For public – no AIC or CIC

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

Lead team presentation: Cost Effectiveness Part 1

1st Appraisal Committee meeting
Committee A
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August 2018

Preview: Cost effectiveness issues 1

- Staying in the recurrence free state for longer gives QALY gains from not dying of disseminated disease. The long term projections of RFS are therefore important:
- The company and the ERG models are reliant on OS predictions that are either known to be flawed or cannot be validated. Are these models robust enough for decision making?
- Given the immaturity of the OS data several methods were tried to predict OS; either relating OS to RFS via a surrogacy approach in a partitioned state mode, or using a post progression state in a Markov model. Which model is most appropriate?

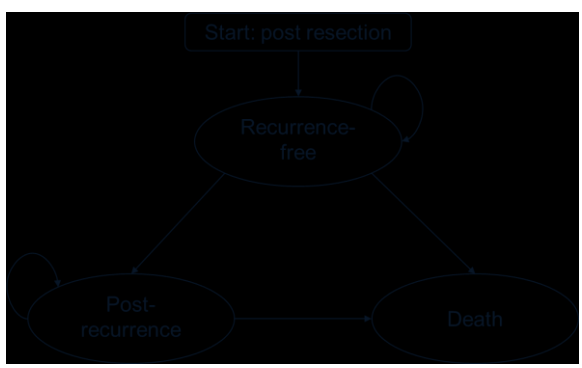
Preview: Cost effectiveness issues 2

- In a Markov model the results are heavily influenced by treatments people received on progression, and whether these were likely to be different post adjuvant compared with post surveillance. What is the committee's view on this?
  - Avoidance of high cost treatments post progression offsets the adjuvant costs
  - highly effective treatments post progression after routine surveillance will reduce QALY gains from adjuvant therapy
    - ERG base case ICER is much higher than the company's because of different assumptions regarding subsequent treatments which increase the overall cost and reduce QALYs gained with adjuvant nivolumab treatment. Which assumptions (and resulting ICERs) most closely reflect of clinical practice?
    - Are the cost effectiveness analyses generalizable to the entire population of interest (CheckMate 238 excluded stage IIIA disease and CA184-029 excluded stage IV disease)?

[redacted]

3

Company's economic model structure



- Company chose partition survival model (PS) for base case
- 2 Markov models also provided
- All 3 models based on same 3 health state structure, 60 year time horizon & 28 day cycle length
- Patient characteristics in the model reflect CheckMate 238 and CA184-029 trials i.e. stage IIIA–IV NED patients with confirmed lymph node involvement

[redacted]

4

Company's key assumptions in their base case model

Assumption	Company's rationale
Nivolumab is equally effective across all disease stages	CheckMate 238 trial: No evidence of difference in effect across stages found; Bucher ITC: similar outcomes ITT and subgroup analysis
OS for Stage IV NED patients can be informed using data for Stage IIIC patients	No data are available on OS for Stage IV NED patients. CheckMate 238 trial: Stage IV NED RFS was found to be similar to Stage IIIC RFS; Clinical experts agreed that if resection is possible with Stage IV NED patients, then outcomes would be very similar to Stage IIIC patients
Stage IIIA patients' natural history RFS prognosis is not expected to have changed between the CA184-029 and CheckMate 238 trials	No rationale provided
The most relevant patient population to model is the CheckMate 238 population once stage and other covariates included are adjusted for	CheckMate 238 trial is our main trial of interest and is more recent

[redacted]

5

Company's key assumptions in their base case (cont.)

Assumption	Company's rationale
Difference in duration of ipilimumab treatment across trials does not impact efficacy	Median number of doses in both trials was 4; outcomes were similar in stage IIIB and stage IIIC patients across the trials and only XXXXXXXXXXXof ipilimumab treatment in the CA184-029 trial
Routine surveillance 'other Grade 3+' AEs same as nivolumab	Comparison of AEs in both trials suggested placebo has more AEs than nivolumab - clinically implausible
Dosing and duration of treatments for local/regional recurrence = adjuvant dose and duration (unless data was unavailable in which case dose and duration assumed to be same as for distant recurrence)	No dosing information on subsequent treatments were available in the CheckMate 238 or CA184-029 trials; literature data were used to inform the dosing. Some subsequent treatments in the local/regional recurrence group are not indicated in the adjuvant setting and trial publications were not available; therefore, metastatic data were used.
Equal health-state utilities were assumed for all treatments	Utility regression equations did not show a large difference in utility, and data were not available to compare all treatments based upon treatment effects (mapped and literature data are used in sensitivity analysis)

[redacted]

6

Overview of data sources for clinical parameters used in company base case

Input	Source
RFS	0-12 weeks • Routine surveillance: HR (derived by fitting a Cox proportional hazards (PHs) 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)

Overview of data sources for other clinical parameters used in company base case

Input	Source
Time-on-treatment	Time on treatment for nivolumab was taken from the CheckMate 238 PLD, which recorded the proportion of patients receiving each dose up to the maximum duration of 1 year
Recurrences rates	Subsequent treatment costs and monitoring costs split by recurrence type and weighted by the proportion of patients who had a local/regional recurrence or a distant recurrence from CheckMate 238 Proportions experiencing each recurrence type similar across CheckMate 238 trial arms - pooled data were used in the model and applied to both nivolumab and routine surveillance
AEs	Immune-related AEs (any grade) and diarrhoea (Grade ≥2) • Nivolumab: CheckMate 238 PLD • Routine surveillance: rates calculated as relative difference in AEs between ipilimumab and placebo in CA184-029 and between ipilimumab and nivolumab in CheckMate 238 Other Grade ≥3 AEs • Both arms: CheckMate 238

[redacted]

8

Summary of utility values used in company base case

State	Utility value: mean (SE)	95% CI	Justification
Utility values for health states defined by progression status			
Recurrence-free	XXXXX	Sampling using variance-covariance matrices assuming multivariate-normal distribution	Assumed equal across treatments. Based on statistical models fitted using EQ-5D data collected in CheckMate 238 trial and covariate for routine surveillance based on mapping from QLQ-C30 to EQ-5D using data collected in both CheckMate 238 and CA184-029 trials
Post-recurrence	XXXXX		
Utility decrements for adverse events			
Immune-related disorders	-0.11	-0.134, -0.09	Based on the Middleton et al. (2016) poster, which looks at disutilities due to AE in the adjuvant melanoma setting
Diarrhoea	-0.09	-0.108, -0.073	
Other AEs	-0.137	-0.165, -0.111	

[redacted]

9

Costs and resource used in company base case (cont.)

Outpatient, laboratory and imaging costs from PSSRU 2017 & NHS reference costs 16/17

Monitoring costs for patients split by timeframe and health state applied within the model

Health state	Year 1 cost (£)	Year 2 cost (£)	Year 3–5 cost (£)	Year 5+ cost (£)
Recurrence-free	XXXXX	XXXXX	XXXXX	XXXXX
Local/regional recurrence (unresectable)	XXXXX	XXXXX	XXXXX	XXXXX
Local/regional recurrence (resectable)	XXXXX	XXXXX	XXXXX	XXXXX
Distant recurrence	XXXXX	XXXXX	XXXXX	XXXXX
Weighted average for post-recurrence monitoring costs*	XXXXX	XXXXX	XXXXX	XXXXX

	Nivolumab (£)	Routine surveillance (£)
Hospitalisation costs – subtotal	XXXXX	XXXXX
Outpatient costs – subtotal	XXXXX	XXXXX
Total cost (per trial patient)	XXXXX	XXXXX

[redacted]

10

Costs and resource used in company base case (cont.)

Note: Key differences are use of high cost follow on treatments (immunotherapy or BRAF agents)

Subsequent treatment frequencies and costs were applied according to the recurrence type experienced and the initial adjuvant treatment received based on patients in CheckMate 238

	Local/regional recurrence		Distant recurrence	
	Nivolumab	RS*	Nivolumab	RS
Ipilimumab	XXXXX	XXXXX	XXXXX	XXXXX
Vemurafenib	XXXXX	XXXXX	XXXXX	XXXXX
Dabrafenib + trametinib	XXXXX	XXXXX	XXXXX	XXXXX
Dabrafenib	XXXXX	XXXXX	XXXXX	XXXXX
Pembrolizumab	XXXXX	XXXXX	XXXXX	XXXXX
Nivolumab	XXXXX	XXXXX	XXXXX	XXXXX
Nivolumab + ipilimumab	XXXXX	XXXXX	XXXXX	XXXXX
Other	XXXXX	XXXXX	XXXXX	XXXXX

*Subsequent treatment data from ipi arm following recurrence

Total subsequent treatment cost applied per recurrence in the model per adjuvant treatment

Recurrence type	Nivolumab	Routine surveillance
Local/regional	£XXXXX	£XXXXX
Distant	£XXXXX	£XXXXX

11

Company base case results

Base case partitioned survival model results (provided at clarification stage, incorporating nivolumab commercial access agreement (CAA))

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Nivolumab	£XXXXX	XXXX	XXXX	£XXXXX	XXXX	XXXX	£8,882
Routine surveillance	£XXXXX	XXXX	XXXX				
ERG estimate incorporating subsequent treatment PASs will be presented in part 2							

Alternative Markov model results (provided at clarification stage, incorporating nivolumab CAA)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Markov option 1 – base case							
Nivolumab	£XXXXX	XXXX	XXXX	£XXXXX	XXXX	XXXX	£8,567
Routine surveillance	£XXXXX	XXXX	XXXX				
Markov option 2 – base case							
Nivolumab	£XXXXX	XXXX	XXXX	£XXXXX	XXXX	XXXX	£18,685
Routine surveillance	£XXXXX	XXXX	XXXX				
ERG estimates incorporating subsequent treatment PASs will be presented in part 2							

[redacted]

12

Company analyses

How did the company's base case PS and Markov models differ?

PS model: uses overall survival (OS) and recurrence-free survival (RFS) data to directly inform the proportion of patients remaining in each of three health states at any given time

- OS data informs the proportion who are in the death state, RFS data informs the proportion who are in the RF state, difference between the two is the proportion in the PR state
- For this appraisal, RFS was informed by an indirect treatment comparison (ITC) between the CA184-029 trial; proportion of patients in the death state at any given cycle was informed by a surrogate relationship between RFS and OS

[redacted]

13

Company analyses

How did the company's base case PS and Markov models differ? (cont.)

Markov 1 (model not used in company base case or favoured by ERG): uses the same RFS modelling from the ITC as per the PS model

- Post-recurrence survival (PRS) uses the same OS data as in the base case PS model
- PRS transition probabilities were estimated from the OS data by applying treatment specific hazard ratios (HRs) derived from the CA184-029 trial data. The ipilimumab group was used to predict a PRS HR for nivolumab and the placebo group was used for routine surveillance

Markov 2 model (favoured by ERG): RFS same approach as for base case PS and Markov 1 models but 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]

14

Company analyses – ERG critique

General comments that apply to both company's PS model (base case) and alternative Markov models

- Largely in line with NICE final scope
- Model population appropriate and reflective of the expected population in the UK
- Use of the Western European population appropriate for the estimation of treatment costs
- Contains relevant health states i.e. recurrence-free, disease recurrence and death
- Time horizon is long at 60 years but appropriate
- Cycle length of 28 days appropriate

[redacted]

15

Company analyses – ERG critique

Clinical efficacy modelling

Partitioned survival model (base case)

- RFS
  - Issues highlighted in clinical evidence section above still remain relevant i.e.
    - Trial differences relating to disease stage not adequately adjusted for
    - reliability of the ITC results compromised by differences between trials in terms of duration of ipilimumab treatment
  - In addition
    - long term estimates of RFS potentially unreliable - calculated using a HR comparing RFS with OS data from Agarwala et al. 2017 (interferon study)
- OS
  - Relies on a surrogate relationship between RFS and OS; approach informed by unpublished study underpinned by data from predominantly interferon-based studies
  - Derived HR from the surrogacy relationship was applied to a baseline generalised gamma survival model; a model that does not support the use of proportional hazards
  - Subsequent treatments received by patients in the two trials are not reflective of current UK clinical practice, according to clinical expert advice sought by the ERG - OS estimates in the placebo group of the CA184-029 trial are likely to be underestimated and, therefore, the relative benefit of nivolumab over routine surveillance is likely to be overestimated
  - OS appears underestimated vs data from CA184-029 (already potentially underestimated because of the less effective subsequent treatments at time of trial)

[redacted]

16

Company analyses – ERG critique

Clinical efficacy modelling (cont.)

Markov model 1 (not used in company base case)
- Avoids need to use surrogacy analysis to predict OS
- Does not resolve the issue of subsequent therapies influencing OS outcomes

Markov model 2 (not used in company base case)
- Allows for the issues of subsequent treatments to be explored
- But uses a range of potentially disparate sources of evidence to inform PRS, so it is unlikely that the estimates of PRS are robust/applicable to the population on which the ITC was formed
- Even if the analysis was considered reliable, the range of ICERs resulting from plausible scenarios demonstrates the potentially serious uncertainty that currently exists within the results

[redacted]

17

Company analyses – ERG critique

AEs, HR-QoL (comments relate to both PSM and Markov models)

AEs
- For the proportions of immune-related AEs and diarrhoea in the routine surveillance group, the risk of AEs from the placebo group of CA184-029 was adjusted for the difference in risks across the ipilimumab groups of the two trials
  - ERG considers approach methodologically incorrect but impact of on ICER likely to be minimal

Utility estimation
- Company's approach to utility estimation generally sound
- ERG considers inclusion of AE decrements using an external source to be unnecessary but unlikely to affect

[redacted]

18

Company analyses – ERG critique

Resources and Costs

- Model inputs for resource use and costs generally suitable with only a few exceptions:
  - Most important is application of subsequent therapy costs - needs to be considered in parallel with the appropriateness of the treatment effectiveness measures and the impact of subsequent therapies on post-progression survival
  - proportion of patients receiving each subsequent therapy based on CheckMate 238 trial – ERG clinical expert suggests that these data are not reflective of UK clinical practice and there would be a greater use of more effective subsequent systemic therapies such as nivolumab following routine surveillance
  - company's scenario using the placebo group of the CA184-029 is even less reflective given the age of the trial, as it includes the use of therapies such as interferon and interleukin, which would not be used in UK clinical practice today
  - If more patients in nivolumab group received cost effective therapies, results may be biased against routine surveillance

- Other (more minor) issues:
  - ERG clinical expert opinion considers the assumptions regarding imaging resource use to be potentially excessive & end of life costs include social care costs but likely to have a negligible impact on the ICER

[redacted]

19

ERG base case – preferred model and assumptions

ERG preferred Markov model 2 because this allowed for exploration of alternative subsequent treatments but with the following adjustments:

- RFS based on the ITC analysis that used censoring for patients who received treatment beyond one year in the ipilimumab group of the CA184-029 trial
- nivolumab applied as subsequent therapy for all patients with a distant recurrence after routine surveillance
- ipilimumab applied as subsequent therapy for all patients with a distant recurrence after adjuvant nivolumab

[redacted]

20

ERG base case results (with Nivolumab CAA)

	Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's alternative model (Markov Option 2)	Total costs (£)	£XXXXX	£XXXXX	£XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	XXXX	XXXX
	ICER			£18,685
RFS using censoring at one-year of treatment continuation	Total costs (£)	£XXXXX	£XXXXX	£XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	14.19	XXXX
	ICER (vs. company)			£18,960
	ICER (all changes)			**£18,960**
Nivolumab as subsequent therapy for distant recurrence after routine surveillance	Total costs (£)	£XXXXX	£XXXXX	£XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	17.05	XXXX
	ICER (vs. company)			**£96,443**
	ICER (all changes)			**£107,787**
Ipilimumab as subsequent therapy for distant recurrence after adjuvant nivolumab	Total costs (£)	£XXXXX	£XXXXX	£XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	17.05	XXXX
	ICER (vs. company)			**£10,202**
	ICER (all changes)			**£32,758**
Estimates incorporating subsequent treatment PASs will be presented in part 2				

ERG scenario analyses and overall conclusions

ERG also performed a variety of scenario analyses using the company's PS model, the company's Markov II model and their own preferred base case

- ICERs range for scenarios tested by ERG using company preferred base case PS model (with nivolumab CAA) was £8,882 to £18,047 per QALY gained
- Most relevant scenario analysis for ERG (Markov 2 model) base case (in which 50% of patients with distant recurrence in each group receive dabrafenib + trametinib) produced an ICER of £15,245

Estimates for this scenario incorporating subsequent treatment PASs will be presented in part 2

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; given that one of the scenarios for the Markov 2 model resulted in an ICER greater than £300k per QALY, the potential impact of the uncertainty is great

[redacted]

22

Equality & Innovation

No equality issues identified

Company comments on innovation:

Nivolumab is 1st checkpoint inhibitor agent licensed for adjuvant therapy in melanoma - a 'step-change' in the management

Routine surveillance cannot diagnose metastases until they are large enough to be detected, nivolumab works by priming the immune system to respond to micrometastases in the first instance: has and made a significant difference in survival for metastatic patients

Anticipated that health-related benefits such as improved RFS and response benefits will be captured in QALY calculation but significance to patients should be viewed as innovative

- curative potential associated with immunotherapies such as nivolumab, and the possible return to normal living in contrast to progression to advanced disease and the burden associated with this
- melanoma disproportionately affects a younger population, this has a significant impact on the working-age population, mainly a loss of economic productivity; such an effect is not captured in the QALY calculation
- nivolumab meets the need for an effective treatment to be offered to patients, removing the psychological burden and anxiety resulting from waiting for potential recurrence of disseminated disease

[redacted]

23

Preview: Cost effectiveness issues 1

Staying in the recurrence free state for longer gives QALY gains from not dying of disseminated disease. The long term projections of RFS are therefore important:

- The company and the ERG models are reliant on OS predictions that are either known to be flawed or cannot be validated. Are these models robust enough for decision making?
- Given the immaturity of the OS data several methods were tried to predict OS; either relating OS to RFS via a surrogacy approach in a partitioned state mode, or using a post progression state in a Markov model. Which model is most appropriate?

[redacted]

24

Preview: Cost effectiveness issues 2

- In a Markov model the results are heavily influenced by treatments people received on progression, and whether these were likely to be different post adjuvant compared with post surveillance. What is the committee's view on this?
  - Avoidance of high cost treatments post progression offsets the adjuvant costs
  - highly effective treatments post progression after routine surveillance will reduce QALY gains from adjuvant therapy
    - ERG base case ICER is much higher than the company's because of different assumptions regarding subsequent treatments which increase the overall cost and reduce QALYs gained with adjuvant nivolumab treatment. Which assumptions (and resulting ICERs) most closely reflect of clinical practice?
    - Are the cost effectiveness analyses generalizable to the entire population of interest (CheckMate 238 excluded stage IIIA disease and CA184-029 excluded stage IV disease)?

[redacted]

25

Back up slides

[redacted]

26

ERG scenario analyses (for company PS model)

	Results per patient	Nivolumab	Routine surveillance	Incremental value
0	**Company's preferred base case (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	13.96	XXXX
	ICER			£8,882
1	**Alternative OS modelling using CA184-029 with scaling factor (mu increased by 0.5) (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	17.83	XXXX
	ICER (compared with base case)			£18,030
2	**RFS using censoring at one-year of treatment continuation (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	14.68	XXXX
	ICER (compared with base case)			£9,066
3	**Combination of Scenario 1 and Scenario 2 (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	LYs	XXXX	17.83	XXXX
	ICER (compared with base case)			£18,047

[redacted] Estimates incorporating subsequent treatment PASs will be presented in part 2

27

ERG scenario analyses (for ERG base case)

	Results per patient	Nivolumab	Routine surveillance	Incremental value
0	**ERG's preferred base case (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	Lys	XXXX	17.05	XXXX
	ICER			£32,758
1	**50% of patients with distant recurrence in each group receive dabrafenib+trametinib (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	Lys	XXXX	14.21	XXXX
	ICER (compared with base case)			£15,245
2	**All patients with distant recurrence in the nivolumab group receive dabrafenib+trametinib (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	Lys	XXXX	17.05	XXXX
	ICER (compared with base case)			£238,154
3	**Using metastatic fractional polynomial-based NMA to inform PRS (with Nivolumab CAA)**			
	Total costs (£)	XXXXX	XXXXX	XXXXX
	QALYs	XXXX	XXXX	XXXX
	Lys	XXXX	15.16	XXXX
	ICER (compared with base case)			£34,354

[redacted] Estimates incorporating subsequent treatment PASs will be presented in part 2

28