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NICE National Institute for Health and Care Excellence

# Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316] – STA

## Lead team presentation: Background and Clinical Effectiveness

1st Appraisal Committee meeting
Committee A
Lead team: Jane Adam, Olivia Wu
ERG: BMJ Technology Assessment Group (BMJ-TAG)
NICE technical team: Juliet Kenny, Eleanor Donegan
August 2018



## Preview: Clinical effectiveness issues

- Adjuvant therapy aims to reduce the number of people who develop incurable metastatic disease. Does the committee accept that nivolumab will cure some people?
- CheckMate 238 compared nivolumab with ipilimumab, which is not used in the adjuvant setting in UK. Recurrence free survival data is limited to 24 months follow up, overall survival data is very immature. What conclusions can be drawn about relapse free survival and the effect on overall survival?
- To assess the effect of adjuvant nivolumab vs routine surveillance an indirect comparison was made using another trial CA184-029 (ipilimumab vs placebo). How reliable are the results for RFS compared with routine surveillance given the trial differences?
- Are the indirect comparison RFS results generalisable to the NHS given the change in classification of stages of melanoma since the trials?
- OS data are available from CA184-029, what is the committee's view of these?
- For people who develop metastatic disease after nivolumab, what treatment options would be available? Does immunotherapy work better as adjuvant or in metastatic disease?
- Would more limited surgery be carried out if this were available?

# Advanced fully resected melanoma

- Melanoma 5th most common cancer in the UK
  - rates increased steadily since 1990s, incidence up by 45% in last decade
- Disease stage describes the extent of disease
  - Stage I and II: no evidence that melanoma has spread anywhere else in body (possibility of microscopic spread) Commonest presentation in England
  - Stage III: melanoma is present in the skin, lymph vessels, or nearby lymph glands
  - Stage IV: melanoma has spread to other distant parts of the body
- ~ 8% (total N=1,100) patients diagnosed at Stage III or IV disease
- No UK-wide statistics available for melanoma survival by stage; data from former Anglia Cancer Network for people diagnosed between 2002-2006 - five-year survival approximately 50-55% for stage III disease and 8-24% for stage IV disease
- People who have had surgery to remove stage III or IV tumours are at high risk of relapse and death; 5-year relapse-free survival is 28-44% for stage III melanoma
- Principle of adjuvant therapy after complete surgical clearance is to remove any microscopic disease either locally or in the bloodstream to reduce the rate of it recurring and resulting in death from disseminated disease

[redacted]

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# Nivolumab

| | |
|---|---|
| **Mechanism of action** | Nivolumab is a human immunoglobulin G4 monoclonal antibody that works by influencing how T-cells respond to cancer cells. Specifically, Nivolumab binds to PD-1 (a protein found on the surface of T-cells) stopping cancer cells blocking it and enabling the body to recognise and destroy micrometastases or individual tumour cells |
| **Marketing authorisation** | As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection |
| **Administration** | Intravenous infusion |
| **Dose** | 3mg/kg every 2 weeks; maximum treatment duration 12 months |
| **Cost (list price)** | £439.00 per 4ml vial; £1,097.00 per 10ml vial.<br>Average cost of a course of treatment £53,771 |
| **Patient access scheme** | A commercial access agreement (CAA) has been approved which provides a simple discount to the list price |

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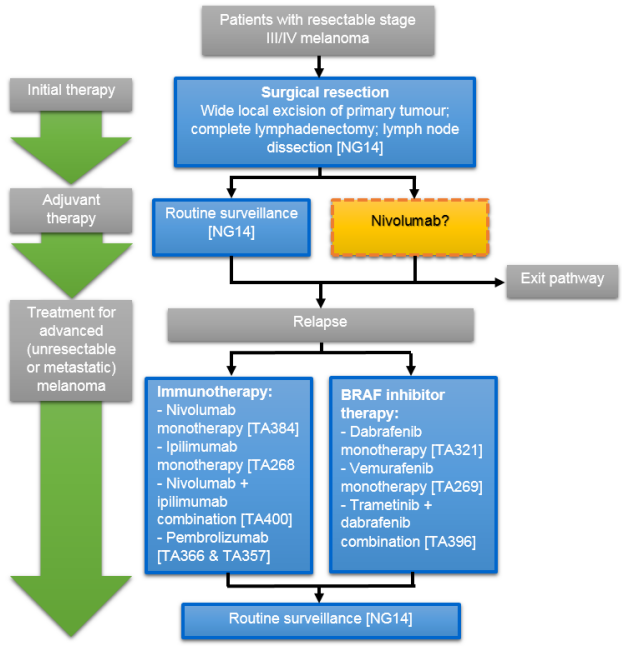
# How is melanoma treated

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# Decision problem – NICE vs. company

Company's decision problem was in line with the NICE scope with the exception of the population

| NICE decision problem population | Company decision problem population |
|---|---|
| People with completely resected Stage III or IV melanoma | Adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection |

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# What evidence is available?

- **No head-to-head trials found for comparison of interest** (adjuvant nivolumab versus routine surveillance)
- Two randomised controlled trials were identified
- Comparator in both cases was **ipilumumab** (another biological therapy **not used in the adjuvant setting in UK clinical practice**):
  - **CheckMate 238: Nivolumab vs. ipilimumab (Weber 2017)**
  - **CA184-029: Ipilimumab vs. placebo (Eggermont 2016)**
- Two trials were combined to provide indirect evidence for the effectiveness of nivolumab vs. routine surveillance

ERG: CheckMate 238 trial of high methodological quality (no comment made on quality of CA184-092)

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# CheckMate 238 (nivolumab vs. ipilimumab; Weber 2017)

| | |
|---|---|
| Design | Multinational, randomised, double-blind, Phase III trial (8 UK sites) |
| Population | N=906 patients (≥15 years of age) undergoing complete resection of stage IIIB, IIIC, or IV melanoma |
| Intervention | Nivolumab (IV every 2 weeks for up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent) (n=453) |
| Comparator | Ipilimumab (IV, 10 mg/kg per kilogram every 3 weeks for four doses and then every 12 weeks for same duration as nivolumab) (n=453 patients) |
| Primary outcomes | Recurrence-free survival (RFS) |
| Secondary outcomes | Overall survival (OS); adverse events; recurrence-free survival according to tumour PD-L1 expression; health-related quality of life (HRQoL). Distant metastasis–free survival (DMFS) was an exploratory end point |
| Follow-up | Primary analysis 18 months (EMA requested analysis 24 months) |
| Stratification groups | Disease stage (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c); PD-L1 status (negative or intermediate vs. positive at 5% cutoff with PD-L1 staining only of tumour cells) |

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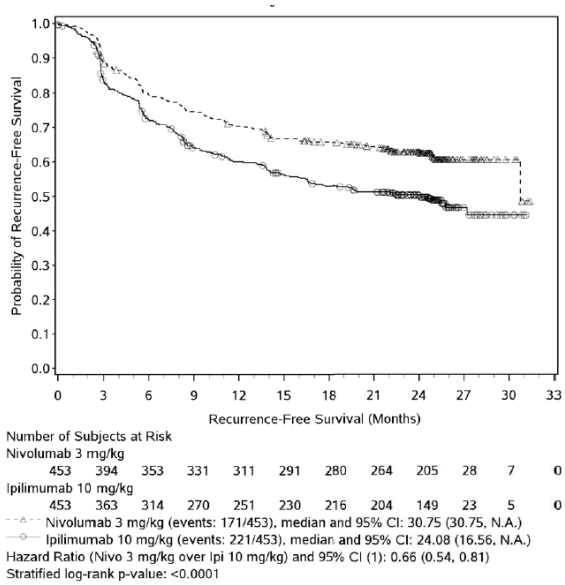
## CheckMate 238 (nivolumab vs. ipilimumab): RFS results

**Intention-to-treat (ITT) 24-month follow-up (Data-cut: 19 December 2017)**




Results of the pre-specified subgroup analyses were mostly consistent with the primary analysis.

Point estimates for following subgroups ≥1:

- mucosal melanoma
- stage IV M1c
- ulceration present plus microscopic lymph node involvement

Results for these groups all had wide CIs that encompassed 1.0

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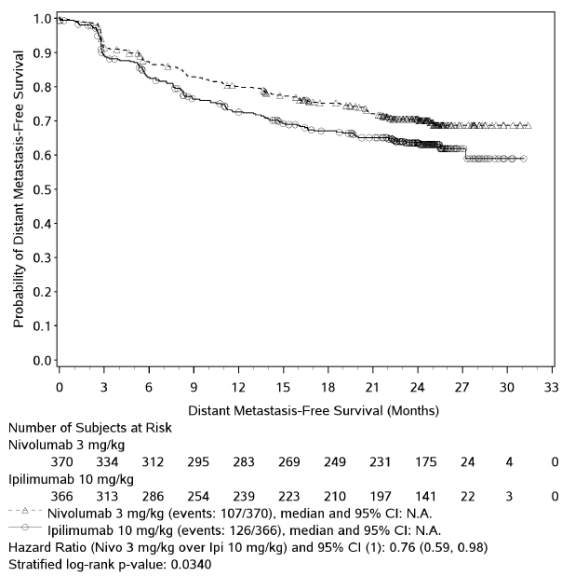
## CheckMate 238 (nivolumab vs. ipilimumab): DMFS results

**ITT 24-month follow-up (Data-cut: 19 December 2017)**

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## CheckMate 238 (nivolumab vs. ipilimumab): OS results

[Redacted CIC content]

- [Redacted CIC content]
- [Redacted CIC content]

[redacted]

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## CheckMate 238 (nivolumab vs. ipilimumab): HRQoL results

**ITT 18-month follow-up (Data-cut: 15 May 2017)**

- HRQoL measured in the trial using various tools including EQ5D. Questionnaire completion rates reported in company submission but actual HRQoL scores are not reported
- Results are summarised narratively by company as follows:

  *'HRQoL scores were maintained after treatment in both groups….. mean summary scale scores for all patients were comparable between treatment groups at baseline; no clinically meaningful deterioration or improvement was observed at any time point for either treatment group for any scale'*

[redacted]

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## CheckMate 238 (nivolumab vs. ipilimumab): Adverse events (AEs)

Safety population 18-month follow-up (Data-cut: 15 May 2017)

| | Nivolumab (n=452) | Ipilimumab (n=453) |
|---|---|---|
| Any AE, n (%) | 438 (96.9) | 446 (98.5) |
| Grade 3–4 | 115 (25.4) | 250 (55.2) |
| Any SAE, n (%) | 79 (17.5) | 183 (40.4) |
| Grade 3–4 | XXXXX | XXXXXX |
| Drug-related SAE, n (%) | XXXX | XXXXXX |
| Grade 3–4 | XXXX | XXXXXX |
| Discontinuations due to drug-related AEs, n (%) | 35 (7.7) | 189 (41.7) |
| Grade 3–4 | 16 (3.5) | 136 (30.0) |
| Treatment-related deaths, n (%) | 0 (0) | 2 (0.4) |

[redacted]

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## CheckMate 238 (nivolumab vs. ipilimumab): ERG critique – RFS, DMFS & OS

- Median **RFS** was reached, BUT the data are immature, with heavy censoring in the KM curve
  - Several clinical subgroups did not demonstrate a statistically significant benefit of nivolumab over ipilimumab but small patient numbers and low event rates
  - Key assumption in the company's base case model is that nivolumab is equally effective across all disease stages. Stage subgroup results show
    - Nivolumab showed as statistically significant benefit in the Stage IIIC (using AJCC 7th edition) subgroup only
    - Change in AJCC staging definitions means that a subset of CheckMate patients would be reclassified. RFS results for the n=XX reclassified Stage IIIA patients (per AJCC 8th edition) in CheckMate 238 demonstrated [redacted AIC content] between nivolumab and ipilimumab
- **OS** [redacted CIC content]
- Median **DMFS** [redacted AIC content] in either treatment group at 24 months' follow-up
  - statistically significant difference between the treatment groups favouring nivolumab
  - DMFS rates were also consistently [redacted AIC content] in the nivolumab group than in the ipilimumab group at 12 months, 18 months and 24 months

[redacted]

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## CA184-029 (ipilimumab vs. placebo; Eggermont 2016)

**NB: *ipilimumab for up to 3 years, no stage IV patients, but includes IIIA***

| | |
|---|---|
| Design | Multinational, randomised, double-blind, Phase III trial |
| Population | N=951 high-risk patients (≥18 years of age) with stage III cutaneous melanoma who had undergone a complete regional lymph node dissection |
| Intervention | Ipilimumab every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred) (n=475) |
| Comparator | Matched placebo (n=476) |
| Primary outcomes | RFS |
| Secondary outcomes | OS; DMFS; adverse events; HRQoL |
| Follow-up | 5.3 years (median) |
| Stratification groups | Disease stage (stage IIIA vs. stage IIIB vs. stage IIIC with one, two, or three positive nodes vs. stage IIIC with four or more positive nodes); geographic region (North America, Europe, or Australia) |

[redacted]

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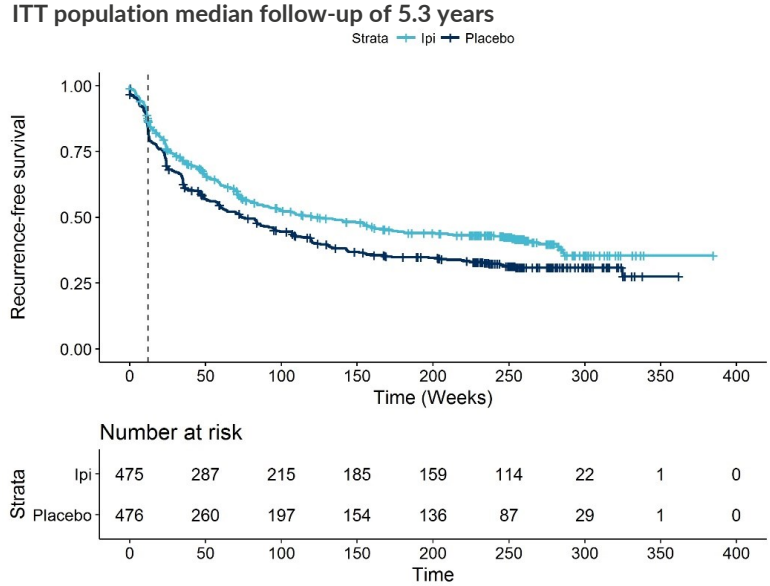
## CA184-029 (ipilimumab vs. placebo): RFS

**ITT population median follow-up of 5.3 years**




**Key:** Ipi, ipilimumab; PBO, placebo.
**Notes:** Dashed line indicates time of first efficacy assessment (12 weeks).

No Kaplan Meier (KM) curves were presented for OS or DMFS result of CA184-029 trial

[redacted]

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# CA184-029 (ipilimumab vs. placebo): RFS, OS, results

ITT population median follow-up of 5.3 years

| | Ipilimumab (n=475) | Placebo (n=476) |
|---|---|---|
| **RFS** | | |
| Events, n (%) | 264 (55.6) | 323 (67.9) |
| Median months (95% CI) | 27.6 (19.3, 37.2) | 17.1 (13.6, 21.6) |
| 5-year RFS rate (95% CI) | 40.8 (36.0, 45.6) | 30.3 (26.0, 34.6) |
| HR (95% CI) | 0.76 (0.64, 0.89) | |
| p-value | <0.001 | |
| **OS** | | |
| Events, n (%) | 162 (34.1) | 214 (45.0) |
| Median months (95% CI) | Not reached | Not reached |
| 5-year OS rate (95% CI) | 65.4 (60.8, 69.6) | 54.4 (49.7, 58.9) |
| HR (95% CI) | 0.72 (0.58, 0.88) | |
| p-value | 0.001 | |

[redacted]

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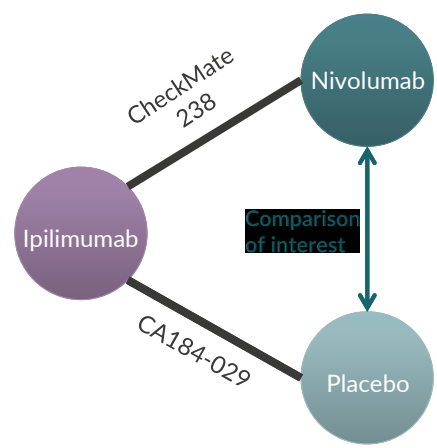
# Indirect treatment comparison (ITC) methods to compare nivolumab with routine surveillance

- Original company submission:
  - ITC only undertaken for RFS
  - Two different methodologies used to predict RFS: (1) individual patient data meta-regression; (2) Bucher method (both methods allow for treatment effect for comparison of interest to be estimated indirectly while preserving randomisation)
  - OS estimates were also required for economic modelling so company estimated these using data from CA184-029 trial and a surrogacy analysis
- [Redacted CIC content]




[redacted]

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# ITC methods (cont.)

**IPD-meta-regression (only feasible for RFS, results used in both company and ERG economic analyses)**

- Analysis conducted at the individual patient level – not the study level
  - All data from both trials combined into a single data set, with each person having a treatment indicator and a trial indicator
  - These two variables are used to determine treatment effects and to account for differences across the two trials that have been adjusted for imbalances in key covariates across trials, as well as differences in treatment effects between the two trials

**Bucher method (results not used in any of the economic analyses presented by company or ERG)**

- Simple form of anchored ITC
- Calculated from summary measures of treatment effect, not IPD
- Hinges on similarity assumption

**Trial heterogeneity a key issue for any ITC, re-cap of key differences between trials:**

- **Inclusion criteria relating to disease stage (CheckMate 238 excluded patients with stage IIIA disease and CA184-029 excluded patients with stage IV disease)**
- **Duration of ipilimumab treatment (XXX had ipilimumab beyond 1 year in CA184-029)**
- **Differences in subsequent treatments received**

[redacted]

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# Modelling OS up to 10 years – surrogacy analysis

Due to the immaturity of the OS data for CheckMate 238, the company took the following approach to modelling OS up to 10 years:

- For routine surveillance: parametric survival models were fitted to the placebo arm of the CA184-029 trial (generalised gamma curve). The curve was adjusted to reflect the population of interest (patients with stage IIIA-IV) using the corrected group prognosis (CGP) method
- For nivolumab: surrogacy analysis was conducted

**Surrogacy analysis**

1. An equation was used to predict a HR for OS for nivolumab versus ipilimumab based on the observed RFS treatment effect (HR) from CheckMate 238
2. Predicted OS HR for nivolumab vs ipilimumab was compared with the observed OS HR for ipilimumab vs placebo (CA184-029 trial) to produce the HR for nivolumab vs placebo
3. HR for nivolumab vs placebo was then applied to the routine surveillance curve estimated from the CA184-029 placebo OS data

After 10 years OS was informed by AJCC version 8 OS registry data (background mortality using general population data used if extrapolations predict a lower mortality)

[redacted]

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# ITC RFS results – ERG critique

- RFS results from IPD meta-regression analysis
  - Results based on ITT (all ipilimumab treatment durations) used in company base case represent 'best case' scenario due to differences between trials in the duration of ipilimumab treatment
  - Clarification stage analysis (where patients in CA184-029 who were still on ipilimumab treatment at one year were censored) represents 'worst case'
    - ERG consider ITT-based results as 'overly optimistic' and prefer more conservative estimates
  - Data for some disease stages was inadequate
  - ITC only informs model up to 10 years, after that RFS estimated by applying a hazard ratio to AJCC version 8 OS registry data (HR was based on interferon trial [Argawala et al. 2017])
- RFS results from Bucher analysis
  - Assumes proportional hazards
  - Results demonstrate
    - treatment effect is [redacted AIC content]
    - [redacted AIC content]
  - When the ipilimumab censored at one-year data were used instead of full ITT ipilimumab dataset, HRs were [redacted AIC content]

[redacted]

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# Company's surrogacy analysis for OS – ERG critique

- Rationale for surrogacy analysis approach was informed by a study (Suciu et al. 2018) that concluded that RFS appears to be a valid surrogate endpoint for OS in Stage II–III melanoma adjuvant therapy. It used 13 interferon trials to derive a regression equation to estimate a HR for OS from a HR for RFS.
- Surrogacy analysis in the company submission (CS) differed from this original analysis
  - Approach used in CS based on ongoing, unpublished study funded by BMS, first part of which is complete and considered to be an update of the previous analysis by Suciu et al. 2018 et. al.
  - [redacted AIC content]
  - whereas Suciu et al. 2018 2018 used [redacted AIC content]
- ERG is unsure about reliability; unaware of any other publications in support of this method
- A publication supplied by the company considered this [redacted AIC content] - The ERG are concerned it is not robust
- It is unclear whether proportional hazards assumption holds for OS for nivolumab versus routine surveillance – if not then results for OS calculated using the surrogacy equation will be flawed
- Final estimates for both nivolumab and routine surveillance informed by CA184-029 placebo arm OS data – estimates in the placebo group of the CA184-029 trial are likely to be underestimated because more effective subsequent treatments are now available

[redacted]

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# Bucher ITC OS results - ERG critique

- [Redacted CIC content]
  - [Redacted CIC content]
- [Redacted CIC content]
  - [Redacted CIC content]
  - [Redacted CIC content]
  - [Redacted CIC content]
  - [Redacted CIC content]
  - [Redacted CIC content]

[redacted]

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# Validity of ITC results: impact of trial differences – ERG critique

- **Differences in subsequent therapies across trials is key issue:**
  - subsequent therapies given in CheckMate 238 more consistent with UK clinical practice (ERG clinical expert)
  - differences likely to be related to advances in clinical practice since CA184-029
  - due to the outcome censoring selected for the ITC analyses, these differences in subsequent therapies will have the largest impact in the analysis of OS
  - ERG is unsure of the exact impact of these differences in subsequent therapies on the ITC results:
    - more effective subsequent treatments will minimise any difference in OS
    - less effective subsequent treatments will have less impact on subsequent OS
    - [Redacted CIC content]

[redacted]

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## Clinical effectiveness issues

- Adjuvant therapy aims to reduce the number of people who develop incurable metastatic disease. Does the committee accept that nivolumab will cure some people?
- CheckMate 238 compared nivolumab with ipilimumab, which is not used in the adjuvant setting in UK. Recurrence free survival data is limited to 24 months follow up, overall survival data is very immature. What conclusions can be drawn about relapse free survival and the effect on overall survival?
- To assess the effect of adjuvant nivolumab vs routine surveillance an indirect comparison was made using another trial CA184-029 (ipilimumab vs placebo). How reliable are the results for RFS compared with routine surveillance given the trial differences?
- Are the indirect comparison RFS results generalisable to the NHS given the change in classification of stages of melanoma since the trials?
- OS data are available from CA184-029, what is the committee's view of these?
- For people who develop metastatic disease after nivolumab, what treatment options would be available? Does immunotherapy work better as adjuvant or in metastatic disease?
- Would more limited surgery be carried out if this were available?

[redacted]

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