Lead team presentation

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

Clinical effectiveness

1st Appraisal Committee meeting

Committee D, 27 September 2017

Lead team: Malcolm Oswald (lay), William Turner (clinical)

Company: Bristol Myers Squibb

Chair: Gary McVeigh

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

Key points for consideration

- Quality of evidence
  - No comparative nivolumab trial data
  - Generalisability of nivolumab studies to UK practice
  - Reliability of simulated treatment comparison. Are all important prognostic factors accounted for?
  - Reliability of network meta-analysis. Are the included studies sufficiently homogeneous?
- Effectiveness of nivolumab
- Evidence for PD-L1 subgroups recommendations
- The company excluded gemcitabine and cisplatin from its base case. Is this appropriate?
- Approach to model survival. Company used a response-based analyses. ERG preferred conventional approach.
- Most plausible ICER
- Any significant health benefits not captured in the model
- End of life

Disease background and management

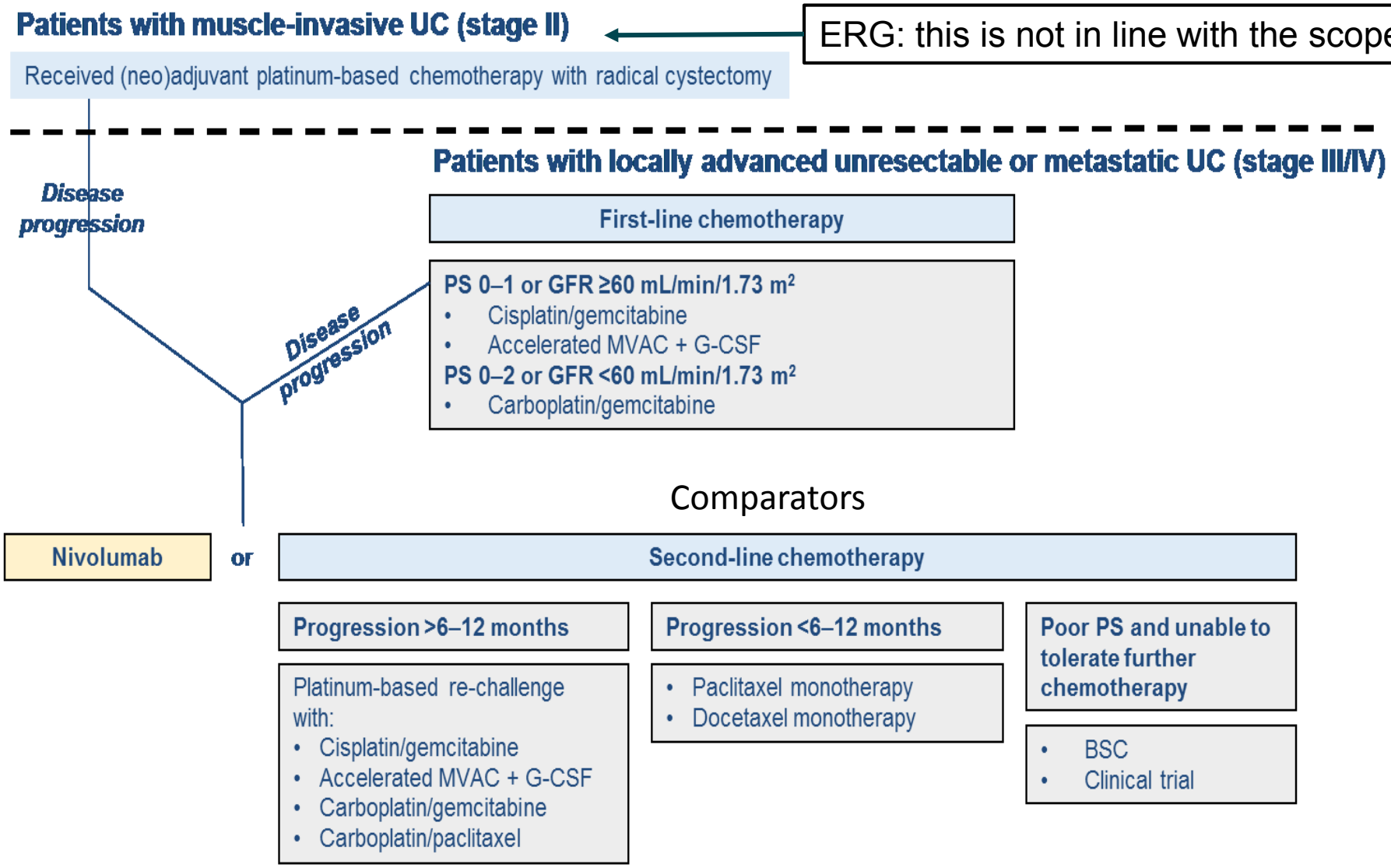
- Urothelial carcinoma – cancer of the transitional cells which form the inner lining of the bladder, urethra, ureter, or renal pelvis.
  - Most common in the bladder and accounts for 90% of bladder cancers
- Around 10,100 new diagnoses of bladder cancer in the UK in 2014 and around 5,400 deaths. Bladder cancer accounts for 3% of new cancer diagnoses
- Majority of diagnoses are in those over the age of 60, with over 55% of cases being diagnosed in people aged 75 and over
- Smoking is the main avoidable risk factor for bladder cancer, linked to an estimated 37% of bladder cancer cases in the UK

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**

Clinical pathway of care



Source: Figure 7, page 23, company submission

Patient perspectives

- Submissions from: Action Bladder Cancer, Fight Bladder Cancer
- “Bladder cancer has a very poor prognosis”
- After platinum chemo, few options, “survival rates...exceptionally poor”
- “Many are unable to tolerate the preferred cisplatin chemo... huge unmet need...patients generally overlooked”
- Nivolumab:
  - “Trials show treatment prolongs life, and for 20% of patients the effects are enduring”
  - “Side effects for the majority are minor and tolerable”
  - “Innovative breakthrough treatment”
  - “For a cancer with so few advances in decades, this gives hope to many”

Clinician perspectives

- Submissions from: British Uro-Oncology Group, Southampton specialist
- Main treatment aims: “to palliate symptoms, improve quality of life and delay time to further progression of disease and improve survival”
- NHS second-line treatment:
  - Paclitaxel commonest regimen
  - With around 10% response rate, many patients decline further chemo
  - Many centres used PD1/PD-L1 inhibitors last year instead of chemo
- Nivolumab:
  - “For use in good performance status patients”
  - Should increase overall survival and health-related quality of life
  - Acceptable side-effect profile
  - Would be administered in specialist clinics in secondary care
  - Facilities and equipment already in place, some training required (e.g. on side-effects)

Decision problem
Deviations from the scope

	Final scope issued by NICE	Decision problem addressed in the company submission
Comparator(s)	• Retreatment with first-line platinum-based chemotherapy (only for people whose disease has had an adequate response) • Paclitaxel • Docetaxel • Best supportive care	• Paclitaxel • Docetaxel • Best supportive care
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates (objective response rate, duration of response) • Adverse effects of treatment • EORTC QLQ-C30 and the EQ-5D-3L)
Subgroup(s)	• None detailed	• PD-L1 expression investigated – not a formal analysis

ERG: Given the paucity of the data all comparators should have been included in the STC

Source: Adapted table 1, page 10-11, company submission

CheckMate 275 and CheckMate 032

Study	CheckMate 275 (N=270)	CheckMate 032 (N=78)
Study design	Multicentre, open-label, single-arm phase II study	Multicentre, open-label, two-stage, multi-arm, phase I/II[a]
Population	Patients with locally advanced unresectable or metastatic UC who had progressed or recurred after at least one previous line of platinum-containing chemotherapy	
Intervention	Nivolumab (IV 3 mg/kg Q2W)	Nivolumab (IV 3 mg/kg Q2W)
Comparators	N/A (single-arm)[a]	
Reported outcomes specified in the decision problem	• ORR • OS • PFS • HRQoL: EORTC, QLQ-C30, EQ-5D-3L • Adverse events (AEs)	• ORR • OS • PFS • EQ-5D-3L • AEs

[a]CheckMate 032 investigated nivolumab or nivolumab combined with ipilimumab in patients with UC, triple-negative breast cancer, gastric cancer, pancreatic adenocarcinoma, small cell lung cancer, and ovarian cancer. Here, presentation of CheckMate 032 refers only to the nivolumab monotherapy UC cohort (n=86) of relevance to this submission.

Source: Table 4, page 26, company submission

Key baseline characteristics

Characteristic	CheckMate 275	CheckMate 032
Mean age years (range)	66 (38–90)	66 (31–85)
% ECOG PS: 0/1/3	53.7 / 45.9 / 0.3	53.8 / 46.2 / 0
Male, n (%)	211 (78.1)	54 (69.2)
% PD-L1: <1% / ≥1%	54.1 / 45.9	53.8 / 31.8
% PD-L1: <5% / ≥5%	69.3 / 30.7	67.9 / 17.9
% metastases at baseline visceral / liver / lymph node	84.1 / 27.8 / 15.9	78.2 / 25.6 / 16.7
% disease setting: metastatic / locally-unresectable	96.7 / 3.3	91.0 / 9.0
% previous therapies: 0 / 1 / 2 / ≥3 & 0 / 1 / 2-3 / >3	28.5 / 42.2 / 21.2 / 8.1	n/a / 33.3 / 53.8 / 12.8
% UK / Non-UK	0 / 100	7.7 / 92.3
Source: Adapted from table 6 (page 35), company submission		

CheckMate 275: Latest efficacy results

Blinded independent review committee

Tumour response	All-treated population (n=270)	PD-L1 <1% (n=146)	PD-L1 ≥1% (n=124)
ORR, n (%) 95% CI	54 (20.0) 95% CI: 15.4–25.3	23 (15.8) 95% CI: 10.3–22.7)	31 (25.0) 95% CI: 17.7–33.6
CR	8 (3.0)	[redacted]	[redacted]
PR	46 (17.0)	[redacted]	[redacted]
SD	60 (22.2)	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Unable to determine[a]	[redacted]	[redacted]	[redacted]
Median Time to response [TTR] (n=54), months IQR	1.94 IQR: 1.84–2.50	1.97 IQR: 1.87–3.48	[redacted]
Median duration of response [DOR] (n=54), months 95% CI	10.35 95% CI: 7.52–NR	10.35 95% CI: 7.43–NR	NR 95% CI: 7.52–NR

[a]BOR was reported as unable to determine in 51 patients (18.5%); main reason was death prior to assessment.

Latest clinical database lock (2nd September 2016)

Source: Table 14 (page 47), company submission

CheckMate 275: Progression free survival

Kaplan-Meier plot

Figure redacted AIC

Median PFS months (95% CI)	
All-treated	2.00 (1.87, 2.63)
PD-L1<1%	1.87 (1.77, 2.04)
PD-L1 ≥1%	3.55 (1.94, 3.71)

Latest clinical database lock (2nd September 2016)
Source: Adapted from figure 13 (page 47), company submission

CheckMate 275: Overall survival

Kaplan-Meier plot

Figure redacted AIC

Median OS months (95% CI)	
All-treated	8.57 (6.05, 11.27)
PD-L1<1%	5.95 (4.37, 8.08)
PD-L1 ≥1%	11.63 (9.10, N/A)

Latest clinical database lock (2nd September 2016)
Source: Adapted from figure 14 (page 48), company submission

CheckMate 032 results

Investigator assessed

Tumour response	Nivolumab (n=78)	PD-L1<1% (n=42)	PD-L1 ≥1% (n=25)
ORR, n (%)	19 (24.4) [95% CI 15.3–35.4]	11 (26.2)	6 (24.0)
BOR, n (%)			
CR	5 (6.4)	1 (2.4)	4 (16.0)
PR	14 (17.9)	10 (23.8)	2 (8.0)
SD	22 (28.2)	11 (26.2)	8 (32.0)
PD	30 (38.5)	18 (42.9)	8 (32.0)
Unable to determine	7 (9.0)	2 (4.8)	3 (12.0)
Median TTR, months (IQR)	1.48 (1.25–4.14)	[redacted]	[redacted]
Median DOR, months (95% CI)	NR (9.92–NR)	[redacted]	[redacted]

Primary clinical database lock (24th March 2016)

Source: Adapted from table 14 (page 47) company submission & table 56 (page 149) company appendix E

CheckMate 032: Progression free survival

Kaplan-Meier plot

Figure redacted AIC

Median PFS months (95% CI)	
No PD-L1*	2.89 (1.05, 6.51)
PD-L1<1%	2.76 (1.41, 6.51)
PD-L1 ≥1%	5.45 (1.41, 11.71)

Primary clinical database lock (24th March 2016); *No quantifiable PD-L1
Source: Figure 27 (page 149), company appendix E

CheckMate 032: Overall survival

Kaplan-Meier plot

Figure redacted AIC

Median OS months (95% CI)	
No PD-L1*	6.51 (1.91, N/A)
PD-L1<1%	9.89 (7.03, N/A)
PD-L1 ≥1%	16.16 (7.59, N/A)

Primary clinical database lock (24th March 2016)
Source: Figure 28 (page 150), company submission

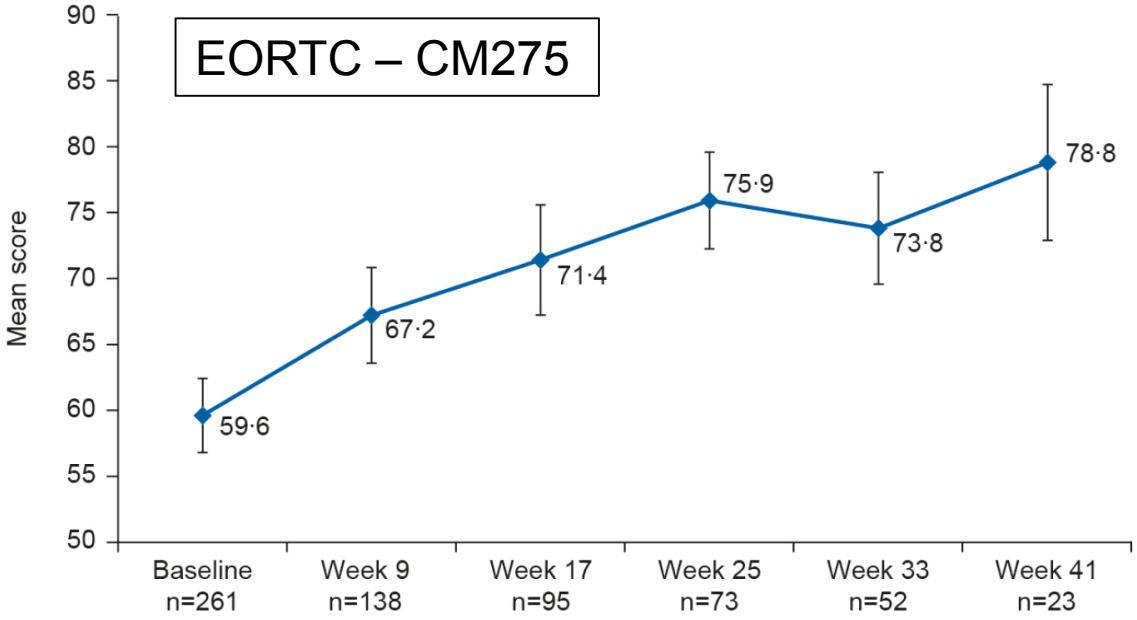
Adverse events

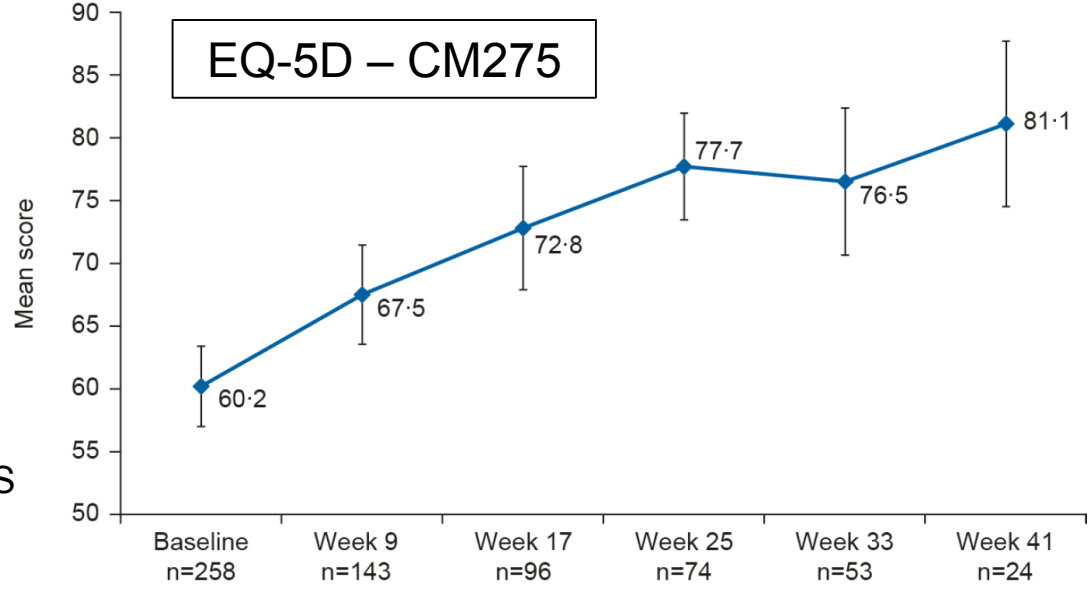
Adverse event, n (%)	CheckMate 275 (n=270)[a]		CheckMate 032 (n=78)[b]	
Deaths	138 (51.1)		36 (46.2)	
Deaths due to study drug toxicity	3 (1.1)		2 (2.6)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All causality AEs	267 (98.9)	137 (50.7)	78 (100)	43 (55.1)
Drug-related AEs	174 (64.4)	48 (17.8)	65 (83.3)	18 (23.1)
All-causality serious AEs	147 (54.4)	99 (36.7)	36 (46.2)	23 (29.5)
Drug-related serious AEs	[redacted]	[redacted]	8 (10.3)	[redacted]
All-causality AEs leading to treatment discontinuation	56 (20.7)	42 (15.6)	6 (7.7)	4 (5.1)
Drug-related AEs leading to treatment discontinuation	13 (4.8)	8 (3.0)	2 (2.6)	2 (2.6)

*Not published – commercially important
Source: Table 23 (page 72/73), company submission

Health-related quality of life (HRQoL)
CheckMate 275 and CheckMate 032

- Assessed via EQ-5D-3L (CheckMate 275 and 032)
- CheckMate 275 also collected responses to the EORTC QLQ-C30
  - Commonly used in oncology trials
- At latest database lock (CM275); 4/9 symptom scales in the EORTC showed improvements. EQ-5D results were consistent with the initial database lock
- CheckMate 032 reported improvements in EQ-5D-3L results over time





Source: EORTC graph, figure 20 (p54), CS
Source: EQ-5D graph, figure 22 (p56), CS

CheckMate results
ERG comment

- No studies directly compared nivolumab with any specified comparator
- Only 6 UK patients were treated, none from the largest trial (CheckMate 275)
- A review undertaken by the company suggests 18.8% of UK patients in have ECOG PS of 0; over 50% in the nivolumab trials had this score
- CheckMate 275 outcomes generally worse than in CheckMate 032
- In CheckMate 032, 23% switched from nivolumab upon disease progression to combination treatment with ipilimumab
- Difference in OS between the PD-L1 < 1% and PD-L1 >= 1% subgroups
  - No ITC for these subgroups, citing limited PD-L1 status evidence in the comparator studies
  - PD-L1 status is unimportant for the comparators given their mode of action, therefore indirect treatment comparison should have been undertaken
  - Lack of information on other baseline characteristics did not preclude their inclusion in the prediction model for the STC, since missing data was imputed

Indirect and mixed treatment comparisons

Dashed lines indicate where simulated treatment comparison has been applied

ompany comment:

Patients in Gondo et al. (2011) had received MVAC in first-line treatment and are therefore not considered to be directly comparable to those receiving gemcitabine and cisplatin re-challenge in current UK clinical practice, as they are gemcitabine naïve

Source: Figure 24 (page 60), company submission

Trials included in STC
ERG comment

- Company only used single arms from each study, therefore losing the advantages of comparability between groups
- Variability in patient populations between the included studies means comparability is unlikely
- Despite some company adjustments, many characteristics were not reported for the comparator studies thus leading to the likelihood of persistent imbalance in both prognostic and effect modifiers
- Majority of data for nivolumab or comparators did not come from UK patients
  - No UK sites in CheckMate 275
  - CheckMate 032 – 6 patients (7.7%) treated in the UK
  - 6 of the 9 studies did not include UK patients

Methodology of the STC

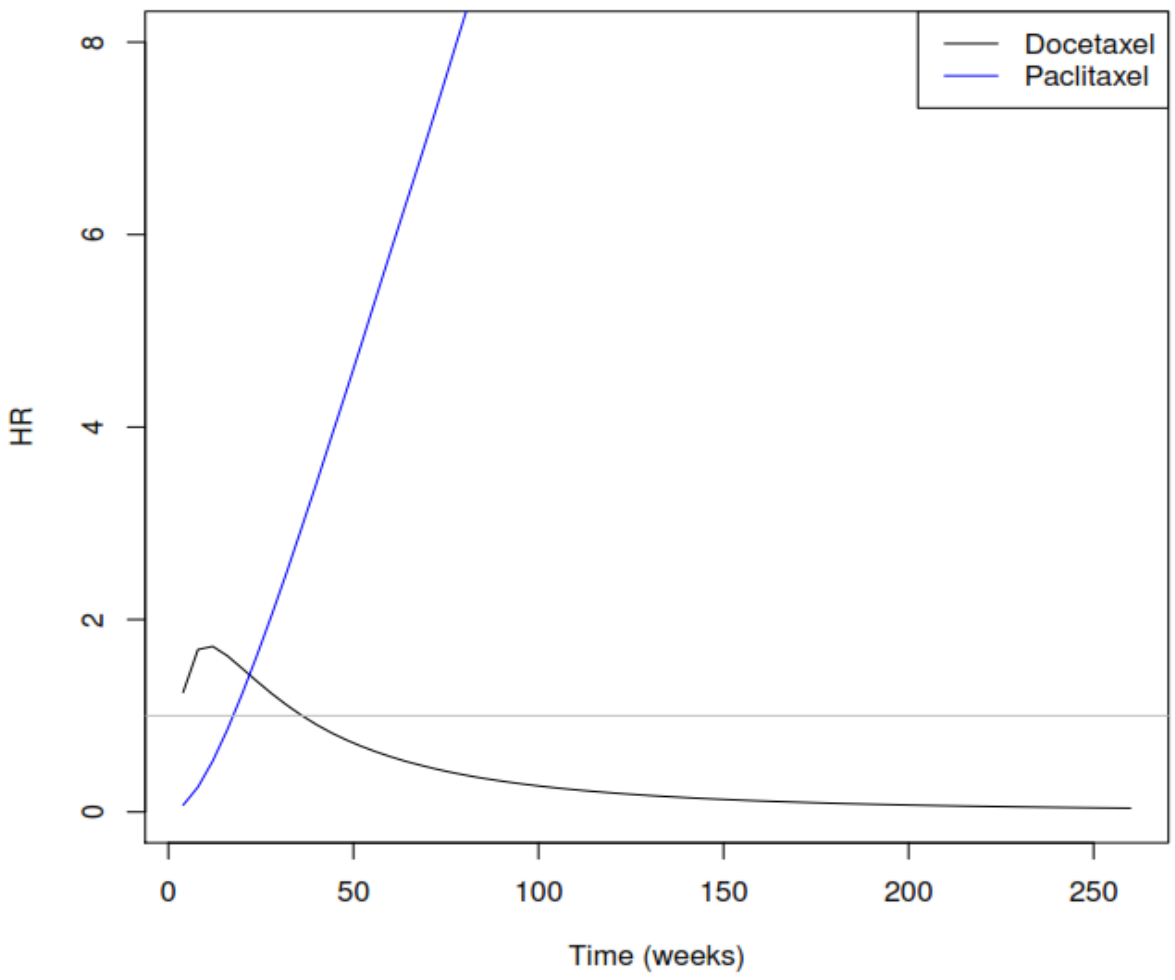
- The company used a population-adjusted method (STC)
- For each outcome, the key steps of the STC approach were:
    1. Use the nivolumab patient data to predict how patients respond to treatment based on key baseline patient characteristics
    2. For each comparator in the network, use baseline characteristics from the comparator trial to predict how patients in the comparator trial might have responded to nivolumab. Compare the real data from the comparator, to the predicted data for nivolumab
    3. Use a meta-analysis to synthesise the results across all of the comparator trials

ERG comment:

- Methods used for the prediction models lacked transparency
- Lack of information from the comparator studies on possible effect modifiers or prognostic variables
- Company 'in-sample' evaluation of residual bias is likely an underestimate

Progression free survival

Network meta-analysis



- PFS was evaluated using a fractional polynomial
- Second order (P1=0, P2=0) fixed effect model was used because it had clinical plausibility and the lowest DIC
- PFS network does not include BSC or platinum-based chemotherapy
- HRs >1 favour nivolumab
- For docetaxel, the HR is initially greater than 1, indicating that patients receiving docetaxel have a higher hazard, but over time the HR decreases

Source: Figure 28 (page 66), company submission

Progression free survival

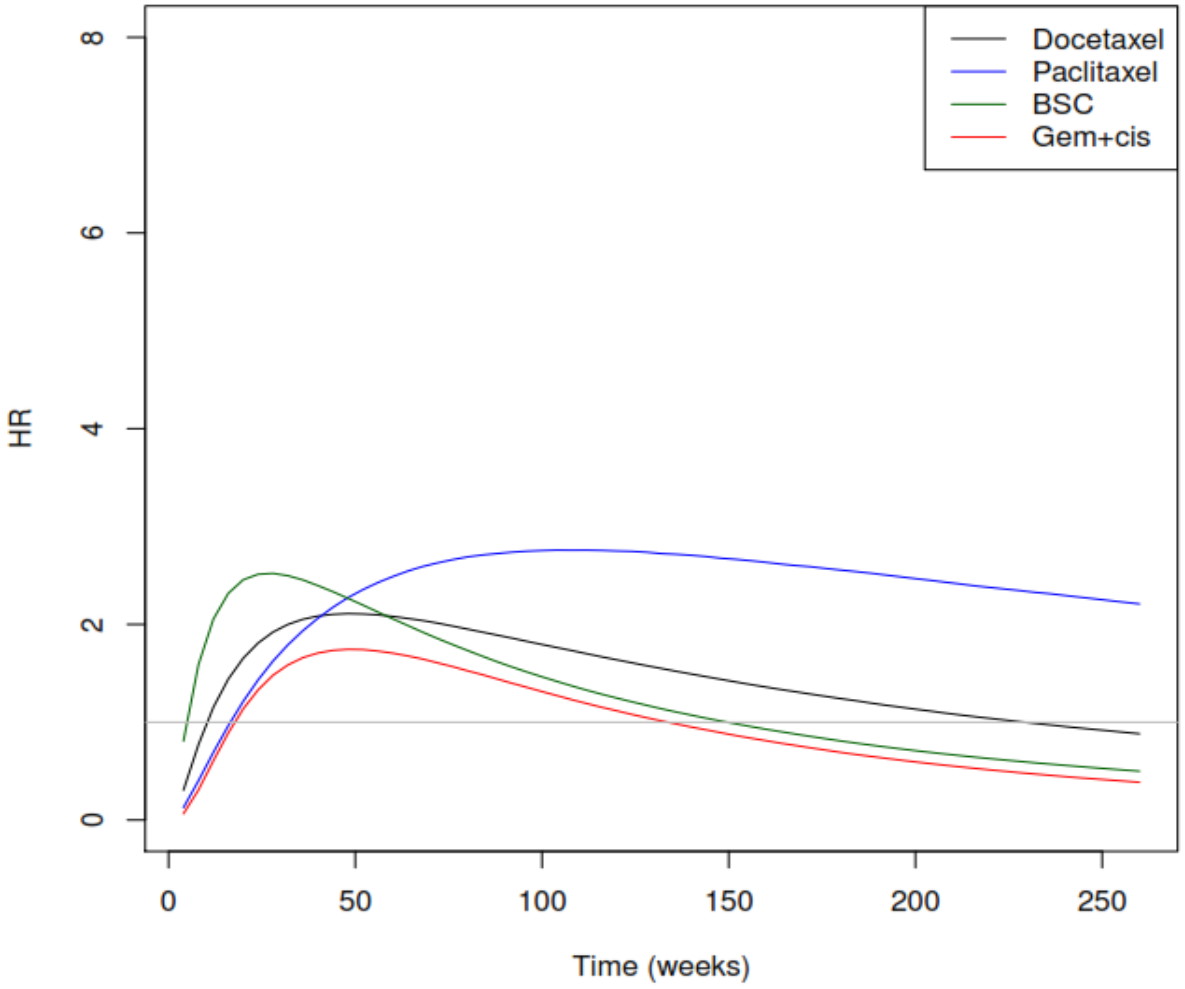
Data included in the STC

Trial ID	Treatment arm	N	PFS definition	Median PFS months (CI)
Sharma et al. (2017) CheckMate 275	Nivolumab	265	Time from first dosing date to the date of the first documented tumour progression, based on BIRC assessments (per RECIST 1.1), or death due to any cause	**2.00** (95% CI 1.87 to 2.63)
Sharma et al. (2016) CheckMate 032	Nivolumab	78	Time from treatment assignment to the date of the first documented tumour progression, as determined by the investigator (per RECIST 1.1), or death due to any cause	**2.78** (95% CI 1.45 to 5.85)
Choueiri et al. (2012)	Docetaxel and placebo	72	Time between random assignment and documented progression per RECIST criteria or death	**1.58** (95% CI 1.48 to 3.09)
Jones et al. (2017)	Paclitaxel	65	NR	**4.1** (80% CI 3 to 5.6)
Petrylak et al. (2016)	Docetaxel	45	Time from random assignment until the first radiographic documentation of objective progression defined by RECIST v1.1 or death resulting from any cause	**2.8** (95% CI 1.9 to 3.6)

Source: Table 25 of CS Appendix D

Overall survival

Network meta-analysis



- A fractional polynomial NMA was favoured over a proportion hazards approach because of different mechanisms of action for the treatments
- A second order (P1=0, P2=0) fixed effect model was used because it provided the most clinically plausible extrapolations
- Estimates hazard ratios (HRs) over time for each pairwise treatment comparison
- HRs > 1 favour nivolumab

Source: Figure 26 (page 63), company submission

Overall survival

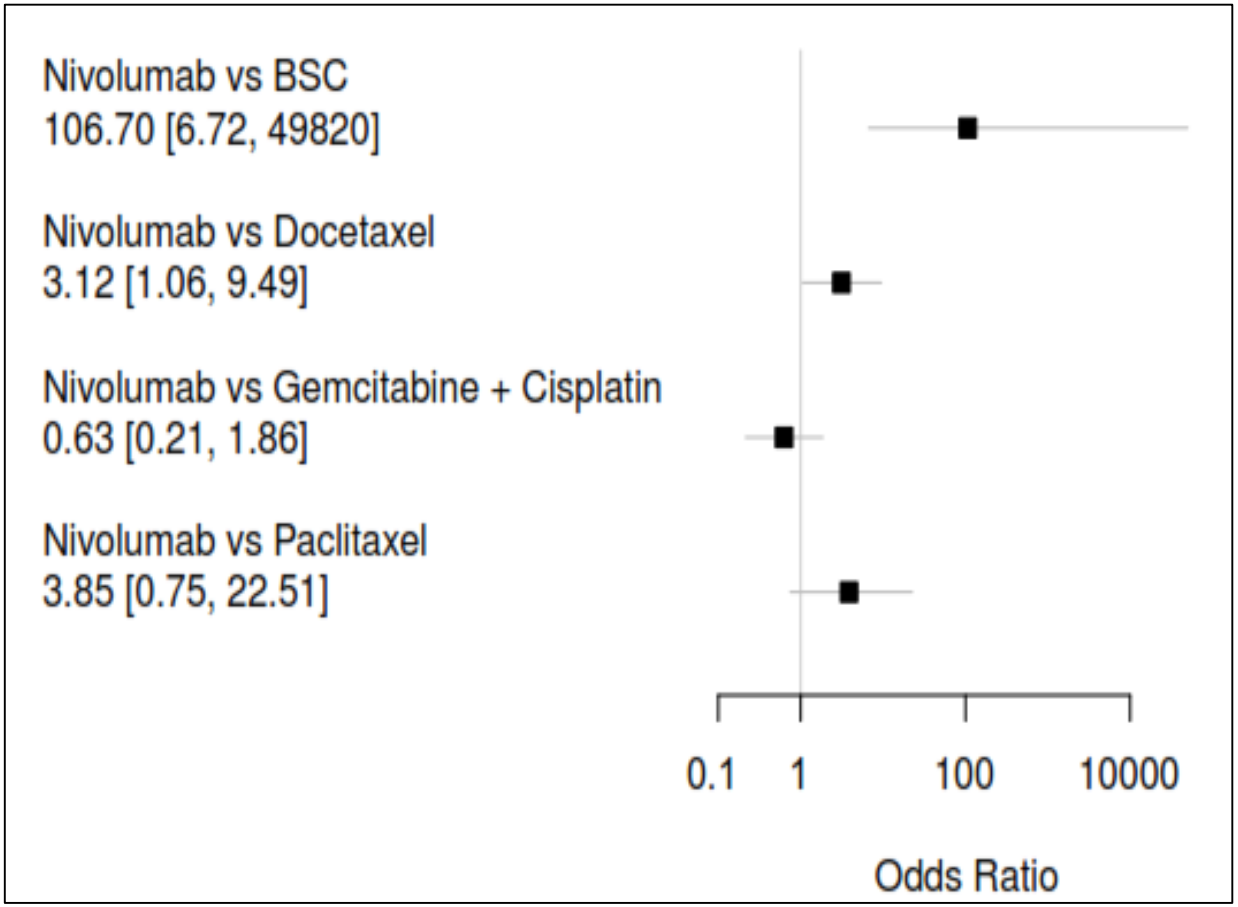
Data included in the STC

Trial ID	Treatment arm	N	Survival definition	Median OS months (CI)
Sharma et al. (2017) CheckMate 275	Nivolumab	265	From first dose and last known date alive or death	**8.74** (95%CI 6.05 to NR)
Sharma et al. (2016) CheckMate 032	Nivolumab	78	From first dose and last known date alive or death	**9.7** (95% CI 7.3 to 16.2)
Bellmunt et al. (2009)	BSC	117	NR	**4.6** (95% CI 4.1 to 6.6)
Choueiri et al. (2012)	Docetaxel and placebo	72	From date of random assignment until date of death	**7.03** (95% CI 5.19 to 10.41)
Jones et al. (2017)	Paclitaxel	65	From the date of randomisation	**8** (80% CI 6.9 to 9.7)
Petrylak et al. (2016)	Docetaxel	45	From random assignment to death resulting from any cause	**9.2** (95% CI 5.7 to 11.7)
Gondo et al. (2011)	Gemcitabine and cisplatin	33	From start of the gemcitabine-cisplatin regimen until date of death or last follow-up	**10.5** (95% CI 3 to 22.9)

Source: Tables 24 and 27 of CS Appendix D

Objective response rate

Network meta-analysis – fixed effects



- ORR was evaluated using an evidence synthesis model for binomial outcomes
- Nivolumab has a higher odds of response than docetaxel or BSC
- No evidence of a difference between nivolumab and the other comparators
- Odds ratio > 1 favours nivolumab

Source: Figure 30 (page 68), company submission

STC results
ERG comment

Overall Response Rate

- Main analysis using the fixed effect model finds that nivolumab is significantly better than BSC and docetaxel
- No significant differences were found for nivolumab compared with paclitaxel and gemcitabine + cisplatin
- In the random effects model nivolumab is only superior to BSC

OS and PFS

- Results show that nivolumab is superior to all comparators at most time points
  - Credible intervals for the HRs are wide, crossing 1 in many cases
- No formal comparison was made of AEs between the comparators
  - However, it appears rates for nivolumab are lower or comparable to those for the comparators
- Naïve indirect comparison results not reported

Clinical effectiveness summary

- No RCTs, single arms in the STC, disconnected network of evidence
- STC methods largely followed DSU TSD18, however without controlling for all baseline characteristics and prognostic variables, it's unclear if all bias will be adjusted for
- Comparison with gemcitabine plus cisplatin excluded from the base-case

ERG Comment:

- It's not clear how the fit of the prediction model was tested
- Small patient numbers and incomplete outcome data
- Survival data are not fully mature in the nivolumab trials
- Uncertainty over the most valid function form for the fraction polynomial model, however it appears valid and flexible for estimating HRs

Regulator comments from EPAR:

- OS outcomes for nivolumab and chemotherapy are similar in those with PD-L1<1%

"..reasonable to assume that the use of nivolumab, also in patients with PD-L<1%, for second line treatment of UC, will provide comparable rates of response to chemotherapy"