Chair's presentation

Nivolumab for treating unresectable or metastatic urothelial cancer after platinum-containing chemotherapy

2nd Appraisal Committee meeting
Committee D, 23 November 2017

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Company: Bristol Myers Squibb

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Evidence review group: Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Key issues for consideration

- Most appropriate approach to model survival
  - Company use a response-based analyses
  - ERG prefer conventional approach
  - Company have presented a piecewise model scenario
- Relevant comparator – company states paclitaxel most relevant
- 2-year treatment stopping rule
- Assumption of lifetime treatment effect
- Updated analysis is based on data from CheckMate 032; Updated CheckMate 275 data presented but not included in the model
- Most plausible ICER
- Robustness of the ICERs given the available evidence
- End of life criteria most likely met, based on weak evidence
  - Highest median modelled OS of any of the comparators was 10.5m
  - Model estimates nivolumab treatment results in at least 16m extension to life compared with current treatment

Nivolumab (Opdivo)
Bristol-Myers Squibb

Marketing authorisation	Nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy
Administration & dose	Intravenous infusion, 3 mg/kg every 2 weeks
Mechanism of action	Antibody that specifically binds to anti-programmed cell death-1 (PD-1) receptor on the surface of immune cells and restores T-cell activity by blocking the inhibitory pathway with PD-L1
Cost	List price: 100mg vial = £1,097.00 Average cost per course (at list price): £54,675* Presented analyses incorporate a simple discount PAS

Source: Table 2 (page 13) company submission
***Based on the economic model developed for this submission**

ACD preliminary recommendation

Not recommended for unresectable UC or mUC after platinum chemotherapy

- Most plausible ICERs higher than those usually considered a cost-effective use of NHS resources, even for end of life treatments
- No RCTs comparing nivolumab with any of the comparators
- Clinical and cost-effectiveness estimates are based on a simulated treatment comparison which was not adequately validated
- Company's approach to modelling survival using a response-based analysis introduced unnecessary complexity, and it produced implausible survival estimates
- Not suitable for the CDF as there are no ongoing studies
- End of life criteria most likely met
  - Highest median modelled OS of any of the comparators was 10.5m
  - Model estimates nivolumab treatment results in at least 16m extension to life compared with current treatment

Remaining uncertainty

Uncertainties	
No comparative trial data	Nivolumab has only been studied in single-arm trials. A simulated treatment comparison and network meta-analysis were required to compare nivolumab with the relevant comparators
Choice of survival modelling approach	• The company prefer to stratify patients according to treatment response • The ERG opted to use standard parametric survival modelling approach
Choice of landmark point in response	• The company opted for an 8 week landmark point (point at which groups are separated) • The ERG took concern that other landmark points weren't adequately explored

ACD consultation comments

Comments received from:

- BMS

General comments:

- Still prefer response-based approach to modelling survival
  - Standard parametric approach not supported by the evidence available; does not characterise the survival benefit expected for immunotherapies such as nivolumab
- BMS state that paclitaxel is most relevant comparator

New evidence included in the company's ACD response:

- Updated survival data from CheckMate 275 and 032
  - Only updated data from 032 included in the updated analysis
- Inclusion of a 2 year stopping rule
- Corrected analysis for patient weight
- Average dose delay of all doses is applied
- Continues treatment benefit and piecewise analysis scenario analyses

Response-based survival modelling

- Company justification:
  - Nivolumab's durable treatment response is not captured in standard models
  - A response-based approach more accurately characterise hazard and survival
- ACD:
  - Response-based model gives implausibly high survival past 5 years
  - People surviving 5 years effectively considered 'cured', not supported by the evidence
- Company ACD response:
  - The current committee preferred approach is inconsistent with previous appraisals for immuno-oncology therapies
  - Committee's statement that 5-year survival estimates of people on other immunotherapies is 10% is opinion based, there is no 5-year data available
  - Nivolumab 5-year survival estimates are >10% in other cancers

- ERG comment on response-based modelling:
  - Did not justify why the conventional approach is inappropriate
  - Unrealistic to assume a constant weighting of responder groups
  - Choice of landmark not fully explored and has unpredictable effect on results

Modelling long-term survival

- At ACM1 the company presented a response-based based time-to-event model which selected the same distribution (generalised gamma) for responder and non-responder groups
- In response to the ACD the company have separately selected the distributions for responder and non-responder curves

Scenario	PFS	OS	TTD
Company base case	Response = Generalised gamma	Response = Generalised gamma	Response = Lognormal
	No Response = Weibull	No Response = Log-logistic	No Response = Weibull
ERG base case	Generalised gamma	Generalised gamma	Generalised gamma

ERG comment
- Lack of justification for the change in choice of curves
- Change in choice of parametric curves did not cause substantial changes to the ICERs

CheckMate 275: Efficacy results

Latest database lock

Tumour response	Nivolumab (n=270) Second database lock: 2nd Sep 2016	Nivolumab (n=270) Latest database lock: 2nd October 2017
ORR, n (%)	54 (20.0) [95% CI 15.4–25.3]	[redacted]
BOR, n (%)		
CR	8 (3.0)	[redacted]
PR	46 (17.0)	[redacted]
SD	60 (22.2)	[redacted]
PD	[redacted]	[redacted]
Unable to determine	[redacted]	[redacted]
Median TTR, months (IQR)	1.94 (1.84–2.50)	-
Median DOR, months (95% CI)	10.35 (7.52–NR)	[redacted]

Source: Table 1 company ACD response appendix

CheckMate 275: PFS & OS

Latest database lock

Figure redacted AIC PFS

Figure redacted AIC OS

	N at risk	OS rate (95% CI)
Median OS		
Number of events/number patients (%)		
12 months OS		
18 months OS		
24 months OS		

CheckMate 032: Efficacy results

Latest database lock

Tumour response	Nivolumab (n=78) Initial database lock: 24th March 2016	Nivolumab (n=78) Latest database lock: June 21st 2017
ORR, n (%)	19 (24.4) [95% CI 15.3–35.4]	[redacted]
BOR, n (%)		
CR	5 (6.4)	[redacted]
PR	14 (17.9)	[redacted]
SD	22 (28.2)	[redacted]
PD	30 (38.5)	[redacted]
Unable to determine	7 (9.0)	[redacted]
Median TTR, months (IQR)	1.48 (1.25–4.14)	[redacted]
Median DOR, months (95% CI)	NR (9.92–NR)	[redacted]

Source: Table 3 company ACD response appendix

CheckMate 032: PFS & OS

New database lock

Figure redacted AIC PFS

Figure redacted AIC OS

	N at risk	OS rate (95% CI)
Median OS		
Number of events/number patients (%)		
12 months OS		
18 months OS		
24 months OS		

Updated clinical evidence
ERG comment

- The latest database cut confirms the company findings based on the original company submission
- Updated data is only for nivolumab – it remains difficult to estimate the effectiveness of nivolumab compared with the comparators in the scope
- Updated data from CheckMate 275 have not been incorporated in the revised base-case analysis - this is a limitation
  - Potential cherry-picking given that the median survival in CheckMate 032 is higher than in CheckMate 275
- The company did not provide detail on the pooling method of both studies when including the updated clinical evidence, therefore it's unclear whether data from both studies were appropriately incorporated in the model
  - The updated results should be treated with caution

2 year stopping rule
Company's new evidence

- A 2-year treatment stopping rule (at which point 100% of patients stop treatment) has been mandated by NHS England as part of the positive recommendations by NICE in other immunotherapy appraisals:
  - Nivolumab [ID811], [ID900], [ID971]
  - A 2-year treatment stopping rule has also been considered in the ongoing appraisal for pembrolizumab within urothelial carcinoma
- Evidence to support the stopping rule available from CheckMate 003
  - CheckMate 003 doesn't include people with urothelial carcinoma

ERG comment

- For ID971 committee's most plausible ICER was without a stopping rule
  - ID811 and ID900 are recommended in the CDF, a stopping rule was not considered appropriate for routine commissioning
- Stopping rule focuses on treatment discontinuation only – reducing treatment costs while assuming effectiveness of continued treatment
  - Continued treatment benefit after discontinuation is uncertain

Other issues
Company amendments

Average patient weight

- Applying a weighting of 50:50 to both trials is inconsistent with the pooling of other trial data in the economic model
- Average weight calculated by weighting across both trials based on trial size

ERG comment
- Use of a weighted mean is reasonable

Dosing

- Included both left- and right-skewed patients to ensure the approach included the average dose delay across all patients – (include delays < 7 days and >14 days)

ERG comment
- Assume a missed dose only when length of delay > 7 days

Revised company base case
Deterministic ICERs

Adopts the ERG preferred base case (ACM1) with the following differences:

- Retention of the responder-based survival modelling approach
- The latest pooled analysis, using the updated data from the CheckMate 032 trial
- 2 year treatment stopping rule
- Weight estimated as weighted average from the CheckMate 032 and 275 trials

Scenario	Technologies	Pairwise vs. Nivolumab			Notes
		Incremental		ICER	
		Cost	QALYs	(£/QALY)	
ACM1 base case	Docetaxel	[redacted]	[redacted]	£44,996	Response-based OS and PFS modelling
	Paclitaxel	[redacted]	[redacted]	£37,643	
	BSC	[redacted]	[redacted]	£38,302	
ACM2 base case 1	Docetaxel	[redacted]	[redacted]	£28,263	Response-based OS and PFS modelling
	Paclitaxel	[redacted]	[redacted]	£23,497	
	BSC	[redacted]	[redacted]	£24,285	
Adopting ERG/committee preferred assumptions					
ACM2 base case 2	Docetaxel	[redacted]	[redacted]	£54,895	ERG/committee preferred survival modelling
	Paclitaxel	[redacted]	[redacted]	£41,195	
	BSC	[redacted]	[redacted]	£45,451	

Source: Table 30 (page 92) company clarification response & tables 6-7 company response to ACD appendix

Scenario analysis

Continued treatment benefit – deterministic ICERs

Scenario	Technologies	Pairwise vs. Nivolumab		
		Incremental		ICER
		Cost	QALYs	(£/QALY)
No continued treatment benefit after 3 years				
Company base case 1	Docetaxel	[redacted]	[redacted]	£27,643
	Paclitaxel	[redacted]	[redacted]	£25,752
	BSC	[redacted]	[redacted]	£23,359
Company base case 2 'ERG'	Docetaxel	[redacted]	[redacted]	£49,468
	Paclitaxel	[redacted]	[redacted]	£44,907
	BSC	[redacted]	[redacted]	£40,640
No continued treatment benefit after 5 years				
Company base case 1	Docetaxel	[redacted]	[redacted]	£27,220
	Paclitaxel	[redacted]	[redacted]	£23,908
	BSC	[redacted]	[redacted]	£23,556
Company base case 2 'ERG'	Docetaxel	[redacted]	[redacted]	£48,780
	Paclitaxel	[redacted]	[redacted]	£41,756
	BSC	[redacted]	[redacted]	£41,243

Source: Tables 10-13 company ACD response appendix

No continued treatment benefit

- Treatment effect on PFS and OS has ceased at 3 or 5 years (i.e. a hazard ratio of 1)

ERG comment

- No option to implement this scenario in the model - unable to validate the results

Scenario analysis

Piecewise model – deterministic ICERs

- Piecewise analysis uses KM data followed by an extrapolation
- Modelling approach used in other immunotherapy (for UC) appraisals
- Company state that this scenario shows that nivolumab is cost-effective versus the relevant comparators irrespective of the survival modelling approach

Scenario	Technologies	Pairwise vs. Nivolumab		
		Incremental		ICER
		Cost	QALYs	(£/QALY)
Continued treatment benefit				
Piecewise analysis	Docetaxel	[redacted]	[redacted]	£39,634
	Paclitaxel	[redacted]	[redacted]	£30,924
	BSC	[redacted]	[redacted]	£33,460
No continued treatment benefit after 3 years				
Piecewise analysis	Docetaxel	[redacted]	[redacted]	£36,156
	Paclitaxel	[redacted]	[redacted]	£34,004
	BSC	[redacted]	[redacted]	£30,666
No continued treatment benefit after 5 years				
Piecewise analysis	Docetaxel	[redacted]	[redacted]	£35,707
	Paclitaxel	[redacted]	[redacted]	£31,439
	BSC	[redacted]	[redacted]	£31,014

ERG revised base-case

Deterministic ICERs

Deviations from the company's revised base-case

- Rejection of response-based survival modelling approach in favour of conventional parametric analysis
- No treatment stopping rule
- Assuming missed dose only when the length of delay > 7 days

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£78,869
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£58,791
BSC	£8,995	0.65	[redacted]	[redacted]	£62,352

Source: Adapted from table 3 ERG addendum

ERG scenario

2-year treatment stopping rule – deterministic ICERs

- Application of a 2 year treatment stopping rule conditional on the revised ERG base-case
  - Costs have stopped at 2 years
  - No impact on clinical outcomes – life time treatment benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£57,253
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£42,480
BSC	£8,995	0.65	[redacted]	[redacted]	£46,968

Source: Adapted from table 4 ERG addendum

ERG comment
Conclusion

- The revised ERG base-case ICERs are estimated to be above £50,000 per QALY gained
  - the large uncertainty regarding (comparative) treatment effectiveness in combination with the lack of appropriate validation, uncertainty around the cost effectiveness of nivolumab remains substantial
  - ICERs need to be treated with caution
- The use of single arm studies to derive effectiveness and the method for the pooling of CheckMate 275 and 032 studies, remain unresolved
- More uncertainty was introduced by lack of clarity surrounding the use of data updates in the model, in particular the omission of the CheckMate 275 update
- Concerns about response-based approach remain:
  - Did not justify why the conventional approach is inappropriate
  - Unrealistic to assume a constant weighting of responder groups
  - Choice of landmark not fully explored and has unpredictable effect on results

Key issues for consideration

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- Relevant comparator – company states paclitaxel most relevant
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