab). http://www.tlv.se/lakemedel/Klinikläkemedelsuppdraget/avslutade-halsoekonomiska-bedomningar/Halsoekonomisk-bedomning-av-Keytruda/

Gamma	Distrib_Monit_Costs_PFS_Dacarbazine	(((2858))^2)/(((2858/2))^2)	((2858))/(((2858/2))^2)
Gamma	Distrib_Monit_Costs_PD	(((11747))^2)/(((11747/2))^2)	((11747))/(((11747/2))^2)
Beta	Distrib_1_month_probability_Serious_AEs_Dacarbazine	0.0164	0.0164*0.0011
LogNormal	HR_OS_Dabra_vs_Dacarb	ln(0.73)	(ln(1.10)-ln(0.49))/(2*1.96)
LogNormal	HR_Progression_Dabra_vs_Dacarb	ln(0.37)	(ln(0.63)-ln(0.22))/(2*1.96)
LogNormal	HR_OS_Ipi_vs_Dacarb	ln(0.69)	(ln(1.26)-ln(0.44))/(2*1.96)
LogNormal	HR_OS_Vemur_vs_Dacarb	ln(0.77)	(ln(1.10)-ln(0.54))/(2*1.96)
LogNormal	HR_Progression_Vemur_vs_Dacarb	ln(0.38)	(ln(0.62)-ln(0.24))/(2*1.96)
LogNormal	HR_OS_Ipi_and_dacarb_vs_Dacarb	ln(0.70)	(ln(0.99)-ln(0.47))/(2*1.96)
LogNormal	HR_Progression_Ipi_and_dacarb_vs_Dacarb	ln(0.76)	(ln(1.33)-ln(0.45))/(2*1.96)
LogNormal	HR_Progression_Pembro_vs_Dacarb	ln(0.47)	(ln(0.76)-ln(0.30))/(2*1.96)
LogNormal	HR_Progression_Nivo_and_Ipi_vs_Dacarb	ln(0.35)	(ln(0.66)-ln(0.21))/(2*1.96)
LogNormal	HR_Progression_Tramet_vs_Dacarb	ln(0.45)	(ln(0.82)-ln(0.25))/(2*1.96)
LogNormal	HR_Progression_Nivol_vs_Dacarb	ln(0.50)	(ln(0.82)-ln(0.36))/(2*1.96)
LogNormal	HR_Progression_Vemur_and_Cobi_vs_Dacarb	ln(0.22)	(ln(0.48)-ln(0.11))/(2*1.96)
LogNormal	HR_Progression_Dabra_and_Tramet_vs_Dacarb	ln(0.21)	(ln(0.37)-ln(0.12))/(2*1.96)
LogNormal	HR_OS_Tramet_vs_Dacarb	ln(0.78)	(ln(1.22)-ln(0.49))/(2*1.96)
LogNormal	HR_OS_Pembro_vs_Dacarb	ln(0.46)	(ln(0.99)-ln(0.26))/(2*1.96)
LogNormal	HR_OS_Nivol_vs_Dacarb	ln(0.45)	(ln(0.71)-ln(0.30))/(2*1.96)
LogNormal	HR_OS_Nivol_and_Ipi_vs_Dacarb	ln(0.48)	(ln(0.90)-ln(0.28))/(2*1.96)

LogNor-mal	HR_OS_Vemur_and_cobi_vs_Dacarb	ln(0.50)	(ln(0.96)-ln(0.26))/(2*1.96)
LogNor-mal	HR_OS_Dabra_and_Tramet_vs_Dacarb	ln(0.55)	(ln(0.84)-ln(0.37))/(2*1.96)
LogNor-mal	HR_Progression_Ipi_vs_Dacarb	ln(0.84)	(ln(1.52)-ln(0.54))/(2*1.96)
LogNor-mal	RR_AEs_ipilimumab_vs_Dacarb	ln(0.87)	(ln(2.08)-ln(0.36))/(2*1.96)
LogNor-mal	RR_AEs_Dabrafenib_vs_Dacarb	ln(1.03)	(ln(2.95)-ln(0.38))/(2*1.96)
LogNor-mal	RR_AEs_Vemurafenib_vs_Dacarb	ln(1.02)	(ln(2.84)-ln(0.36))/(2*1.96)
LogNor-mal	RR_AEs_Pembrolizumab_vs_Dacarb	ln(0.49)	(ln(1.27)-ln(0.19))/(2*1.96)
LogNor-mal	RR_AEs_Nivolumab_vs_Dacarb	ln(0.61)	(ln(1.26)-ln(0.29))/(2*1.96)
LogNor-mal	RR_AEs_Nivolumav_and_ipili-mumab_vs_Dacarb	ln(1.28)	(ln(3.88)-ln(0.46))/(2*1.96)
LogNor-mal	RR_AEs_Vemurafenib_and_cobi-metinib_vs_Dacarb	ln(1.10)	(ln(5.08)-ln(0.23))/(2*1.96)
LogNor-mal	RR_AEs_Dabrafenib_and_trametinib_vs_Dacarb	ln(1.03)	(ln(3.20)-ln(0.34))/(2*1.96)
LogNor-mal	RR_AEs_Ipil_and_dacarb_vs_Dacarb	ln(1.51)	(ln(3.57)-ln(0.58))/(2*1.96)
LogNor-mal	RR_AEs_Trametinib_vs_Dacarb	ln(1.02)	(ln(2.84)-ln(0.36))/(2*1.96)
Beta	Distr_uPD_perorale_combi	0.751	0.10*0.751
Beta	Distr_uPFS_perorale_combi	0.751	0.10*0.751
Beta	Distr_uPFS_immunotherapies	0.80	0.10*0.80
Beta	Distr_uPD_immunotherapies	0.70	0.10*0.80