FOR PUBLIC – NO ACIC DATA

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

Chair's presentation – Part 1

2nd 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
October 2018

Key issues for consideration

- Are the committee's concerns about the uncertainty in the clinical evidence reasonable?
- The trial excluded people with stage IIIA disease, is this relevant to the decision?
- The partitioned survival and Markov II models have been updated. What are the certainties and uncertainties related to these?
- The partitioned survival model now uses the trial OS evidence instead of a surrogacy analysis. Can the results now be considered to be robust?
- Is the committee satisfied that the impact of subsequent treatments has been captured?
- Does the committee consider that there is sufficient clinical and cost effectiveness evidence to support a change in the routine pathway of care for patients in the NHS?
- Should adjuvant nivolumab be recommended for use in the CDF?

2

Nivolumab

Mechanism of action	Monoclonal antibody binds to PD-1 (a protein on the surface of T-cells) stopping cancer cells blocking it and enabling the immune system to recognise & act against cancer cells
Marketing authorisation	Adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease after complete resection
Administration/dose	Intravenous infusion, 3mg/kg every 2 weeks; up to 12 months
Cost (list price)	£439.00 per 4ml vial; £1,097.00 per 10ml vial. 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

ACD Preliminary recommendation

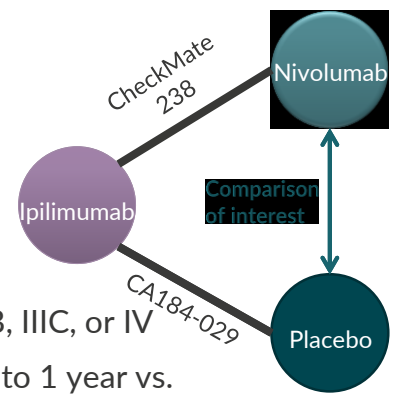
Nivolumab is not recommended, within its marketing authorisation, as monotherapy for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease

[redacted]

3

Clinical evidence

- **No head-to-head trials found for comparison of interest**
- Two randomised controlled trials:
  - **CheckMate 238:**
    - **Population:** N=906 patients with stage IIIB, IIIC, or IV
    - **Comparison:** Nivolumab: 2 weekly iv up to 1 year vs. ipilimumab: mg/kg per kilogram 3 weekly iv x 4 doses then every 3 months
  - **CA184-029:**
    - **Population:** N=951 patients with stage III cutaneous melanoma
    - **Comparison:** Ipilimumab: 10mg/kg every 3 weeks iv X 4 doses then every 3 months up to a maximum of 3 years vs. **placebo**

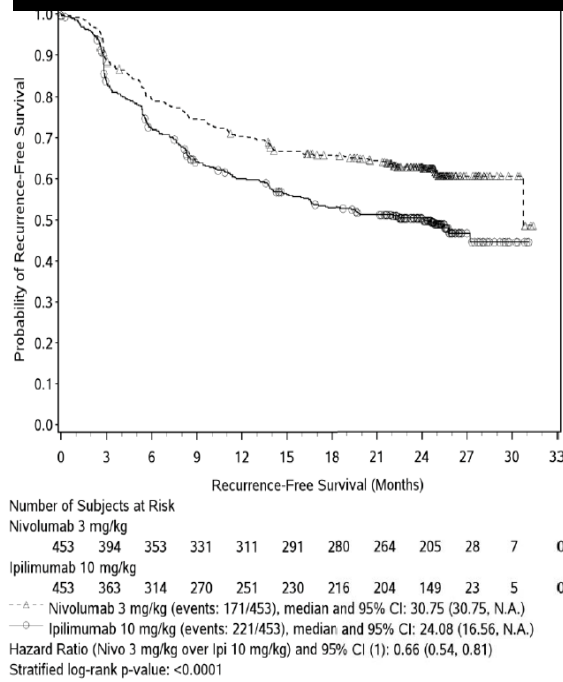


[redacted]

4

CheckMate 238 (nivolumab vs. ipilimumab): RFS results

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



ERG Critique

Median RFS reached, BUT immature data with heavy censoring in the KM curve.

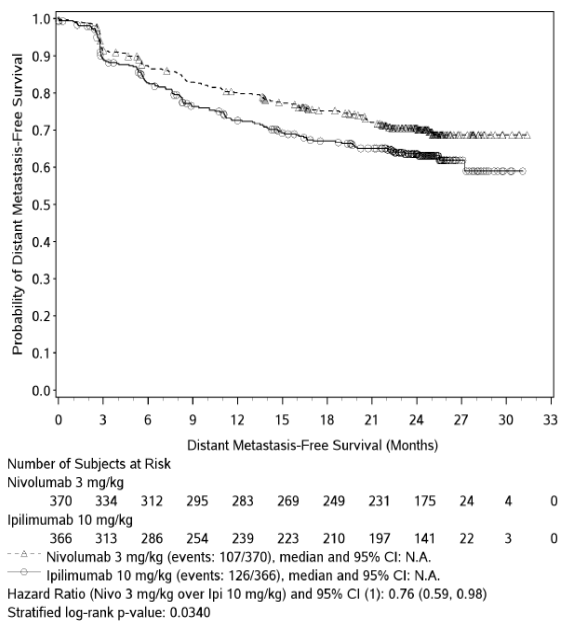
Nivolumab assumed to be equally effective across all disease stages BUT stage subgroup results show only statistically significant benefit in the Stage IIIC (using AJCC 7th edition).

AJCC 8th edition reclassification. Subset of n=43 reclassified Stage IIIA patients in CheckMate 238 demonstrated no statistically significant difference between nivolumab and ipilimumab

5

CheckMate 238 (nivolumab vs. ipilimumab): DMFS results

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



ERG critique

Median **DMFS** XXXXXXX in either treatment group at 24 months' follow-up

- statistically significant difference between the treatment groups favouring nivolumab
- DMFS rates were also consistently XXXXXX in the nivolumab group than in the ipilimumab group at 12 months, 18 months and 24 months

6

CheckMate 238 (nivolumab vs. ipilimumab): OS results

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

[redacted]

ERG critique: OS data are extremely immature

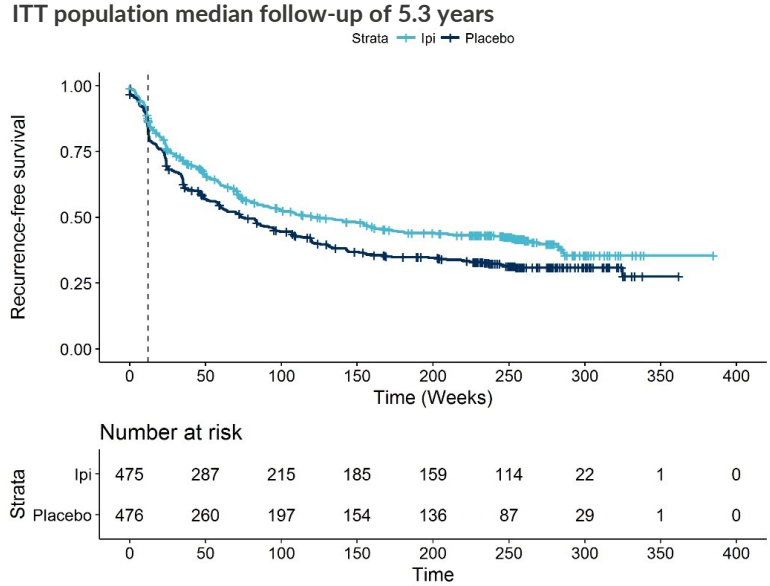
- Unplanned analysis not included in the company's original submission but provided at clarification stage
- Formal interim OS analysis (as outlined in study protocol) will take XXXXXXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXXX

[redacted]

7

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]

8

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

ITT median follow-up 5.3 yrs.	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)	
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	

Trial heterogeneity was a key issue for 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 (recruited 2008-2011)

[redacted]

9

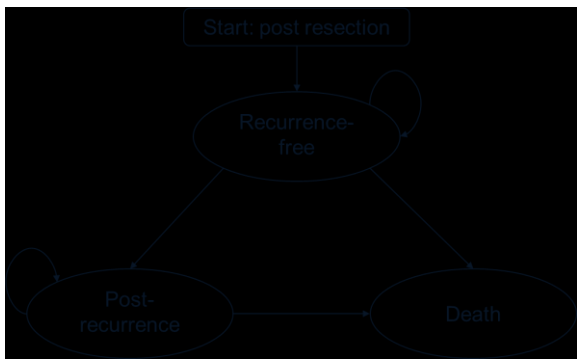
Indirect treatment comparison (ITC) methods

- RFS
  - Two different methodologies used to predict RFS:
    - IPD-meta-regression results used in both company and ERG original models
    - Bucher method provided to validate the IPD analysis but not used in any of the models
  - Reliability and generalisability of ITC results used in models called into question by trial heterogeneity
- OS
  - Original company submission did not include any ITC for OS - OS data for company's original base case derived from a surrogacy analysis

[redacted]

10

Company's original economic model structure



- Company originally provided 3 models:
  - 1 partition survival model (base case), plus
  - 2 alternative Markov models
- Patient characteristics in the model reflect CheckMate 238 and CA184-029 trials i.e. stage IIIA–IV patients with confirmed lymph node involvement

ERG comments
- Model population appropriate
- Use of the Western European population appropriate for costs
- Contains relevant health states
- Time horizon is long at 60 years but appropriate
- Cycle length appropriate

[redacted]

11

Overview of data sources in company's original base case partitioned survival model

Input	Source
RFS	0-12 weeks • Routine surveillance: HR (derived by fitting a Cox proportional hazards model to the ipilimumab groups of the CheckMate 238 and CA184-029 trials, with censoring applied at 12 weeks) applied to the KM data from the placebo group of CA184-029 trial • Nivolumab: KM data from CheckMate 12 weeks to 10 years: • Both arms: Parametric survival models from the PLD meta-regression of CheckMate 238 and CA184-029 Year 10 onwards: • Both arms: HR applied to AJCC version 8 OS registry data (HR was based on interferon trial)
OS	Up to 10 years: • Routine surveillance: parametric survival models for CA184-029 trial data • Nivolumab: estimated surrogacy analysis (underpinned by a HR that was based on unpublished study) Year 10 onwards: • Both arms: AJCC version 8 OS registry data (background mortality using general population data used if extrapolations predict a lower mortality)

Comparing the company's original models

Partitioned survival model (company base case): ICER (excluding commercial arrangements for subsequent treatments) £8,882

- Overall survival (OS) and recurrence-free survival (RFS) data directly informed the proportion of patients in each of three health states
- RFS was informed by an indirect treatment comparison (ITC) and patients in the death state was informed by a surrogate relationship between RFS and OS

Markov 2 model (favoured by ERG): ICER (excluding commercial arrangements for subsequent treatments) £18,685

Same approach for RFS as partitioned survival model, different approach for estimating OS:

- local/regional recurrence: survival curves were fitted to data from the CA184-029 trial
- distant recurrence: survival curves based on range of data sources, including data from drug trials for advanced and/or metastatic melanoma and registry data
- curves were then weighted to produce estimates expected to be reflective of the relevant population

[redacted]

13

ERG original base case (excluding excluding commercial arrangements for subsequent treatments)

- ERG's original base case based on the company's alternative Markov II model
- 3 changes:
  - RFS based on the ITC analysis that used censoring for patients who received treatment ipilimumab beyond one year in CA184-029 trial
  - nivolumab applied as subsequent therapy for patients with a distant recurrence after routine surveillance
  - ipilimumab applied as subsequent therapy for patients with a distant recurrence after adjuvant nivolumab
- ICER incorporating all above changes, nivolumab CAA in adjuvant and metastatic setting and ipilimumab PAS in metastatic setting: **£32,758 (vs. company estimate of £18,685)**
- ICER incorporating subsequent treatment commercial arrangements was higher

ERG concluded

- ERG base case is still a very uncertain analysis and only partially mitigates the uncertainty in the company's analysis
- company's analysis no less certain than other scenarios

[redacted]

14

Committee's considerations re: original submission – clinical issues

- CheckMate 238: Nivolumab more effective treatment than ipilimumab for RFS but OS data are extremely immature
- RFS ITC results may not be reliable/generalisable – likely that nivolumab is effective but magnitude of benefit is uncertain
  - RFS ITC with patients who had ipilimumab after a year censored 'worst case' scenario but this conservative approach is preferred (i.e. committee agreed with ERG)
  - Methods to adjust for differences in trial inclusion criteria may not have been adequate (stage IIIa excluded from CheckMate 238; stage IV from CA184-029)
  - Results of the ITC only informed part of the company's analysis for RFS – risks before 12 weeks/after 10 years predicted using other methods and data sources- overall approach was extremely complex; use of multiple data sources, some of which were potentially inappropriate, added to uncertainty in ITC
- Low risk of serious adverse events but some people could get long-term irreversible adverse effects - careful assessment of likely benefits of preventative treatment is important

[redacted]

15

Committee's considerations re: original cost effectiveness models

- Overall structure, cycle length, time horizon and population were not contentious
- Company's base case was underpinned by OS estimates from a flawed surrogacy analysis so only Markov II was considered further
- Multiple disparate data sources to inform post-relapse survival in Markov II models – requires more scrutiny
- Company's Markov II ICER was much higher than their base case ICER and ERG's Markov II ICER higher still - difference between the company's and ERG's Markov II estimates driven by the different assumptions regarding the proportions of patients receiving different subsequent treatments (RFS adjustments had less impact)
- Estimates used by the company for further immunotherapy after adjuvant nivolumab were lower than would be expected and this made the company's estimate of cost effectiveness unreliable
- RFS estimates used in all models were also uncertain (see clinical issues section)
- Given these uncertainties, all ICERs were considered uncertain – therefore not possible to assess whether nivolumab has plausible potential to be cost effective i.e. no to CDF

[redacted]

16

ACD consultation responses

- Consultee comments from:
  - Company:
  - Melanoma Focus
  - British Association of Skin Cancer Specialist Nurses (BASCSN)
  - Melanoma UK
  - Melanoma Fund (previously called Myfanwy Townsend Melanoma Research Fund)
- Web comments from:
  - 2 Consultant physicians
  - 1 Patient
  - 1 Carer

[redacted]

17

Consultation comments - snapshot

Disappointment with decision/current practice is not popular with patients

"huge sense of disappointment that this treatment has met with rejection from NICE [...] Watch and wait does not sit well with the patient community" (Melanoma UK)

Belief that RFS gains will translate to OS gains

"Adjuvant Nivolumab appears to be effective in reducing the rates of recurrence [...] It is recognised that the data from the clinical trial are immature [...] however, in multiple studies, in multiple different cancer types an improved RFS can translate into better overall survival. " (Consultant Clinical Oncologist)

AEs need consideration at individual level but should not prevent access

"rarer permanent toxicities are something that concerns me, but the auto-immune management strategies are so much better now, and the management of the destruction of thyroid/pituitary function is something we learn to manage, and with better multi-disciplinary teams at specialist centres these are picked up earlier - Please dont let this be a criteria for refusing adjuvant treatment" (Carer)

Nivolumab is a good candidate for CDF

"would support access to nivolumab through the CDF now, to enable patients to receive it before they progress" (BASCSN)

[redacted]

18

Melanoma Focus comments - summary

- Trials provide sufficient evidence of efficacy; nivolumab works similarly well to pembrolizumab *"drugs are used interchangeably in practice"*
- Plausible potential for cost effectiveness can be assessed *"durable effects of immunotherapy and the large benefit that can accrue in the adjuvant setting nivolumab has the potential to be cost effective"*
- OS benefit is *"not proven"* but *"unaware of any adjuvant therapy with an RFS effect of the magnitude reported for checkpoint inhibition that has failed to yield an OS benefit"* and committee need to consider that *"Time without cancer is very important to patients, even when relapse ultimately transpires"*
- In CA184-029 median number of ipilimumab cycles received was 4; (only 13% the full course)
- Similarity of RFS curves for patients treated with ipilimumab in CheckMate 238 and CA184-029 *"provides the most reliable data from which we can infer can that nivolumab produces a significant improvement in relapse-free survival as compared to observation"*
- *"NHS England does not approve combination immunotherapy for patients who had previous adjuvant therapy […] at least 50% of eligible treatment naïve metastatic patients will be treated with combination ipilimumab + nivolumab […] suggests that second-line therapy will be relatively more expensive after observation than for those patients who receive adjuvant therapy"*
- *"Subgroup analysis from CA184-069 showed no clear impact of stage/number of nodes involved/microscopic versus macroscopic disease etc. on overall survival benefit with ipilimumab"* – supports use of ipilimumab as a comparator
- Nivolumab should be funded through CDF and OS data reviewed at end of 2019

Company response to ACD – provided 2 updated models to replace original CE models

Revised base case 1: updates the original partitioned state survival model	Revised base case 2 updates the original Markov II model
Attempts to address committee concerns re: • original surrogacy analysis by completely revising approach to estimating OS **(Revision 1)** • uncertainties in the RFS projections by using more conservative ITC results with patients who received ipilimumab >1 year censored **(Revision 2)** • administration costs by adopting costs suggested by NHSE **(Revision 3)** But, issues re: subsequent treatments are not addressed	Attempts to address committee concerns re: • uncertainties in the RFS projections by using more conservative ITC results with patients who received ipilimumab >1 year censored **(Revision 1)** • administration costs by adopting costs suggested by NHSE **(Revision 2)** • original assumptions re: *proportions* of patients receiving different subsequent treatments by updating proportions in nivolumab arm **(Revision 3)** Also removed treatments for local/regional recurrence **(Revision 4)** But, issues re: *effectiveness* of subsequent treatments not addressed

[redacted]

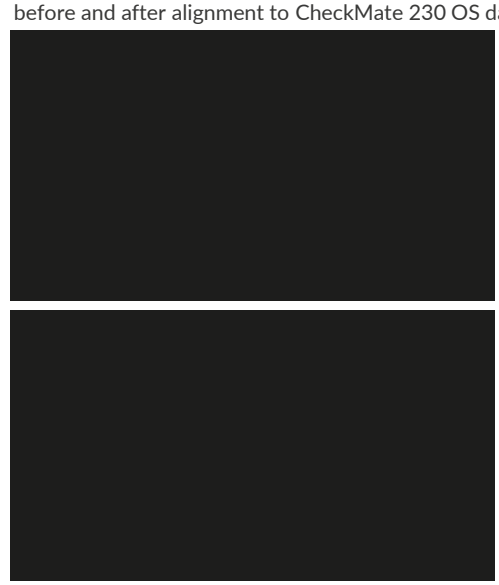
20

Revised base case 1 – updated partitioned survival model (1)

Revision 1: OS

- Originally OS estimates based on data from surrogacy analysis
- In revised model, company used ERG's original 'Scenario 1' analysis:
  - Parametric survival curve (generalised gamma distribution) fitted to OS data from CA184-029 and adjusted for trial differences/to align to population of interest as per RFS curves
  - 0.5 then added to the *mu* parameter of underlying survival function to better align curve with nivolumab arm of currently available KM data from CheckMate 238
  - Assumes nivolumab and ipilimumab equally effective for OS

Revised OS extrapolation: Adjusted generalised gamma curves before and after alignment to CheckMate 230 OS data



[redacted]

21

Revised base case 1 – updated partitioned survival model (2)

Revision 2: RFS estimates

- Adopted ERG's ITC with patients who received ipilimumab for >1 year censored and also note:
  - HRs from the Bucher analyses (not used in the economic models) are in line with the IPD meta-regression results (used in models) and both were in line with HR for pembrolizumab vs. placebo from Keynote 054 trial

Revision 3: updated administration costs

- Company noted NHSE concerns re: missing administration costs:
  - Clarified administration costs were included in the model for all treatments including subsequent therapies BUT
  - Adopted NHSE alternative approach to calculate these costs
    - NHS reference costs code SB12Z (day case and regular day/night £259.76) used in original submission for adjuvant nivolumab - SB13Z NHS reference cost suggested by NHS England is £299.68 (£5,883 per patient) has now been applied

[redacted]

22

Revised base case 1 – updated partitioned survival model results (including nivo and ipi discounts only)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Original base case							
Nivolumab	XXXXXX	XXXX	XXXX	XXXXXX	XXX	XXX	£8,882
RS	XXXXXX	13.96	XXX				
Revision 1: CA184-029 OS curves adjusted using CheckMate 238 OS data (as per original ERG 'Scenario 1' analysis							
Nivolumab	XXXXXX	XXXX	XXXX	XXXXXX	XXX	XXX	£18,030
RS	XXXXXX	17.83	XXX				
Revision 2. RFS ITC using censoring at 1 year of ipilimumab treatment in CA184-029							
Nivolumab	XXXXXX	XXXX	XXXX	XXXXXX	XXX	XXX	£9,066
RS	XXXXXX	14.68	XXX				
Revision 3. Nivolumab admin costs use SB13Z from NHS reference costs*							
Nivolumab	XXXXXX	XXXX	XXXX	XXXXXX	XXX	XXX	£9,059
RS	XXXXXX	13.96	XXX				
1 + 2 + 3 (all revisions implemented)							
Nivolumab	XXXXXX	XXXX	XXXX	XXXXXX	XXX	XXX	£18,423
RS	XXXXXX	17.83	XXX				
PSA ICER: £18,417; probability of cost-effectiveness: at £20,000/QALY = 60.0%; at £30,000/QALY = 92.4%							

Revised base case 1 – updated partitioned survival model – ERG comments

Revision 1: OS estimates

- Concerns still remain
  - Relative treatment effect is still derived from CA184-029 trial
    - means the difference in subsequent treatments received in the CA184-029 trial partly drives the difference in OS
    - the benefit is likely to be overestimated in favour of nivolumab because of the lack of effective immunotherapies used in the placebo group of the CA184-029 trial

Revision 2: RFS estimates

- Company's approach for modelling RFS is reasonable
  - 1-year censored ipilimumab data from CA184-029 most appropriate in the ITC
  - Keynote 054 (pembrolizumab trial) results do not validate nivolumab versus placebo ITC – only show they are plausible

Revision 3: updated administration costs

- Change is appropriate

[redacted]

24

ERG scenarios for company's updated base case 1 – partitioned survival model (including nivo and ipi discounts only)

No reliable way to account for the potential OS benefit of current post-recurrence therapies – scenarios to show impact of adjusting routine surveillance OS curve: (1) assumed no difference in OS (routine surveillance OS curve equal to the nivolumab curve) i.e. represents absolute worst case scenario; (2) threshold analysis to determine level of OS gain required to ensure ICER <30,000/QALY

	Results per patient	Nivolumab (1)	RS (2)	Incremental value (2-1)
0	Company's base case 1 (Partitioned survival)			
	Total costs (£)	XXXXXX	XXXXXX	£29,204
	QALYs	XXXX	XXX	XXX
	LYs	XXXX	17.83	XXX
	ICER			£18,423
1	Setting routine surveillance OS equal to nivolumab			
	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXX	XXXX	XXX
	LYs	XXXX	20.77	XXX
	ICER (compared with base case)			£80,401
2	Threshold for OS gain for nivolumab to be cost-effective (adjusting only placebo OS scale)			
	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXX	XXX	XXX
	LYs	XXXX	19.26	XXX
	ICER (compared with base case)			£29,832

25

Revised base case 2 - updated Markov II model (1)

Revision 1 (RFS estimates) and Revision 2 (updated administration costs)

- Same as updated base case 1 (see earlier slide)

Revision 3: proportions of patients receiving different subsequent treatments

- In original model both arms reflected proportions receive by patients in CheckMate 238
- In updated model, subsequent treatments received by patients *in **nivolumab arm*** dependant on timing of relapse: early relapses (before 2 years) receive ipilimumab; late relapses receive same treatments patients in the routine surveillance arm of model i.e. as per CheckMate 238 ipillimumab arm
- 2nd line treatments also included (not split by timing of recurrence; assumed to be same as CheckMate 238 ipillimumb arm)
- **No change to ipilimumab arm** – company argue RWD support original assumptions (see next slide)
- No change to how effectiveness of subsequent treatments was estimated – based on wide range of data sources from prior NICE appraisals and CheckMate 067 patient level analyses

Revision 4: treatment costs for local/regional recurrence

- Included in original model but now removed because no adjuvant therapies are provided for local/regional recurrence in UK current practice – more conservative approach

[redacted]

26

Revised base case 2 - updated Markov II model (2)

Subsequent treatments RWD vs. CheckMate 238

Treatment	IPSOS			W'ton	CheckMate 238		
	1L	2L	All	All	Ipi 1L	Ipi 2L	Ipi all
Total immunotherapies	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Anti-PD1s	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Pembrolizumab	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Nivolumab	XXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Nivolumab + ipilimumab	XXXX	XXX	XXXX	XXX	XXX	XXX	XXX
Other immunotherapies	XXXX	XXXX	XXXX	XXX	XXX	XXX	XXX
Ipilimumab	XXXX	XXXX	XXXX	XXX	XXX	XXX	XXX
BRAF/MEK inhibitors	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Vemurafenib	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Dabrafenib + trametinib	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Dabrafenib	XXX	XXX	XXX	XXX	XXX	XXX	XXX

[redacted]

27

Revised base case 2 – updated Markov II model results (including nivo and ipi discounts only)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Original Markov 2							
Nivolumab	XXXXXX	XXXX	XXX	XXXXXX	XXX	XXX	£18,685
RS	XXXXXX	14.08	XXX				
Revision 1. RFS using censoring at 1 year of ipi treatment in CA184-029							
Nivolumab	XXXXXX	XXXX	XXX	XXXXXX	XXX	XXX	£18,960
RS	XXXXXX	14.19	XXX				
Revision 2: Nivolumab admin costs use SB13Z from NHS reference costs							
Nivolumab	XXXXXX	XXXX	XXX	XXXXXX	XXX	XXX	£19,076
RS	XXXXXX	14.08	XXX				
Revision 3: Subsequent treatment for nivolumab data split by time of recurrence (2 years) and using ipi arm from CheckMate 238							
Nivolumab	XXXXXX	XXXX	XXX	XXXXXX	XXX	XXX	£14,661
RS	XXXXXX	14.08	XXX				
Revision 4: No subsequent therapy costs for local/regional recurrence							
Nivolumab	XXXXXX	XXXX	XXX	XXXXXX	XXX	XXX	£22,084
RS	XXXXXX	14.08	XXX				
1 + 2 + 3 + 4 (all revisions implemented)							
Nivolumab	XXXXXX	XXXX	XXX	XXXXXX	XXX	XXX	£18,018
RS	XXXXXX	14.19	XXX				
PSA ICER £18,027; probability of cost-effectiveness: at £20,000/QALY = 52.1%; at £30,000/QALY = 93.4%							

Revised base case 2 – updated Markov II model scenario analysis (including nivo and ipi discounts only)

- Company presented five scenarios to explore sensitivity of ICER to different assumptions around subsequent treatments
- Concluded "these analyses demonstrate that nivolumab is cost-effective when clinically plausible scenarios are explored":
  - Scenario 1: used IPSOS RWD instead of CheckMate 238 to determine proportions of subsequent treatments received by patients in model
  - Scenario 2: used Wilmington RWD instead of CheckMate 238 to determine proportions of subsequent treatments received by patients in model
  - Scenario 3: Same proportions of subsequent treatments received in each arm of model (based on CheckMate 238 (ERG which arm? Assume routine surveillance?) and post-recurrence survival also determined by CheckMate 238
  - Scenario 4: Re-challenge occurs at 6 months instead of 2 years – otherwise the same as revised Markov II base case
  - Scenario 5: Re-challenge occurs at 6 months instead of 2 years – otherwise the same as revised Markov II base case

The resulting ICERs ranged from £16,913 to £18,151

[redacted]

29

Revised base case 2 – updated Markov II model – ERG comments

Revision 1 (RFS estimates) and Revision 2 (updated administration costs)

- Both ok (see earlier slide)

Revision 3: proportions of patients receiving different subsequent treatments

- **Still concerned with the company's approach to modelling**
  - Compared to CheckMate 238 RWD suggest:
    - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
    - XXXXXXXXXXXXXXXXXXXXXXX (Wilmington data)
    - XXXXXXXXXXXXXXXXXXXXXXXX (Wilmington and IPSOS data)
  - Wilmington data is preferred; limitation, not split by line of therapy, company assumed same proportions across lines.
  - **No evidence to support assumption that PD1 re-challenge at 2 years is effective**
  - **Data to inform treatment-specific post-recurrence survival still problematic** - populations in trials used do not necessarily match the population of interest for this appraisal and also may not be consistent across the trials - results may not be comparable/applicable

Revision 4: treatment costs for local/regional recurrence

- OK. This is probably a conservative assumption

[redacted]

30

ERG exploratory analysis – updated ERG base case (including nivo and ipi discounts only)

Markov II model structure with following adjustments: (1) ERG used Wilmington RWD to determine proportions of subsequent treatments received (2) Patients who receive nivolumab in the adjuvant setting and then experience recurrence will receive ipilimumab in metastatic setting.

ERG emphasise model is still highly uncertain due to underlying OS data

Results per patient	Nivolumab	RS	Incremental value
Company's base case 2 (Markov Option 2)			
Total costs (£)	XXXXXX	XXXXXX	XXXXXX
QALYs	XXX	XXX	XXX
LYs	XXXX	14.19	XXX
ICER			£18,018
Using Wilmington Health Care subsequent treatment data			
Total costs (£)	XXXXXX	XXXXXX	XXXXXX
QALYs	XXX	XXX	XXX
LYs	XXXXX	14.12	XXX
ICER (compared with company ICER)			£18,151
ICER with all changes incorporated			£18,151
Ipilimumab as subsequent therapy for patients with a distant recurrence after adjuvant nivo			
Total costs (£)	XXXXXX	XXXXXX	XXXXXX
QALYs	XXX	XXX	XXX
LYs	XXXXX	14.12	XXX
ICER (compared with company ICER)			£18,863
ICER with all changes incorporated			£19,129

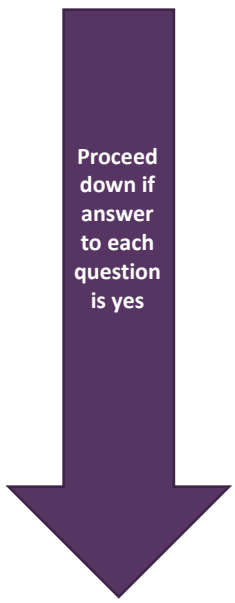
Key issues for consideration

- Are the committee's concerns about the uncertainty in the clinical evidence reasonable?
- The trial excluded people with stage IIIA disease, is this relevant to the decision?
- The partitioned survival and Markov II models have been updated. What are the certainties and uncertainties related to these?
- The partitioned survival model now uses the trial OS evidence instead of a surrogacy analysis. Can the results now be considered to be robust?
- Is the committee satisfied that the impact of subsequent treatments has been captured?
- Does the committee consider that there is sufficient clinical and cost effectiveness evidence to support a change in the routine pathway of care for patients in the NHS?
- Should adjuvant nivolumab be recommended for use in the CDF?

[redacted]

32

CDF recommendation criteria



Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data? and 5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.