Public slides – part 1 (Redacted)

Chair's presentation

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

3rd Appraisal Committee meeting
Committee D, 11 April 2017

Lead team: Malcolm Oswald, Matt Bradley, William Turner

Chair: Gary McVeigh

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

NICE technical team: Thomas Paling, Thomas Strong, Christian Griffiths

Company: Bristol-Myers Squibb

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 proposed CDF discount

Source: Table 2 (page 13) company submission
***Based on the economic model developed for ACM2 submission**

FAD recommendation (suspended)

Not recommended for unresectable urothelial or metastatic urothelial carcinoma 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 (STC) which was not adequately validated. The results should be treated with caution
- Not suitable for the CDF as there are no planned or ongoing studies that could address the key clinical uncertainties identified
- End of life criteria most likely met

Updated value proposition

- BMS has submitted:
  - Proposal for a Commercial Access Agreement through the Cancer Drugs Fund
  - Updated STC using CheckMate-032 (June 2017) and CheckMate-275 (October 2017) data ('*ACM3 data*')
- All cost-effectiveness estimates include committee's preferred assumptions from ACM2. This includes using a non-response-based, conventional, survival analysis
- Company explore using a 2-year stopping rule, with continued treatment benefit scenarios
- Company consider value proposition is *well below* the end of life threshold for cost-effectiveness

Updated clinical evidence
Summary of changes

- Company consider a different fractional polynomial model a better fit to updated clinical evidence based on DIC values
- ERG note that the updated STC has substantially different hazard ratios. They consider this highlights the lack of reliability of the STC

	ACM2 STC	ACM3 STC
CheckMate data	032 – June 2017 275 – April 2016	032 – June 2017 275 – October 2017
OS fractional polynomial model	2nd order with fixed effects (P1=0, P2=0)	2nd order with random effects (p1=1, p2=1)
PFS fractional polynomial model	2nd order with fixed effects (P1=0, P2=0)	2nd order with fixed effects (p1=1, p2=1)
Cost-effectiveness estimates; no stopping rule; lifetime treatment benefit		
Vs. paclitaxel	£50,385	£32,990
Vs. docetaxel	£67,729	£36,643

Updated clinical evidence
ERG comment (I)

- ERG considers it **inappropriate** to use the updated STC. They highlight:
  - It is unclear why the hazard ratios have changed so substantially, and the results lack face validity
  - Updated STC comparator overall survival predictions significantly underestimates the observed OS and PFS data
  - Method for incorporating the new data cut and updated STC in the economic model is not well reported

- Limitations in the STC analysis identified previously have not been addressed. These include:
  - Not entirely clear how fit of prediction models assessed. The final model had far fewer covariates than originally considered
  - Many baseline characteristics not available across comparator trials
  - Few patients for comparison and not all studies provided data for all outcomes
  - Not all study outcomes are based on independent review
  - External test of validity showed insufficient reduction in bias or was inapplicable

Updated clinical evidence

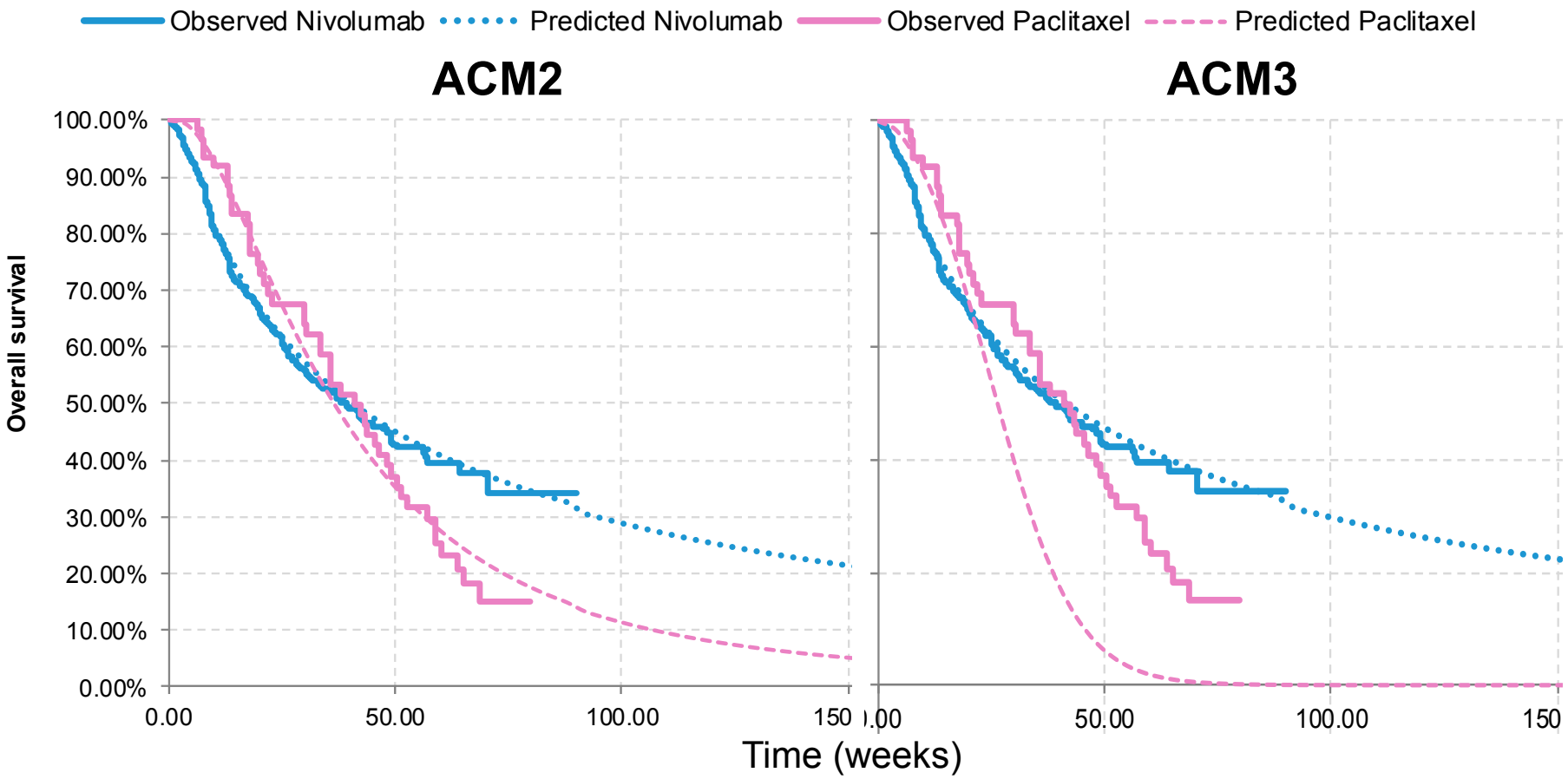
ERG comment (II) - substantially different hazard ratios

	ACM2 STC	ACM3 STC
CheckMate data	032 – June 2017 275 – April 2016	032 – June 2017 275 – October 2017
Docetaxel versus nivolumab OS hazard ratios (95% Credible Interval)		
0-4 weeks	0.31 (0.09–0.84)	0.26 (0.06, 1.09)
8-12 weeks	1.15 (0.75–1.72)	0.74 (0.17, 2.92)
20-24 weeks	1.81 (1.25–2.62)	1.92 (0.46, 7.56)
44-48 weeks	2.11 (1.46–3.00)	4.67 (1.13, 18.85)
68-72 weeks	2.01 (1.14–3.37)	5.31 (1.22, 22.69)
92-96 weeks	1.83 (0.80–3.87)	3.70 (0.69, 18.50)
BSC versus nivolumab OS hazard ratios (95% Credible Interval)		
0-4 weeks	0.81 (0.33–1.79)	0.60 (0.08, 4.47)
8-12 weeks	2.05 (1.36–3.08)	1.29 (0.18, 9.43)
20-24 weeks	2.51 (1.69–3.72)	2.56 (0.36, 18.66)
44-48 weeks	2.27 (1.57–3.25)	4.68 (0.65, 34.19)
68-72 weeks	1.86 (1.17–2.85)	4.78 (0.66, 34.47)
92-96 weeks	1.51 (0.82–2.66)	3.36 (0.46, 24.77)

Adapted from table 1 (page 10), ERG report

Updated clinical evidence
ERG comment (III)

- ERG considers updated STC is a poor visual fit to the observed data



⊙ ***Should the new data-cut be used to estimate cost-effectiveness?***

ERG comment

Stopping rule and continued treatment benefit

- ERG unclear why 2-year stopping rule is appropriate and prefer not to include a stopping rule, as it introduces substantial uncertainties
- If a 2-year stopping rule is included, ERG consider the continued treatment benefit should stop 3 years from the model start, as ERG consider 5 years may be over-estimating the continued treatment benefit
- The company's continued treatment benefit is implemented by adjusting the comparator arm (as nivolumab is treated as a reference arm)
  - This results in negligible differences as the proportion of people alive in the comparator arm <1% after 2 years (with updated ACM3 data)
- ERG explore an alternative approach, which alters the nivolumab survival curves by applying the docetaxel hazard ratios at the time point
- ERG's consider their method may still be biased in favour of nivolumab, because subsequent treatment may be best supportive care

⊙ ***Should a 2-year stopping rule be included?***
⊙ ***Should company's or ERG's continued treatment benefit be included?***

Cost-effectiveness estimates

ACM2 data

	Nivolumab Vs.	Incr. Costs	Incr. QALY	ICER	Change
ACM2 data; 2 year stopping rule					
Lifetime treatment effect	paclitaxel	[redacted]	[redacted]	£36,217	-
	docetaxel	[redacted]	[redacted]	£48,953	-
ACM2 data; 2 year stopping rule; Company's continued treatment benefit					
3 year treatment effect	paclitaxel	[redacted]	[redacted]	£40,153	+£3,936
	docetaxel	[redacted]	[redacted]	£50,343	+£1,390
5 year treatment effect	paclitaxel	[redacted]	[redacted]	£37,020	+£803
	docetaxel	[redacted]	[redacted]	£48,953	+£0
10 year treatment effect	paclitaxel	[redacted]	[redacted]	£36,219	+£2
	docetaxel	[redacted]	[redacted]	£48,953	+£0
ACM2 data; 2 year stopping rule; ERG's continued treatment benefit					
3 year treatment effect	paclitaxel	[redacted]	[redacted]	£41,332	+£5,115
	docetaxel	[redacted]	[redacted]	£58,881	+£9,928
5 year treatment effect	paclitaxel	[redacted]	[redacted]	£37,920	+£1,703
	docetaxel	[redacted]	[redacted]	£52,147	+£3,194
10 year treatment effect	paclitaxel	[redacted]	[redacted]	£36,662	+£445
	docetaxel	[redacted]	[redacted]	£49,777	+£824

Cost-effectiveness estimates

ACM3 data

	Nivolumab Vs.	Incr. Costs	Incr. QALY	ICER	Change
ACM3 data; 2 year stopping rule					
Lifetime treatment effect	paclitaxel	[redacted]	[redacted]	£24,208	-
	docetaxel	[redacted]	[redacted]	£27,623	-
ACM3 data; 2 year stopping rule; Company's continued treatment benefit					
3 year treatment effect	paclitaxel	[redacted]	[redacted]	£24,208	**£0**
	docetaxel	[redacted]	[redacted]	£27,609	**-£14**
5 year treatment effect	paclitaxel	[redacted]	[redacted]	£24,208	**£0**
	docetaxel	[redacted]	[redacted]	£27,619	**-£4**
10 year treatment effect	paclitaxel	[redacted]	[redacted]	£24,208	**£0**
	docetaxel	[redacted]	[redacted]	£27,623	**£0**
ACM3 data; 2 year stopping rule; ERG's continued treatment benefit					
3 year treatment effect	paclitaxel	[redacted]	[redacted]	£34,566	**+£10,358**
	docetaxel	[redacted]	[redacted]	£40,153	**+£12,530**
5 year treatment effect	paclitaxel	[redacted]	[redacted]	£29,230	**+£5,022**
	docetaxel	[redacted]	[redacted]	£33,656	**+£6,033**
10 year treatment effect	paclitaxel	[redacted]	[redacted]	£25,492	**+£1,284**
	docetaxel	[redacted]	[redacted]	£29,158	**+£1,535**

Cancer Drugs Fund

- When the uncertainty in clinical and cost effectiveness data is too great to recommend for routine use, the committee can recommend in CDF if:
  - ICERs have plausible potential to be cost-effective
  - Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
  - Data collected (including research underway) will be able to inform subsequent update (normally within 24 months)
- Company consider Checkmate-032 and Checkmate-275 primary data source for CDF. [redacted] patients remain in trials; estimated completion by end of 2019
- No planned or ongoing comparative studies of nivolumab for unresectable or metastatic urothelial bladder cancer

⊙ ***Will the planned data collection reduce the identified uncertainty?***
⊙ ***Could nivolumab be recommended through the CDF?***

Key issues for consideration

- Should the new data-cut be used to estimate cost-effectiveness?
- Should a 2-year stopping rule be included?
- Should the company's or ERG's continued treatment benefit methodology be included?
  - Which continued treatment benefit scenario should be used for decision-making?
- Will the planned data collection reduce the identified uncertainty?
- Could nivolumab be recommended through the CDF?
- What is the most plausible ICER?