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NICE National Institute for Health and Care Excellence

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

Chair's introduction

2nd Appraisal Committee meeting, 15th June 2016

# Nivolumab

- Marketing Authorisation – received in April, 2016
  - Indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults
  - Before the MA was granted, nivolumab was available through MHRA's Early Access to Medicines Scheme (EAMS)
- Mechanism of Action
  - Targets PD-1 receptor on the surface of lymphocytes, part of immune checkpoint pathway
- Dosage and Administration
  - 3 mg/kg every 2 weeks, by intravenous infusion over 60 minutes
- Cost
  - List price: £439.00 per 40-mg vial
  - Estimated total cost of course of treatment £31,960 (assumes 12.6 doses on average). Annual cost £68,995 (assumes 26 doses)
  - Patient Access Scheme: Economic dose cap – Company covers the cost of nivolumab after 26 doses (1 year). The costs of administering nivolumab still need to be borne by the NHS beyond 1 year

# NICE Scope decision problem (1)

| | |
|---|---|
| Population | People with previously treated locally advanced or metastatic non-squamous non-small cell lung cancer |
| Intervention | Nivolumab |
| Outcomes | • Overall survival<br>• Progression-free survival<br>• Response rates<br>• Adverse effects of treatment<br>• Health-related quality of life |

# NICE Scope decision problem (2)

| | |
|---|---|
| Comparators | Non-squamous EGFR-TK mutation negative or unknown tumours:<br>After one prior therapy:<br>- Docetaxel monotherapy<br>- Erlotinib<br>- Nintedanib in combination with docetaxel<br>- Crizotinib (only for patients with ALK positive mutation status)<br>- Ceritinib (only for patients with ALK positive mutation status; subject to ongoing NICE appraisal)<br>- Best supportive care<br><br>After two prior therapies:<br>- Docetaxel monotherapy<br>- Erlotinib (if not received previously; subject to ongoing NICE appraisal)<br>- Best supportive care |

***Company decision problem:***

*Base case economic analysis is limited to nivolumab compared with:*

- *Docetaxel monotherapy*
- *Nintedanib in combination with docetaxel*

# NICE Scope decision problem (3)

| | |
|---|---|
| Comparators | Non-squamous EGFR-TK mutation positive tumours:<br>After one prior therapy:<br>- Platinum therapy (in combination with gemcitabine, vinorelbine, pemetrexed or a taxane)<br>- Single agent gemcitabine and vinorelbine (for people for whom platinum therapy is not appropriate)<br>- Afatinib, erlotinib or gefitinib (if no previous EGFR-TKI therapy received due to delayed confirmation of mutation status; erlotinib and gefitinib subject to ongoing NICE appraisal)<br><br>After two prior therapies (an EGFR-TKI and one other therapy):<br>- Docetaxel monotherapy<br>- Erlotinib<br>- Nintedanib in combination |

***Company decision problem:***

*Base case economic analysis is limited to nivolumab compared with:*

- *Docetaxel monotherapy*
- *Nintedanib in combination with docetaxel*

# ACD preliminary recommendations

- Nivolumab is not recommended for treating locally advanced or metastatic non squamous non small cell lung cancer in adults whose disease has progressed after chemotherapy.

# Rationale for ACD recommendations

- Nivolumab is a clinically-effective compared with docetaxel, nintedanib plus docetaxel
- It is innovative and meets the criteria to be considered a life-extending, end-of-life treatment
- The most plausible ICERs were much higher than could be considered a cost-effective use of NHS resources using the Committee's preferred assumptions for the comparisons with docetaxel and nintedanib plus docetaxel
- For the comparison with BSC, cost-effectiveness evidence was not presented, the Committee was unable to make a positive recommendation for nivolumab compared with BSC

# Clinical evidence

CheckMate-057 randomised controlled trial comparing nivolumab with docetaxel in adults with non-squamous NSCLC after one prior platinum doublet-based chemotherapy regimen

| | 12 months interim analysis | | 18 months analysis | |
|---|---|---|---|---|
| | Nivolumab | Docetaxel | Nivolumab | Docetaxel |
| **Overall survival (OS)** | | | | |
| **Median** | 12.2 months (9.7 to 15.0) | 9.4 months (8.1 to 10.7) | - | - |
| **Hazard ratio** | 0.73 (0.59 to 0.89), p = 0.002 | | 0.72 (0.60 to 0.88), p=0.001 | |
| **OS rate** | 51% (45 to 56) | 39% (33 to 45) | 39% (34 to 45) | 23% (19 to 28) |
| **Progression-free survival (PFS)** | | | | |
| **Median** | 2.3 months (2.2 to 3.3) | 4.2 months (3.5 to 4.9) | - | - |
| **Hazard ratio** | 0.92 (0.77 to 1.11), p=0.39 | | 0.91 (0.76 to 1.09) p value was not presented | |
| **PFS rate** | 18.5% (14 to 23) | 8% (5 to 12) | - | - |

Brackets show 95% confidence intervals.
Source: company submission, tables 16-18

# Company's comparison nivolumab vs. nintedanib plus docetaxel and BSC

- Hazard ratio analysis results of the indirect treatment comparison were not valid
- The company also presented results in terms of differences in restricted means survival time (RMST)
- In the model instead of the results of the indirect comparison, HRs based on a comparison of the KM curves from LUME-Lung 1 study (adenocarcinoma population) were applied to the docetaxel arm of the model
  - OS: It was assumed that the two curves are equal up to 6 months; thereafter, a HR of 0.75 (95% CI 0.60-0.93) was applied to the docetaxel arm
  - TTD: the two curves are equal up to 2 months; thereafter a HR of 0.98 (95% CI 0.73-1.33) was applied to the docetaxel arm


Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; HR, hazard ratio; OS, overall survival; TTD, time to treatment discontinuation

# Cost-effectiveness evidence (company)

- **versus docetaxel**: estimated by extrapolation from 12 months data from CheckMate-057 (generalised gamma curve used)
- **versus docetaxel plus nintedanib**: HR for OS and time to treatment discontinuation estimated from KM curves of LUME-Lung1 study (generalised gamma curve used)
  - OS: HR of 1 (up to 6 months); thereafter 0.75 (95% CI 0.60-0.93)
  - Time to treatment discontinuation: HR of 1 (up to 2 months); thereafter 0.98 (95% CI 0.73-1.33)
- Utility values: Derived from EQ-5D results from CheckMate-057
  - Progression-free health state 0.739
  - Progressed disease health state 0.688


Abbreviations: KM, Kaplan-Meier; HR, hazard ratio; OS, overall survival

# Company's base case results
## (using the economic dose cap PAS for nivolumab)

| | Incr. costs | Incr. QALYs | ICER |
|---|---|---|---|
| Nivolumab PAS (26 dose cap) | | | |
| Nivolumab | | | |
| Docetaxel | £37,733 | 0.73 | 51,805 |
| Nintedanib + docetaxel | £24,880 | 0.49 | 50,421 |

Abbreviations: Incr., incremental; QALY, Quality adjusted life years; ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme

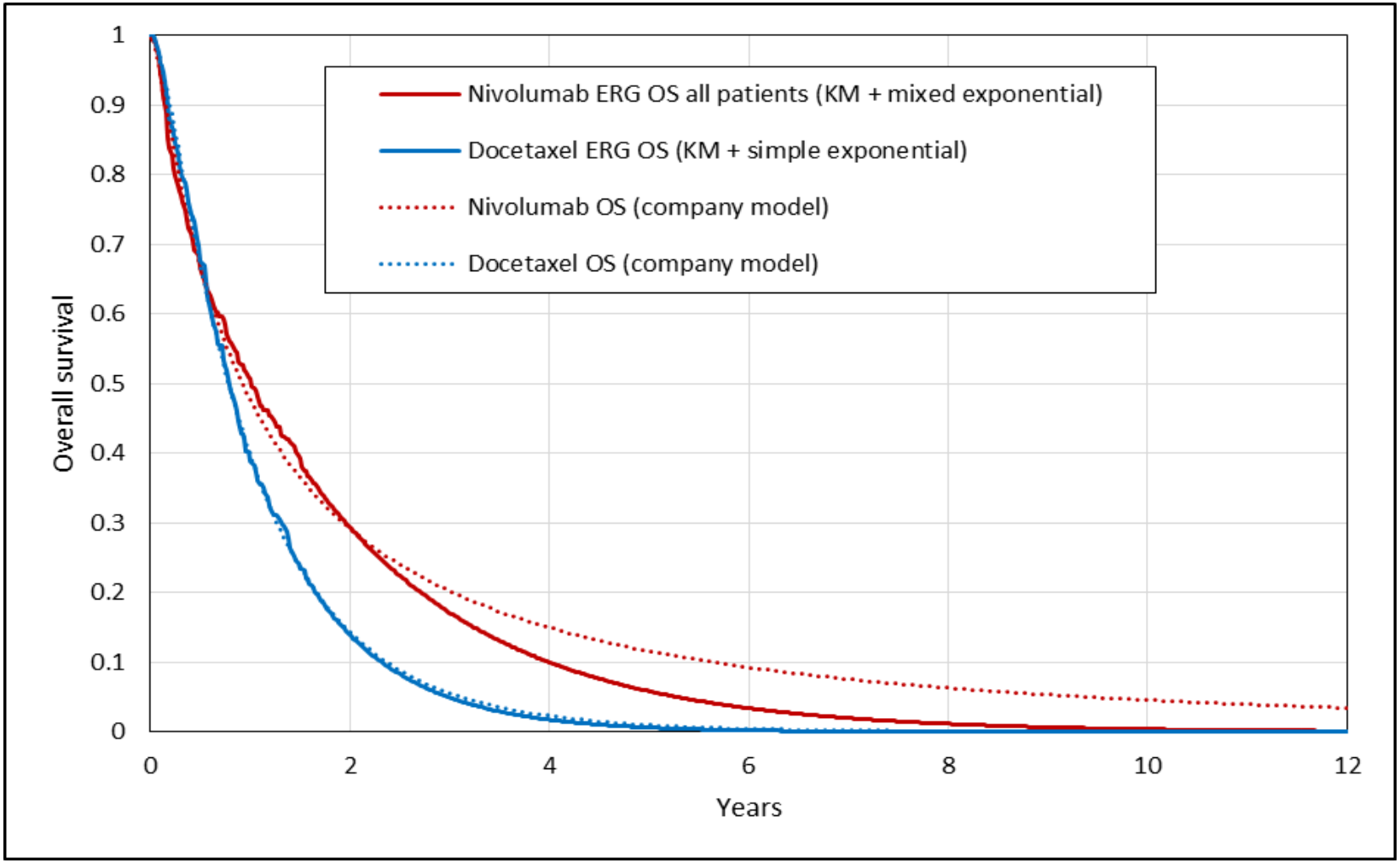
NB. Table does not include the PAS for nintedanib

# ERG's critique

- More mature 18 months data rather than 12 months data from CheckMate-057 should be used
- For the comparison with nintedanib plus docetaxel more mature data from the LUME-Lung 1 trial should be used
- Using time to treatment discontinuation to estimate progression-free survival is implausible; time to treatment discontinuation data should only be used for estimating costs and AEs associated with treatment
- Use exponential curve for extrapolation instead of the generalised gamma curve (suggested by the company), because constant hazard of death can be observed in CheckMate 057
- Developed a mixed exponential curve for OS to account for patients receiving nivolumab after progression in CheckMate 075 (25%)
- Use different utility values, adjusted for the decline in EQ-5D response in CheckMate-057 (see slide 21 later)
- Correct calculation errors in the model (administration and dosage costs)


Abbreviations: AE, adverse events; OS, overall survival

# ERG comments: Overall survival projections for nivolumab vs. docetaxel




Source: ERG report figure 19

# Committee's preferred assumptions

- For modelling overall survival:
  - Use 18 months data and an exponential curve for extrapolation. For the comparison with nintedanib plus docetaxel, use more mature data of LUME-Lung 1, as introduced by the ERG.
- For modelling progression-free survival:
  - Use progression-free survival data for modelling health state costs and QALYs and time to treatment discontinuation data for modelling treatment costs and AEs. Use exponential curve for extrapolation.
- Correct calculation errors in the model (administration costs, dosing)
- Use the utility values adjusted with the results of van den Hout et al. study (2006), as calculated by the ERG (progression-free health state 0.713; progressed-disease health state 0.476)

# ICER results ACD
## (with Committee's preferred assumptions)

| | Incr. costs | Incr. QALYs | ICER |
|---|---|---|---|
| With nivolumab PAS | | | |
| Nivolumab | | | |
| Docetaxel | 29,407 | 0.323 | 91,089 |
| Nintedanib + docetaxel | 11,180 | 0.120 | 93,355 |

Abbreviations: Incr., incremental; QALY, Quality adjusted life years; ICER, Incremental cost-effectiveness ratio

NB: Table does not include the PAS for nintedanib

- Cost-effectiveness evidence compared with BSC was not presented, therefore the committee it was unable to make a positive recommendation for nivolumab compared with BSC.
- In conclusion the committee did not recommend nivolumab as a cost-effective use of NHS resources for people with locally advanced or metastatic non-squamous NSCLC after chemotherapy.

# ACD consultation

- Comments received from consultees
  - Company (BMS)
  - Roy Castle Lung Cancer Foundation
  - National Lung Cancer Forum for Nurses
  - Joint submission from the National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists
- Comments received from commentator
  - Comparator company (Boehringer Ingelheim)
- Web comments received from
  - NHS professionals

# Long term overall survival benefit

- With the new immuno-oncologic treatments it is possible that the mortality rate of people who survive long-term is going to return to the rate of the age adjusted general population
- CheckMate-003 can be used to validate the long term extrapolation data and it shows decreasing hazard of death
- Company suggests that the evidence used by the ERG to support the constant hazard of death is based on evidence on traditional cytotoxic chemotherapy; therefore using exponential model is not appropriate
- Suggests to use log-normal curve for extrapolation, instead of their initial generalised gamma curve, which also assumes a decline in the mortality rate

# Results of 24 months data cut from CheckMate-057

| | 12 months analysis | | 18 months analysis | | 24 months analysis | |
|---|---|---|---|---|---|---|
| | Nivolumab | Docetaxel | Nivolumab | Docetaxel | Nivolumab | Docetaxel |
| **Overall survival (OS)** | | | | | | |
| **Median (months)** | 12.2 (9.7 to 15.0) | 9.4 (8.1 to 10.7) | - | - | 12.2 (9.7 to 15.1) | 9.5 (8.1 to 10.7) |
| **Hazard ratio** | 0.73 (0.59 to 0.89) p = 0.002 | | 0.72 (0.60 to 0.88) p=0.001 | | 0.75 (0.63 to 0.91) | |
| **OS rate** | 51% (45 to 56) | 39% (33 to 45) | 39% (34 to 45) | 23% (19 to 28) | 29% | 16% |
| **Progression-free survival (PFS)** | | | | | | |
| **Median (months)** | 2.3 (2.2 to 3.3) | 4.2 (3.5 to 4.9) | - | - | 2.3 (2.2 to 3.4) | 4.3 (3.4 to 4.9) |
| **Hazard ratio** | 0.92 (0.77 to 1.11), p=0.39 | | 0.91 (0.76 to 1.09) p value was not presented | | 0.89 (0.75 to 1.07) p value was not presented | |
| **PFS rate** | 18.5% (14 to 23) | 8% (5 to 12) | - | - | 12% | 1% |

# Modelling progression-free survival

- The company maintain that using time to treatment discontinuation data is appropriate for modelling progression-free survival
- Patients were allowed to receive treatment after progression and therefore it was possible that they continued to receive clinical benefit of nivolumab
- Using progression-free survival data only for modelling health-state occupancy and not for modelling the costs and adverse events associated with nivolumab means that patients who were receiving treatment beyond progression are receiving no benefits, but are accruing the costs of treatment

# Comparison with nintedanib

- The company point to key differences between CheckMate-057 and LUME-Lung 1 studies, and to NICE methods guidance to argue against the ERG unadjusted comparison.

# Utility values

- The patient populations of the van den Hout study and CheckMate-057 cannot be considered equivalent
- The utility value used by the ERG for the progressed-disease health state is an under-estimation for the patient population under consideration
- The company presented a revised utility value for the progressed-disease health state. This is a weighted utility, incorporating a disutility to account for end-of-life, based on van den Hout et al. (2006), to the estimate based on CheckMate-057 data.

| Utility values | Company original values | ERG values | Company new values |
|---|---|---|---|
| Progression-free | 0.739 | 0.713 | 0.739 |
| Progressed-disease | 0.688 | 0.476 | 0.657 |

# Updated results presented by the company at ACD stage (nivolumab list price)

- Uses 24 months data from CheckMate057
- Uses time to treatment discontinuation to model progression-free survival
- Log normal model for extrapolation
- For the comparison with nintedanib uses the original hazard ratios [OS: HR of 1 (up to 6 months); thereafter 0.75 (95% CI 0.60-0.93); TTD: HR of 1 (up to 2 months); thereafter 0.98 (95% CI 0.73-1.33)]
- Uses revised utility value for the progressed disease health state (0.650)

| | **Deterministic results** | | | **Probabilistic results** | | |
|---|---|---|---|---|---|---|
| | Incr. costs | Incr. QALYs | **ICER** | Incr. costs | Incr. QALYs | **ICER** |
| Nivolumab | | | | | | |
| Docetaxel | 52,206 | 0.49 | **106,653** | 52,834 | 0.48 | **110,658** |
| Nintedanib plus docetaxel | 38,549 | 0.22 | **177,698** | 38,814 | 0.21 | **182,189** |

# Other comments

- Nivolumab is a new and innovative treatment, its adverse events appear to be more tolerable than the currently available treatment options
- Non-squamous NSCLC is a devastating disease with limited treatment options available currently, with high unmet medical need

# Subgroup based on PD-L1 expression level raised on consultation

- Nivolumab seems to be more effective in a subgroup of patients with higher PD-L1 expression level
- The level of PD-L1 expression should be used to model survival outcomes, it would be important to consider the OS curves for the subgroups with different PD-L1 expression level

# ERG's response to the company's comments on the ACD (I)

- Long term overall survival benefit
  - The ERG had used a mixed model to account for the differences in survival between the subgroups who have been treated post-progression (25%) and those who have not
  - It also used exponential extrapolation because after 7 months it could be observed that the hazards were constant for each group
  - Other limiting factor of the company's approach: it's replacing the Kaplan-Meier data with the extrapolated model, whereas the ERG's approach is using the Kaplan-Meier data from CheckMate-057 up until 18 months and then extrapolates it until the end of the time horizon of the model

# Nelson-Aalen Cumulative Hazards Plot, Patients With NSCLC From CheckMate-003

Source: Figure 1 from company's ACD response
This figure is academic-in-confidence

# Cumulative hazard plot of OS for NSCLC patients in Checkmate-003

Source: Figure 2 from ERG's ACD addendum; adapted from adapted from original BMS company submission (BMS 2015h)
This figure is commercial-in-confidence

# Cumulative hazard plot of OS from pooled analysis of ipilimumab in melanoma

Source: Figure 3 from ERG's ACD addendum; adapted from Schadendorf (2015)
This figure is academic-in-confidence

# ERG's response to the company's comments on the ACD (II)

- CheckMate-003 and other trials of immuno-oncologic agents
  - The plateau of the Kaplan-Meier data is biologically implausible; it assumes that after a certain point the risk of death drops to zero
  - Due to censoring issues the long-term survival beyond 4 years is obscured in CheckMate-003
  - The decreasing hazard assumption is based on whole trial data; however after a certain point the hazards become constant (both in the case of CheckMate-003 and in the melanoma trials)

# ERG's response to the company's comments on the ACD (III)

- Comparison with nintedanib
  - The company's method assumes that the proportional hazard assumption holds, however it does not hold
  - The ERG also considers that the results of the unadjusted comparison should be treated with caution, but so should the company's method
- Time to treatment discontinuation (TTD) data and PFS
  - TTD is linked to the cost of treatment
  - Benefits are linked to health states rather than treatment status – PFS and post-progression survival should be used to calculate QALYs
  - The benefits of post-progression treatment are already in the EQ-5D results of CheckMate-057. Therefore the company's approach would lead to double counting

# ERG's response to the company's comments on the ACD (IV)

- Utility values
  - Self selection bias in EQ-5D completion rates in CheckMate-057
  - This is still true with the new utility value suggested by the company for the progressed-disease health state
  - The ERG has estimated a new utility value for the progressed-disease health state which accounts for the 25% of patients who received treatment after progression

| Utility values | Company original values | ERG values | Company new values | ERG new values |
|---|---|---|---|---|
| Progression-free | 0.739 | 0.713 | 0.739 | 0.713 |
| Progressed-disease | 0.688 | 0.476 | 0.657 | 0.480 |

# Summary of ICERs

- Economic dose cap PAS for nivolumab included
- Table does not include the PAS for nintedanib
- All ICERs are deterministic

| ICERs | Company original base case | Committee's preferred base case (ERG's model) | Company new base case* | ERG updated base case (amended utility value) |
|---|---|---|---|---|
| Nivolumab | | | | |
| Docetaxel | 51,805 | 91,089 | 72,370 | 90,913 |
| Nintedanib plus docetaxel | 50,421 | 93,355 | 100,342 | 93,770 |

Abbreviations: Incr., incremental; QALY, Quality adjusted life years; ICER, Incremental cost-effectiveness ratio

*Company new base case ICERs with economic dose cap PAS calculated by the ERG.

# Key issues for consideration

- Assumptions in the company's economic model – appropriate and plausible?
  - ***Survival projections:***
  - What are the most appropriate methods:
    - For modelling OS
    - For modelling PFS
  - Is the use of time to treatment discontinuation data for modelling PFS or only treatment related costs and AEs plausible?
  - ***Comparison with nintedanib plus docetaxel:***
  - What is the most appropriate method for this comparison?
  - ***Utility values:***
    Most plausible utility scores to use in model?
- What are the most plausible ICERs?
  - For those who can have docetaxel
  - For those who cannot have docetaxel (comparator is BSC)
- Does the company want to make a case for inclusion in the CDF?