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The Cost Effectiveness and Relapse-Reduction Benefit of Introducing Adjuvant Nivolumab for Patients with Completely Resected Melanoma with Lymph Node Involvement or Metastatic Disease in the UK

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Introduction

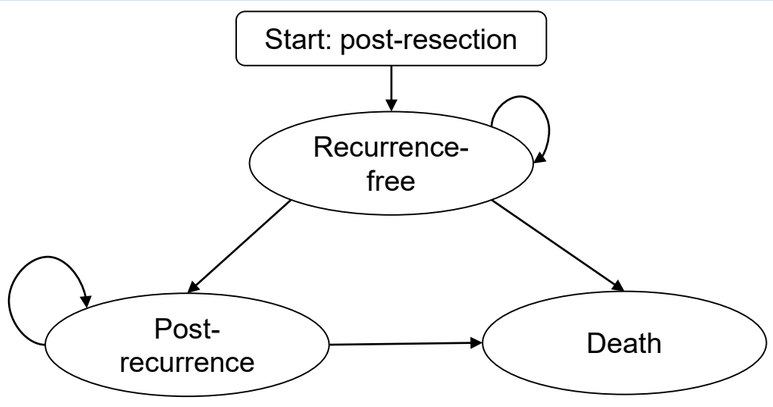
- Several adjuvant treatments for melanoma were recently approved by the National Institute for Health and Care Excellence (NICE) in the UK for use in the National Health Service (NHS), including nivolumab, pembrolizumab and dabrafenib plus trametinib.[1,2,3]
  - Considering that routine surveillance was the previous standard of care, these new options impact both patient outcomes and costs to the NHS.
  - Nivolumab, a programmed cell death 1 (PD-1) inhibitor, has already demonstrated long-term durable clinical benefit as monotherapy or in combination with ipilimumab and is available for use in many indications, including advanced melanoma.[4]
- The objective of this study was to compare the cost effectiveness and relapse-reduction benefit of adjuvant nivolumab versus routine surveillance in patients with lymph node involvement or metastatic disease following complete surgical resection. Study results were used to inform the NICE health technology assessment submission for this indication.

Methods

Model structure

- A three health-state recurrence-based state-transition model was developed with a 60-year time horizon and a 28-day cycle length (**Figure 1**).
- The structure differs from other adjuvant melanoma models submitted to NICE[2,3] as transitions between local/regional and distant recurrence are not explicitly modelled due to data being immature.
- Costs and quality-adjusted life years (QALYs) were discounted at 3.5%, as per NICE guidance.[5]

Figure 1. Model diagram

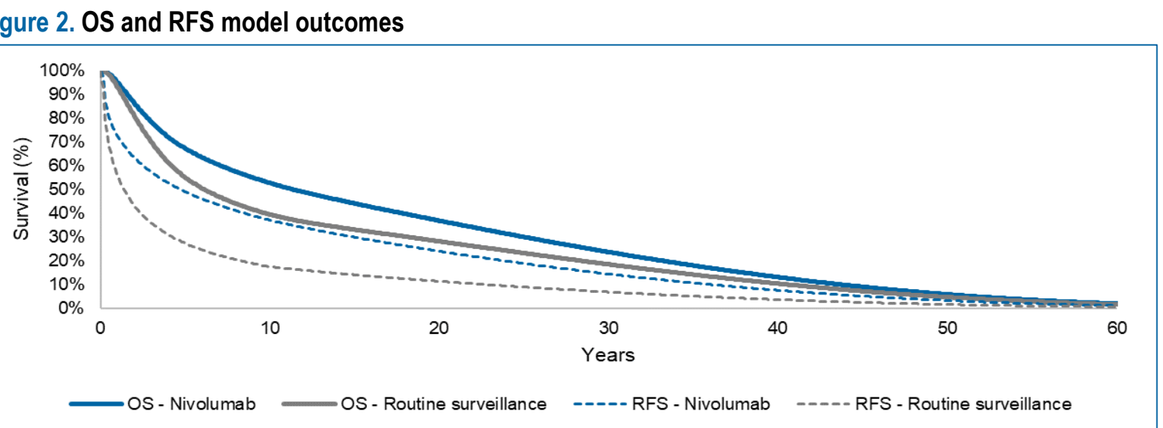


Note: Post-recurrence includes local/regional and distant recurrences. Costs and efficacy are pooled in this health state.

Survival

- A patient level meta-regression of Phase III trial data was used to estimate recurrence-free survival (RFS) and indirectly compare nivolumab (CheckMate 238, which compared nivolumab with ipilimumab[6] [using a 2-year data cut]) with placebo (CA184-029, which compared ipilimumab with placebo[7]) using ipilimumab as a common comparator between trials.
- Post-recurrence survival was estimated by weighting the survival curves estimated for each type of recurrence (local/regional or distant).[8]
  - Local/regional recurrence survival was estimated using post-local/regional recurrence data from CA184-029 as post local/regional outcomes were not expected to have changed much since the time of the trial.
  - Distant recurrence survival was estimated from weighting individual survival curves from a range of metastatic melanoma therapies. The survival curve for each treatment was based on reported outcomes from the literature and patient-level data obtained from the CheckMate 067 trial, which investigated nivolumab, ipilimumab, and nivolumab in combination with ipilimumab.
  - Re-challenge of anti-PD-1s in the metastatic setting was tested assuming that any patient who has a distant recurrence within 2 years of receiving adjuvant nivolumab would not receive any subsequent anti-PD-1 treatment and would instead be treated with ipilimumab.
- Long-term survival was based on the American Joint Committee on Cancer 8th edition[9], and applied to both treatment arms at 10 years.
- **Figure 2** presents the overall RFS and overall survival (OS) estimates from the model outcomes over the 60-year time horizon.

Figure 2. OS and RFS model outcomes



OS, overall survival; RFS, recurrence-free survival.

Costs

- Drug costs were based on prices reported in the Monthly Index of Medical Specialities, with known patient access scheme discounts included for the cost-effectiveness calculations.
  - The cost of nivolumab was based on the method of moments. Assuming a log-normal distribution for body weight, the proportion of patients requiring each number of vials was calculated based on the distribution derived from the individual patient weights.
- Frequency of administration for nivolumab was taken from the CheckMate 238 trial: 3 mg/kg every 2 weeks for up to 1 year.
- Disease monitoring costs were calculated based on frequencies collected from a survey from UK clinicians.
  - These were split by recurrence type (recurrence-free, local/regional and distant) and time point (Year 1, Year 2, Year 3–5 and Year 5+).
  - Unit costs for resource use and administration were taken from NHS reference costs 2016/17 and the Personal Social Services Research Unit 2017.[10,11]
- Adverse events were grouped into three categories: immune-related disorders (any grade), diarrhoea (Grade 2+) and other adverse events (Grade 3+). Incidence rates were taken from CheckMate 238 and CA184-029.
- Subsequent treatment costs for patients with a distant recurrence were based on data from CheckMate 238 and differed depending on the time point before or after re-challenge.
  - As the current standard of care at the time of the analysis was routine surveillance in the adjuvant setting, no subsequent treatment costs were applied for patients who had a local/regional recurrence.
  - Subsequent radiotherapy and surgery costs were also included.
  - Subsequent treatment data from the ipilimumab arm were used for both treatment arms as this was more reflective of UK practice when compared to UK real-world sources.
- Terminal care costs were based on the average per-person cost of health and social care for different cancer types.[12]
- A summary of key cost inputs can be found in **Table 1**.

Table 1. Model cost inputs

Input	Nivolumab	Routine surveillance	Source
Adjuvant drug costs	40 mg vial £439[a] 100 mg vial £1,097[a]	£0	MIMS[13]
Administration costs	£300	£0	NHS reference 16/17 (SB13Z)[10]
Disease monitoring (monthly cost)			
Recurrence-free			Clinician survey NHS reference 16/17[10] PSSRU 2017[11]
Year 1	£156		
Year 2	£160		
Year 3-5	£111		
Year 5+	£21		
Post-recurrence			
Year 1	£249		
Year 2	£247		
Year 3-5	£168		
Year 5+	£30		
Adverse event costs	£355	£316	CheckMate 238/CA184-029[6,7]
Terminal care costs	£6,399		Round et al, 2015[12]

[a]These costs do not include the patient access scheme discount.
MIMS, Monthly Index of Medical Specialists; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Health-related quality of life

- Utility inputs were based on observed EQ-5D® data from CheckMate 238 using a regression model to adjust for progression status, baseline utility and disease stage.
  - The same utilities were used for both treatment arms, which showed a decrement of 0.09 between the recurrence-free and post-recurrence health state.
- Disutilities for adverse events were also included; these were based on data reported by Middleton et al. 2016[14] (−0.11 for toxicity [outpatient]; −0.16 for toxicity [inpatient]; −0.09 for diarrhoea), with the durations taken from CheckMate 238.

Results

Deterministic

- The main cost driver was adjuvant treatment. However, adjuvant treatment reduced downstream costs of disease monitoring, subsequent therapy and terminal care costs as a result of improved RFS benefit.
  - Incremental base case model results are presented in **Table 2**.
  - In the nivolumab arm, subsequent treatment costs were reduced by 25% and end of life costs were reduced by 10% due to improved RFS and OS compared to routine surveillance.

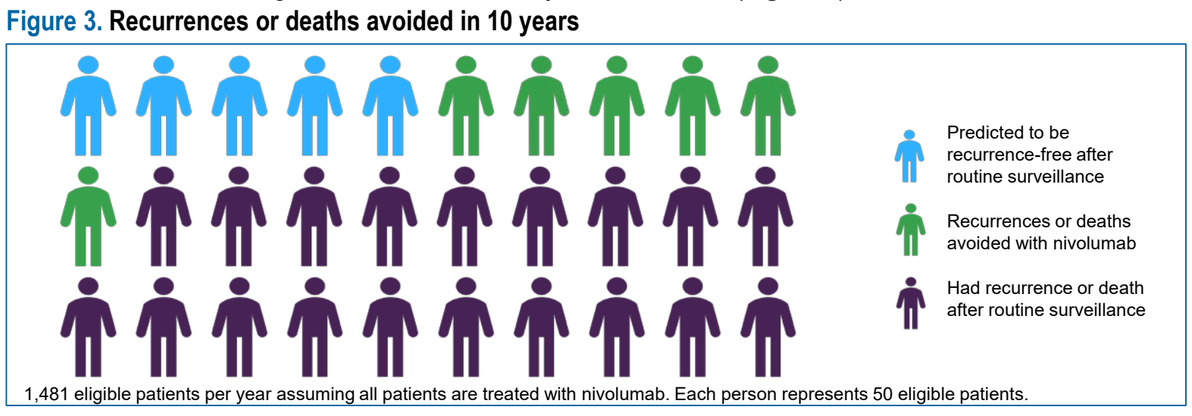
Table 2. Base case model results and key scenarios

Model result		Incremental	
Costs[a]		£32,624	
Life years		3.42	
QALYs		1.81	
ICER – cost per QALY gained		£18,018	
Key scenario[b]	**Base case**	**Scenario**	**ICER – cost per QALY**
Dosing and drug costs			
Dosing method	Method of moments	Cost per mg	£17,250
Patient population			
Disease stage	Stage IIIA/B/C & IV	Stage IIIA	£18,525
		Stage IIIB	£17,736
		Stage IIIC	£18,821
		Stage IV	£18,821
Survival			
CheckMate 238 RFS data cut	2-year RFS data	3-year RFS data[c]	£16,358
Long-term registry	Applied at 10 years	Not applied	£17,056
PD-1 re-challenge time point	2 years	6 months	£17,467
		1 year	£17,737
		No re-challenge	£18,863
Utility			
Utility source	CheckMate 238	Middleton et al	£15,341
AE disutilities	Applied	Not applied	£17,986
General model settings			
Time horizon	60 years	20 years	£23,165
		30 years	£19,595
		40 years	£18,469
Discount rate	3.5% for costs and QALYs	1.5%	£13,816

[a]These costs include patient access scheme discounts for available Bristol-Myers Squibb products. [b]For a full list of assumptions please refer to TA558[1]. [c]A 3-year data cut was not available at the time of the base case analysis.
AE, adverse event; ICER, incremental cost-effectiveness ratio; PD-1, programmed cell death 1; QALY, quality-adjusted life year; RFS, recurrence-free survival.

- Clinical experts predict that between 25% and 40% of patients remain recurrence free over a lifetime[15]. The model predicted that at 10 years, 17% patients remain recurrence-free after routine surveillance, with an additional 20% remaining recurrence-free after adjuvant nivolumab (**Figure 3**).

Figure 3. Recurrences or deaths avoided in 10 years

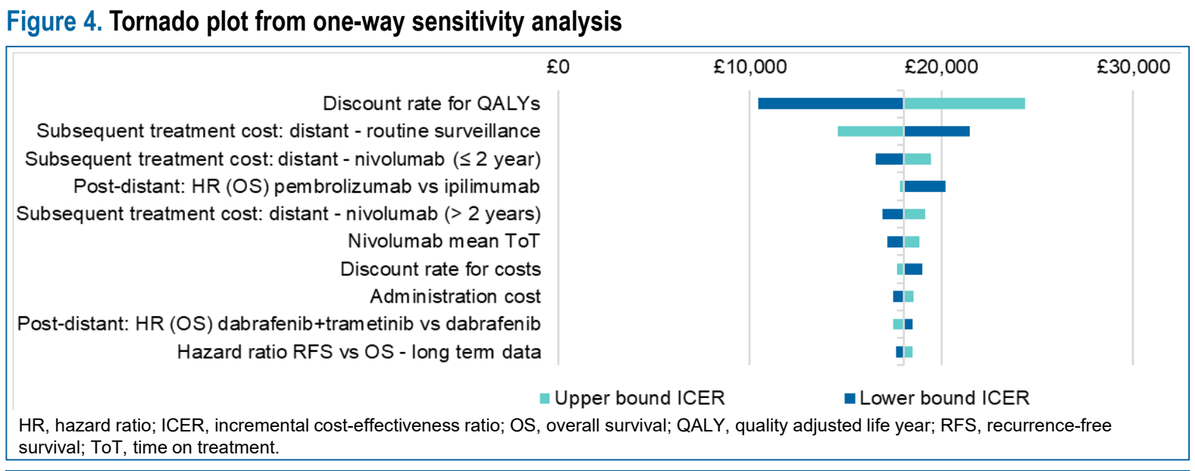


1,481 eligible patients per year assuming all patients are treated with nivolumab. Each person represents 50 eligible patients.

Sensitivity analysis

- One-way sensitivity analysis demonstrated that the top inputs that had the largest impact on the incremental cost-effectiveness ratio (ICER) were the discount rate for QALYs and subsequent treatment costs. However, for all upper and lower bounds tested, the ICER remained below the £30,000 per QALY willingness-to-pay threshold (**Figure 4**).
- Probabilistic sensitivity analysis using 1,000 iterations resulted in an ICER of £18,003, which is close to the deterministic ICER.
  - The probability of nivolumab being cost effective at the £30,000 willingness-to-pay threshold is 96.9%.
- Key scenario analyses demonstrated that the base case results are robust to changes in key model parameters and assumptions and more mature RFS data improves the cost-effectiveness (**Table 2**).

Figure 4. Tornado plot from one-way sensitivity analysis



HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year; RFS, recurrence-free survival; ToT, time on treatment.

Conclusions

- Despite the limited availability of data and the assumptions required for estimating post-recurrence survival by using different data sources due to OS data being immature, the model structure allowed for a full exploration of uncertainty around key clinical parameters that interest decision makers.
  - As trial data mature, alternative model structures or more complex modelling may be employed.
- The cost-effectiveness model demonstrates that adjuvant nivolumab is a highly cost-effective treatment option.
  - The results show that nivolumab as adjuvant treatment decreases relapses, increases OS and reduces downstream treatment costs versus routine surveillance.
  - The sensitivity analysis demonstrates that the deterministic results are robust and consistently within the £30,000 per QALY willingness-to-pay threshold.
  - More mature RFS data improve the cost-effectiveness.
  - Longer-term follow-up data, including long-term data on immunotherapy re-challenge, will allow further exploration.
- Nivolumab has demonstrated reduced risk of relapse compared to an active comparator (ipilimumab) in the CheckMate 238 study, and compared to routine surveillance via an indirect treatment comparison.
- Nivolumab has the potential to offer long-term benefits for patients, reducing the risk of advanced disease progression, which is associated with increased health costs and poor survival outcomes.

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