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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Nivolumab for treating advanced (unresectable or metastatic) melanoma

ERRATUM

Replacement pages following the factual accuracy check by
Bristol Myers Squibb

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Date completed 16th November 2015

- arm is outside of the NICE final scope and thus is not reported on in detail in the CS. The ipilimumab 3mg/kg arm of this trial allows a direct comparison between nivolumab and ipilimumab. A total of 945 patients were randomised, 316 to nivolumab and 315 to ipilimumab, as shown in CS Figure 8, p. 62. The remaining 314 patients were randomised to the combination therapy.
- CheckMate 037[9] recruited patients who progressed on or after prior anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy (ipilimumab) and (if BRAF mutation-positive) BRAF inhibitor therapy. This was an open-label study with the comparator the investigator's choice of one of two chemotherapy options, either DTIC 1000mg/m2 or carboplatin area under the curve 6 + paclitaxel 175mg/m^2. Both comparators were administered every three weeks. In total 405 patients were randomised (272 to nivolumab and 133 to ICC (CS Figure 9, p. 63).

The ERG presents a summary of trial characteristics in
Table 1.

Table 1 - Summary of characteristics of the included trials

	CheckMate 066 (n=418)	**CheckMate 067 (n=631)[a]**	**CheckMate 037 (n=405)**
Phase	Phase III	Phase III	Phase III
Blinding	Double blind	Double blind	Open label
Population	Previously untreated patients with advanced melanoma	Previously untreated patients with advanced melanoma	Previously treated patients with advanced melanoma
BRAF mutation status	Without BRAF mutation	With or without BRAF mutation	With or without BRAF mutation
PD-L1 status	PD-L1-positive, negative or indeterminate classification	PD-L1-positive, negative or i indeterminate classification	PD-L1-positive, negative or indeterminate classification
Comparator	DTIC	Ipilimumab	ICC
Primary outcome(s)	OS	OS, PFS	ORR, OS
Start date	January 2013	June 2013	December 2012
Status	Terminated[b]	Ongoing	Ongoing
Cut-off (database lock)	5 August 2014	17 February 2015	30 April 2014 (clinical database lock) 20 May 2014 (IRRC database lock)
Currently available primary/survival outcomes	1 year OS PFS	PFS	ORR PFS
Expected availability of further data	18 month OS: November 2015; 2 year OS: Q4 2016	OS and PFS: Q4 2016	OS and PFS: November 2015; OS extended follow/up: June 2016

DTIC = dacarbazine; ICC = investigator's choice chemotherapy (dacarbazine or carboplatin plus paclitaxel; IRRC = independent radiology review committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q4 = quarter 4.

[a] Nivolumab monotherapy and ipilimumab monotherapy arms. The trial included a third arm of combined nivolumab and ipilimumab treatment, which not included in this ERG report.

preserve randomisation through inclusion of the trial as a covariate in the analyses. Both methods are therefore appropriate in this respect.

The ERG also notes that no justification is given for use of the Weibull parametric model instead of other parametric models which also report the HR metric, in CS Table 36 for comparison with the adjusted indirect comparison. Use of the Gompertz model for TTP post 100 days (as used in the economic model) would have produced an HR of 0.35 compared to the HR of 0.38 for the Weibull model, which was slightly less comparable to the 0.37 HR in the adjusted indirect comparison. Gompertz model-based HRs might have been used throughout Table 36 instead, for example, and might not have given such a favourable comparison to the adjusted indirect figures as the Weibull model. Therefore, a justification for use of this model in the CS would have been informative.

(ii) Indirect comparison of nivolumab to BRAF inhibitors

This comparison informed the cost-effectiveness analysis for BRAF mutation-positive patients, and also comprises comparisons of treatments from trials using a common comparator. CS Table 25 describes the comparisons made and CS Figure 35 illustrates the network diagram, replicated in Figure 1 in this report. For nivolumab compared to vemurafenib, patient-level data from CheckMate 066[4] (nivolumab arm) was compared to aggregate data from the BRIM-3 trial[12] (vemurafenib arm) linked together by DTIC, which was a comparator in both trials. The ERG assumes that patient-level data from the BRIM-3 trial were not available to the company, whereas patient-level data were available for both nivolumab and ipilimumab in the BRAF mutation-negative network, since the company markets both drugs. However, the CS goes on to describe a process to create pseudo patient-level data for vemurafenib from Kaplan-Meier curves (CS P. 118, and see below).

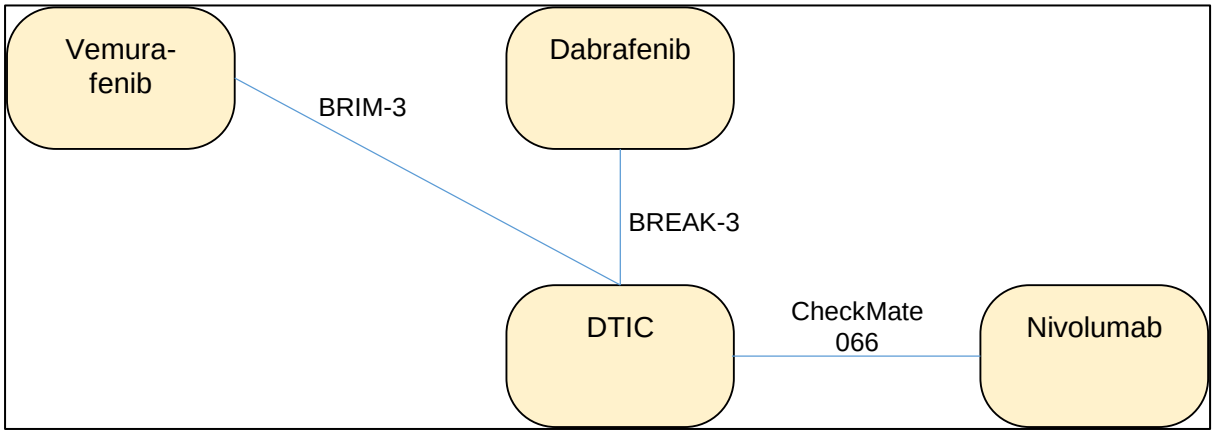

Figure 1 - Network diagram for nivolumab and BRAF inhibitors

Table 2 - Response analysis

	CheckMate 066		CheckMate 067		CheckMate 037	
	Nivolumab (n=210)	**DTIC (n=208)**	**Nivolumab (n= 316)**	**Ipilimumab (n= 315)**	**Nivolumab[a] (*PP*: n= 120) (*ITT*: n=122)**	**ICC (*PP*: n= 47) (*ITT*: n=60)**
Objective response rate (ORR)						
Responders, n (%) (95% CI)	84 (40.0)[b] (33.3, 47.0)	29 (13.9)[b] (9.5, 19.4)	138 (43.7)[b] (38.1, 49.3)	60 (19.0)[b] (14.9, 23.8)	*PP*: 38 (31.7)[c] (23.5, 40.8)	5 (10.6)[c] (3.5, 23.1)
					ITT: 38 (31.1)[c] (23.1, 40.2)	5 (8.3)[c] (2.8, 18.4)
Best overall response CR, n (%) PR, n (%)	 16 (7.6) 68 (32.4)	 2 (1.0) 27 (13.0)	 28 (8.9) 110 (34.8)	 7 (2.2) 53 (16.8)	*PP*: 4 (3.3) 34 (28.3)	0 5 (10.6)
					ITT: 4 (3.3) 34 (27.9)	0 5 (8.3)
Unweighted ORR difference, % (95% CI)	26.1 (18.0, 34.1)		24.7[d]		*PP*: 21.0 (6.8, 31.7)	
					ITT: 22.8 (10.5, 32.7)	
Estimated odds ratio (95% CI) p-value	4.06 (2.52, 6.54) <0.0001		3.40 (2.02, 5.72) <0.0001		Not reported	
Duration of response						
Median (range), months	Not reached (0.0, 12.5)	5.98 (1.1, 10.0)	Not reached	Not reached	*PP*: Not reached (1.4+, 10.0+)	3.5 (1.3+, 3.5)
Time to treatment response						
Median (range), months	2.10 (1.2, 7.6)	2.10 (1.8, 3.6)	2.8 (2.3, 12.5)	2.8 (2.5, 12.4)	*PP*: 2.1 (1.6, 7.4)	3.5 (2.1, 6.1)

CI = confidence interval; CR = complete response; DTIC = dacarbazine; ITT = intention-to-treat; ORR = Objective response rate; PP = per-protocol; PR = partial response rate.
[a] CheckMate 037[9] reports both ITT and PP analyses for tumour response. [b] Confirmed response (CR+PR) as per RECIST v1.1 criteria, investigator-assessed.
[c] Confirmed response (CR+PR) as per RECIST v1.1 criteria, assessed by independent radiological review committee. [d] 95% CI not reported in the CS or in the trial publication.[5]

p<0.001), and constipation (HR=0.51 [95% CI 0.34 to 0.76]; p<0.001). Subscales of the EORTC QLQ-C30 that demonstrated no significant difference in time to first decline between nivolumab and DTIC were fatigue (HR=0.74 [95% CI 0.55 to 1.00]), diarrhoea (HR=0.87 [95% CI 0.53 to 1.43]), and financial difficulties (HR=0.66 [95% CI 0.41 to 1.05]). The time to first decline in the EQ-5D utility index favoured nivolumab (HR=0.55 [95% CI 0.38 to 0.80]; p=0.002) whereas there was no significant difference between nivolumab and DTIC for the time to first decline of EQ-5D VAS scores (HR=0.82 [95% CI 0.59 to 1.14]).

In contrast to the time to first decline in HRQoL, the CS provides only a brief summary of the Cox proportional hazards regression analysis results for time to first improvement in HRQoL (CS p. 88). The CS reports that time to first improvement favoured nivolumab over DTIC (i.e. HR > 1.0) for four of the 15 subscales of the EORTC-QLQ-C30. These were: global health (HR=1.52; p=0.043); physical functioning (HR=1.92; p=0.027); fatigue (HR=1.69; p=0.008); and dyspnoea (HR=2.20; p=0.013) (no 95% CI for the HR were reported). The CS also reports that time to first improvement in the EQ-5D utility index favoured nivolumab (HR=1.86; p=0.002).

Although time to first decline appears to favour nivolumab for most of the HRQoL scales assessed, including the EQ-5D utility index, the ERG notes that the method of analysis is not clearly explained in the CS, particularly with regard to whether unbalanced attrition between the trials arms after week 13 could have influenced the reported outcomes (the CS does not explicitly state which time periods are covered by the regression analyses). The ERG also notes that any initial improvements in HRQoL suggested by these Cox proportional hazards regression analyses did not appear to translate into longer-term HRQoL benefits to patients. For these reasons, and given the interim nature of the analyses, the ERG suggests that these findings should be interpreted with caution.

In summary, based on the interim HRQoL evidence presented in the CS and in the company's clarification response, the ERG agrees with the company's conclusion that nivolumab does not impair HRQoL (relative to baseline), but the ERG notes that there is no current evidence that nivolumab leads to a consistent and sustained improvement in HRQoL. Although the company's analyses suggest that nivolumab has a favourable time to first decline in HRQoL and, to a lesser extent, favourable time to first improvement in HRQoL when compared to DTIC, the best available evidence from the initial analyses does not currently suggest that this translates into longer-term HRQoL benefits.

Table 3 - Objective response rate by PD-L1 expression status

	CheckMate 066 ITT analysis		**CheckMate 067** Post-hoc ITT analysis		**CheckMate 037** PP objective response set IRRC assessment	
	Nivolumab n=(210)	**DTIC n=208)**	**Nivolumab (n=316)**	**Ipilimumab (n=315)**	**Nivolumab (n=120)**	**ICC (n=47)**
PD-L1-positive patients, n (%)	74 (35.2)	74 (35.6)	80 (25.3)	75 (23.8)	55 (45.8)	22 (46.8)
Responders, n (%)(95% CI)	39 (52.7) (40.8, 64.3)	8 (10.8) (4.8, 20.2)	-	-	24 (43.6) (30.3, 57.7)	2 (9.1) (1.1, 29.2)
Unweighted ORR difference, % (95% CI)	-		-		34.5 (12.2, 49.2)	
ORR %	-	-	57.5	21.3	-	-
Odds ratio (59% CI)	-	-	5.03 (2.44, 10.37)		-	-
PD-L1-negative/in-determinate patients, n (%)	136 (64.8)	134 (64.4)	Not reported	Not reported	64 (53.3)	23 (48.9)
Responders, n (%)(95% CI)	45 (33.1) (25.2, 41.7)	21 (15.7) (10.0, 23.0)			13 (20.3) (11.3, 32.2)	3 (13.0) (2.8, 33.6)
Unweighted ORR difference, % (95% CI)	-		-		7.3 (-13.4, 21.5)	
ORR %	-	-	41.3%	17.8%	-	-
Odds ratio (59% CI)	-		3.25 (2.05, 5.13)		-	

CI = confidence interval; DTIC = dacarbazine; ICC = investigators choice chemotherapy; IRCC = independent radiological review committee; ORR = objective response rate; PD-L1 = programmed death-ligand-1.

In all of the trials, objective response rates were higher in nivolumab-treated patients with positive PD-L1 status than in nivolumab-treated patients with PD-L1 negative status. Both groups experienced higher response rates than patients treated with alternative drugs. However, the ERG notes that the lower bound of the 95% CI around the unweighted ORR difference between treatments in the PD-L1-negative subgroup fell below zero, indicating a potential better response for ICC treated patients in this subgroup. The trial journal publication[9] notes that these analyses, although pre-defined, were 'exploratory' and 'descriptive in nature' (p. 381) and that the patient sample sizes in some of the subgroups

Table 4 - Objective response rate by BRAF mutation status (CheckMate 037)

	Nivolumab (n=120)	**ICC (n=47)**
BRAF mutation-positive n (%)	26 (21.7)[a]	11 (23.4)[a]
Responders n (%)	6 (23.1)	1 (9.1)
ORR % (95% Exact CI)	23.1 (9.0, 43.06)	9.1 (0.2 41.3)
Unweighted ORR difference % (95% CI)	14.0 (-17.1, 34.4)	
BRAF mutation-negative n (%)	94 (78.3)[a]	36 (76.6)[a]
Responders n (%)	32 (34.0)[a]	4 (11.1)[a]
ORR % (95% Exact CI)	34.0 (24.6, 44.5)	11.1 (3.1, 26.1)
Unweighted ORR difference % (95% CI)	22.9 (6.2, 35.0)	

CI = confidence interval; ICC = investigator choice of chemotherapy; ORR = objective response rate.
[a] % calculated by ERG.

Nivolumab-treated patients experienced higher response rates than those treated with ICC, irrespective of BRAF mutation status. However, response rates were highest in patients with BRAF mutation-negative status. Furthermore, the lower bound of the 95% CI around the unweighted ORR difference between treatments in the BRAF mutation-positive subgroup fell below zero, indicating a potential better response for ICC treated patients in this subgroup. As described above, these subgroup analyses should be interpreted with caution due to the small sample size within each stratum.

3.3.5 Summary of adverse events

Adverse events (AE) are reported in CS section 4.12 (p. 134-145), and summaries of overall rates of AE and discontinuations due to AE are presented in CS Table 46 (CS p. 136) for CheckMate 066,[4] Table 48 (CS p. 140) for CheckMate 067[5], and Table 50 (CS p. 143) for CheckMate 037.[9] These data from the CS are replicated here in **Error! Reference source not found.**.

Cost effectiveness analysis results

Results from the economic model are presented (CS Section 5.7.1, p. 206-7) as incremental cost per QALY gained for nivolumab compared with its comparators for BRAF-mutation-negative for and BRAF mutation-positive patients. Total and incremental costs, life years gained (LYG) and QALYs were also reported, along with a breakdown of total costs. Results are presented with drug prices based on list prices and then for drug prices assuming PAS prices for the comparator treatments. Total costs are reported as commercial in confidence by the company for all treatments, in order to avoid calculation of the confidential PAS prices for ipilimumab and vemurafenib.

For BRAF-mutation-negative patients an incremental cost per QALY gained of £23,583 was reported for nivolumab versus DTIC (see Table 17). For BRAF-mutation-positive patients an incremental cost per QALY gained of £7,346 was reported for nivolumab versus ipilimumab (see Table 6).

Table 5 - Base case cost effectiveness results for BRAF mutation-negative patients (drug prices based on list price, CS Table 80)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DTIC	[redacted]	1.23			
Ipilimumab	[redacted]	2.64	£48,429	1.41	Excluded due to extended dominance
Nivolumab	[redacted]	4.31	£72,578	3.08	£23,583

Table 6 - Base case cost effectiveness results for BRAF mutation-positive patients (drug prices based on list price, CS Table 81)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Ipilimumab	[redacted]	2.44			
Nivolumab	[redacted]	4.27	£13,374	1.82	£7,346
Dabrafenib	[redacted]	1.69	£6,228	-2.57	Excluded due to dominance
Vemurafenib	[redacted]	1.70	£24,659	-2.56	Excluded due to dominance

In the deterministic sensitivity analyses of nivolumab, the results were presented in terms of net benefit with a willingness to pay threshold of £50,000 per QALY. The analyses showed that the

mutation-positive patients, the impact was similar with ICERs (nivolumab vs ipilimumab) ranging from £8,836 to £9,144, deviating from the base case ICER of £7,346.

Table 7 - Using the Weibull, log-normal, log-logistic and generalised distributions for the nivolumab arm to model time to progression at list price (BRAF mutation-negative patients)

Treatment	Distribution	Incremental Costs (vs DTIC)	Incremental QALYs (vs DTIC)	ICER (vs DTIC)	ICER (vs ipilimumab)
Nivolumab	Base case[1]	£72,578	3.08	£23,583	£14,513
Nivolumab	Weibull	£72,237	2.73	£26,483	£18,117
Nivolumab	Lognomal	£72,085	2.67	£27,027	£18,874
Nivolumab	log-logistic	£72,137	2.69	£26,829	£18,594
Nivolumab	generalised gamma	£72,098	2.67	£26,980	£18,806

1: Gompertz

Table 8 - Using Weibull, log-normal, log-logistic and generalised gamma distributions for the nivolumab arm to model time to progression at list price (BRAF mutation-positive patients)

Treatment	Distribution	Incremental Costs (vs ipilimumab)	Incremental QALYs (vs ipilimumab)	ICER (vs ipilimumab)
Nivolumab	Base case[1]	£13,374	1.83	£7,346
Nivolumab	Weibull	£13,060	1.48	£8,836
Nivolumab	Lognomal	£12,890	1.41	£9,144
Nivolumab	log-logistic	£12,947	1.43	£9,025
Nivolumab	generalised gamma	£12,903	1.41	£9,120
Nivolumab dominates dabrafenib and vemurafenib for all analyses				

1: Gompertz

4.3.2 Modelling progression-free survival using a range of distributions for BRAF inhibitors

For PFS, it was observed that the type of survival curve chosen for the BRAF inhibitors influenced the costs associated with the treatment arms in BRAF mutation-positive patients. The ERG explored this further by assigning a range of distributions (exponential, Gompertz, log-logistic, log-normal and Weibull) to the PFS in the BRAF inhibitors. Assigning different distributions influenced the total costs for both dabrafenib and vemurafenib but total QALYs in both the treatment arms remained similar to the base case values as shown in Table 29. As in the base case, the ICERs for both the BRAF inhibitors (vs nivolumab) remained dominated for the scenarios with different survival distributions.

CheckMate 067, has not been included in the company's analysis due to lack of available OS data.

5 End of life

The CS discusses the end of life criteria in Table 52 and states that advanced melanoma is associated with a short life expectancy, with median survival estimates of 6-10 months. Survival analyses of CheckMate 066 trial data indicate that nivolumab offers an extension to life of at least three months compared to palliative chemotherapy (DTIC). However, the survival benefit compared to ipilimumab is not yet fully established, pending follow-up OS data from CheckMate 067.[5] The CS reported that the expected number of new cases and relapsed cases of advanced melanoma in England in 2016 is 1,577. The CS therefore concluded that nivolumab is suitable for consideration as a life-extending treatment at the end of life.

The ERG also notes that in TA319[16] for ipilimumab for advanced melanoma, the Appraisal Committee was satisfied that ipilimumab met the criteria for being a life-extending, end of life treatment.

6 Innovation

The CS states that nivolumab should be considered innovative, representing a step-change in the management of advanced melanoma. The arguments in support of this include the stated significant clinical improvement associated with the drug, demonstrated through 45-50% of patients estimated to still be in remission two years after treatment initiation, based on extrapolation from the on-going Phase III RCTs. Furthermore, the CS reports that the Medicines and Healthcare products Regulatory Agency awarded nivolumab a Promising Innovative Medicine (PIM) designation for the treatment of advanced melanoma. Nivolumab was approved to treat advanced melanoma and locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) through the Early Access to Medicines Scheme. The criteria for drugs to be supported under this scheme include evidence that the product is likely to offer significant advantage over methods currently used in the UK.

7 DISCUSSION