NICE National Institute for Health and Care Excellence

ID811 Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer

Third Appraisal Committee Meeting

7 August 2016

For Public

Appraisal History

- 1st Committee meeting 18 November 2015 ACD issued.
  - List price. Nivolumab not recommended
- 2nd Committee meeting 10 February 2016 FAD issued to C&Cs only
  - List price. The appeal stage of this appraisal topic was suspended: the FAD withdrawn, it was not published on the NICE website and its content remains confidential. The company that markets nivolumab (Bristol-Myers Squibb), requested to make a further submission including a patient access scheme. In recognition of the exceptional nature of this request, NICE agreed that the appraisal can be referred back to the appraisal committee
- 3rd Committee meeting 10 August 2016
  - Simple discount PAS proposed by the company to the DH

Key issues for discussion

- Most plausible ICER with PAS
- Should treatment duration limited? Is it plausible patients continue to benefit from nivolumab after stopping treatment at 2 years?
- Could this be an appropriate candidate for the CDF? Would additional data 2 years from now satisfy that uncertainty?
- Unmet need of patients with sqNSCLC
- Any equality, innovation, PPRS considerations?

Nivolumab

- Nivolumab is an inhibitor of *PD-1*, part of the immune checkpoint pathway
- Marketing authorisation for treating locally advanced or metastatic squamous NSCLC after prior chemotherapy – granted July 2015
  - Before the MA was granted, nivolumab was available through MHRA's Early Access to Medicines Scheme (EAMS)
  - MHRA awarded nivolumab a Promising Innovative Medicine (PIM) designation
- CheckMate-017: nivolumab was associated with significant improvements in overall survival, progression-free survival and overall response rates vs docetaxel
- Economic model:
  - Company base-case ICER: £85,950 per QALY gained

CM017 Kaplan-Meier Overall Survival curves (June 2015 data)

Committee considerations and preliminary recommendations in the ACD

- Squamous NSCLC causes distressing symptoms and has few treatment options – important unmet need
- Nivolumab is a clinically effective treatment option – gains in OS and PFS in the trial, and valuable benefits seen in clinical practice
- Economic model:
  - ERG's approach to OS and PFS was more appropriate
  - Utility scores uncertain – limitations in company and ERG analyses
  - ERG's approaches to treatment costs were mostly appropriate
- Innovative treatment
- End-of-life criteria were met
- Most plausible ICER for list price nivolumab compared with docetaxel was at least £140,000 per QALY gained

*Nivolumab was **not recommended***

ACD, appraisal consultation document; ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Revised analyses following ACD vs Committee considerations in the ACD (nivolumab list price)

	Company	ERG
Original Analyses	ICER: £85,950	ICER: £132,989
Revised Analyses following ACD	**ICER: £91,870**	**ICER: £154,352**
Assumptions		
ERG's PFS estimates	✓ Follows Committee's preferred assumption, exponential model but updated to 18-month data	✓ Follows Committee's preferred assumption, exponential model with updated to 18-month data
ERG's OS estimates	✘ Uses new extrapolation – log-logistic (18-month data), mortality cap	✓ Follows Committee's preferred assumption, exponential model with updated to 18-month data
Limitations in both company and ERG utilities	✘ Uses company's original utilities in new base case, alternative utilities in scenario	– New utilities based on CheckMate-017 and Dutch trial
Duration based on time to discontinuation	✘ Treatment duration based on PFS	✓ Follows Committee's preferred assumption, with updated data
Docetaxel not limited to 4 cycles	✓ Follows Committee's preferred assumption	
Drug costs: **• Revised costs of 2nd line** **• Revised costs of 3rd line** **• Common admin cost** **• Drugs given at start of cycle**	✓ Follows Committee's preferred assumptions	

Committee's preferred assumptions agreed at ACM2

- Extrapolating progression-free and overall survival using exponential models using 18 month follow up data from CM017
- Amended drug costs using eMIT and same administration costs
- Utility values
  - most appropriate values progression-free and progressed-disease health states would be between those presented by the company (0.750 and 0.592, respectively) and those from the ERG (0.65 and 0.43, respectively)
  - reasonable to use a utility value of 0.509 in the progressed-disease health state for decision-making
- Treatment duration from CM017
- Not limiting docetaxel to a max of 4 cycles
- AEs adequately modelled

Introduction of Patient Access Scheme

- Simple confidential PAS
- will apply to all indications for nivolumab
  - Nivolumab as monotherapy for advanced unresectable or metastatic melanoma (TA384)
    - recommended
  - Nivolumab with ipilimumab for advanced unresectable or metastatic melanoma (TA400)
    - recommended
  - Nivolumab for advanced renal cell carcinoma after prior therapy (ID853)
    - subject of ongoing appraisal

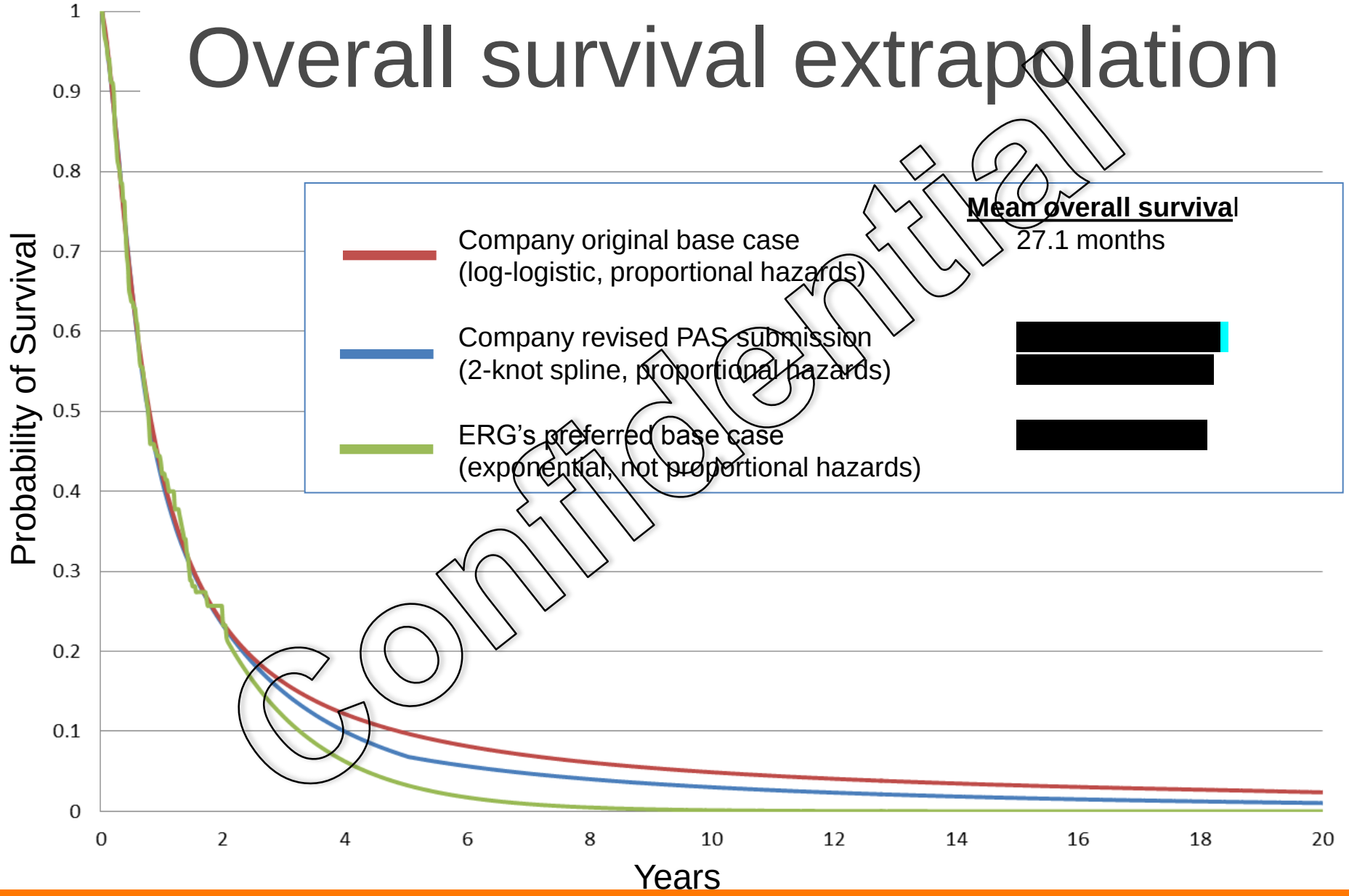
Company's revised PAS base case

- Company presented revised economic model using following assumptions
  - ERG's approach to extrapolating progression-free survival
  - For modelling OS, it used a 2-knot spline hazards model (lies between ERG and BMS base case); not ERG approach for OS extrapolation (which was exponential curve)
  - ERG's modelling of treatment duration for nivolumab and docetaxel
  - Amended drug costs
  - BMS utility estimates (PF=0.750, PD=0.592); not committee's preferred utility estimates (PF=0.693, PD=0.509)

Justification for stopping rule

- CM003, a dose ranging nivolumab study across tumour types including NSCLC had protocol-specified stopping rule at 96 weeks (1.8 years); 6 of 7 patients who responded (complete or partial) maintained that response beyond 96 weeks
- Based on CM003, clinicians agreed that limiting maximum nivolumab treatment duration could be supported
- CM153 is investigating a 1-year stopping rule – first data from this study is expected Q4 2016; fewer patients than expected completed a year of treatment

Overall survival extrapolation



ERG critique of company's revised OS modelling

- ERG identified issues with company's application of 2-knot spline model for OS in its revised base case
- Methodological
  - 2-knot spline model links 3 curves; this suggests three heterogeneous subgroups of patients with different survival profiles – No justification made for this (for example, clinical data or opinion)
- Implementation
  - 2 knot spline model applied incorrectly – OS overestimated

    Company reports [redacted] total life years for nivolumab using 2-knot spline hazard model

    When corrected, ERG reports [redacted] total life years for nivolumab, which increases company base case ICER with simple discount PAS applied by £7,000

Unmet need of patients with sqNSCLC

- No new agents have been licensed for previously treated advanced sqNSCLC for over 10 years.
- The unmet need is particularly significant for sqNSCLC patients, who typically do not have epithelial growth factor receptor (EGFR) or anaplastic lymphoma receptor tyrosine kinase (ALK) mutations, and therefore cannot be treated with agents targeted for these mutations
- Docetaxel has limited efficacy and adverse effects
- Erlotinib used less and less in this population

Key issues for discussion

- Most plausible ICER with PAS
- Should treatment duration limited? Is it plausible patients continue to benefit from nivolumab after stopping treatment at 2 years?
- Could this be an appropriate candidate for the CDF? Would additional data 2 years from now satisfy that uncertainty?
- Unmet need of patients with sqNSCLC
- Any equality, innovation, PPRS considerations?

Revised simple discount PAS ICERs

	Company's revised PAS analysis	ERG's revised PAS analysis
Company's original base case £85,950 (list price) [redacted]	Deterministic ICER (nivolumab vs. docetaxel): [redacted] (list price) £66,055 (with PAS) £73,449 (with PAS and ERG OS correction) PSA ICER: £57,057 (with PAS) *Scenario analysis:* *2 year stopping rule is applied :* deterministic ICER £52,918 (with PAS) PSA ICER £46,496 (with PAS)	Deterministic ICER [redacted]
ERG's original analysis £132,989 (list price)		
Committee's preferred analysis £109,000 – £129,000 (list price)		
ERG's PFS estimates	✓ Follows Committee's preferred assumption using 18-month data	
ERG's OS estimates	✘ Uses new extrapolation – 2 knot spline (18-month data)	✓Follows committee pref – exponential model
Limitations in both company and ERG utilities	✘ Uses company's original utilities in new base case	✓Values between those presented by company and ERG
Duration based on time to discontinuation	✓ Treatment duration based TTD	
Docetaxel not limited to 4 cycles	✓ Follows Committee's preferred assumption	
Drug costs: • **Revised costs of 2nd line** • **Revised costs of 3rd line** • **Common admin cost** • **Drugs given at start of cycle**	✓ Follows Committee's preferred assumptions	