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NICE National Institute for Health and Care Excellence

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Lead team presentation

1st appraisal meeting - Committee D

Chair: Peter Jackson

Lead team: Giles Monnickendam, Rebecca Payne and Carole Pitkeathley

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Company: Bristol Myers Squibb (BMS)

Evidence Review Group (ERG): ScHARR (The University of Sheffield)

26th May 2022

Key issues

Key issues from ERG report for discussion	Impact
Issue 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator	
Issue 2: The use of semi-parametric models to fit to disease free survival (DFS) Kaplan Meier (KM) estimates	
Issue 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population	
Issue 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population	
Issue 8: Uncertainty surrounding the assumed cure point	
Additional issues: Subsequent treatments & post DFS modelling	

Resolved Issues

Issue 3: (utility data from Janssen et al) has been resolved during technical engagement: the company updated their submission to use age-dependent utility data from Ara and Brazier

Issue 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274 – ERG provide scenario analysis with an older age

Issue 5: (% of DFS events being deaths) – Company and ERG use pooled data in both arms

Issue 9: (lack of subgroup analysis) – License wording restricts to PD-L1 ≥1% and company updated submission provided clinical and cost-effectiveness analysis for this population

Note: following the company's updated submission, the ERG noted 2 further issues, which they corrected in the company's base case and scenario analysis (model correction + subsequent atezolizumab scenario costs)

Resected high-risk invasive urothelial cancer

Overview of the condition

- Affects transitional cells forming inner lining of the bladder, urethra, ureter, and renal pelvis
- 8,686 new cases in England in 2017
- Affects more men than women (a 3:1 ratio) and incidence increases with age; over half of cases diagnosed in people aged 50 years and over
- Outcomes influenced by how far cancer cells invade bladder layers and commonly described as either non muscle-invasive (NMIBC) or muscle-invasive bladder cancer (MIBC)
- Radical surgery can be performed with the intention of cure but a significant proportion experience disease recurrence

Subgroups and staging

- Estimated that 90% or more of urothelial cancers (UC) arise in the bladder with up to 10% being upper tract urothelial cancer (UTUC)
- Focus of this appraisal is people with muscle-invasive urothelial cancer (MIUC) who have undergone radical surgery and are at high risk of recurrence;
  - MIUC comprises MIBC and UTUC

Patient perspective

Submission from Action Bladder Cancer UK

- Bladder cancer poorly understood and not well known by the public
- Treatment for muscle invasive bladder cancer is drastic, less effective, can be invasive and disease can often recur
- Radical cystectomy is life changing: some may live well without their bladder, but others can suffer from leakages – causing distress and embarrassment
- Many patients are older (in their 60s and 70s) and may have other health issues
- Chemotherapies not well tolerated. Significant number of patients unable or unwilling to take cisplatin (factors such as age and other health conditions)
- Lack of treatment options, therefore a high unmet need: causes high level of physical, emotional and mental stress for both patients and their carers
- Bladder cancer patients in general feel overlooked – outcomes have not improved in many years and compares poorly to other cancers
- Nivolumab represents an innovative treatment, potential lifeline and hope
  - offers potential to prolong and improve life. It is generally well tolerated

> *"Chemotherapy was the first time it sunk in that I was in trouble. Having that stuff injected in you is not a moment I remember with any good feelings - in fact it was the first time I wept (but not the last, as it turned out)…Nine weeks of chemo later, I had somehow spent the last four months on autopilot - floating from one scan to another, from one appointment to another - almost looking down on myself going through this experience."*

Patient perspective

Submission from Fight Bladder Cancer UK

- Most important advantage of nivolumab is increased disease-free survival. Health-related quality of life did not deteriorate in the nivolumab arm compared to placebo
- Pressure on carers to help support their loved ones. Carers report substantial impact on their ability to work, travel, and ability to spend time with family and friends
- Fight Bladder Cancer UK obtained quotes from patients with bladder cancer and carers

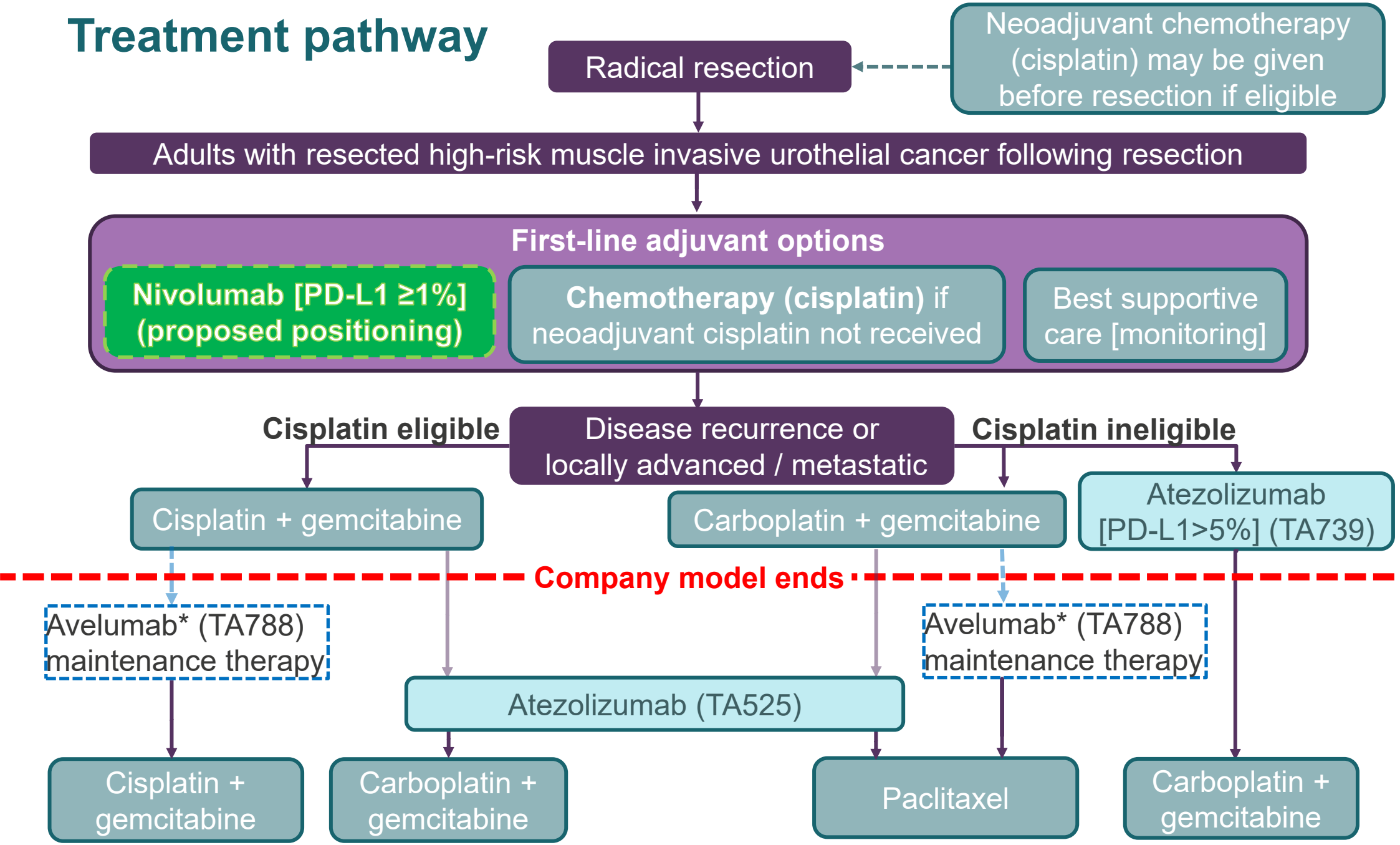
Quotes from patients:

- *"It has been 2 years since I had my radical cystectomy. My health is unpredictable at best. I've struggled with stomach-ache and cramps, diarrhoea, vomiting, breathlessness, phantom pain where things were removed. I have an itchy rash spreading over the area around my stomach. I have good days, bad days, and OK days"*
- *"Two years ago, I was a jabbering mess sat waiting for my operation. Spent 7 days in hospital, home for Christmas and the next few weeks were very hard, but I managed to get back to work full time within 6 weeks. Not going to lie, it was tough but now I am happy with my lot, my life has not changed that much living with a bag, and I am grateful for it every day as it saved my life. Just waiting for results of my annual CT scan now (the waiting is always the worst)."*

Quote from a carer:

- *"My Dad had 13 infusions so far, every 2 weeks. He has completed 6 months on this now. My oncologist says, after recent scans and general condition of my father, the disease can be considered as stable. Thankfully, he had no major side effects from nivolumab so far. He will continue on the same with scan after next 4 infusions"*

Treatment pathway



The company provide a scenario which includes subsequent atezolizumab (TA739) in the BSC arm, ERG provide a scenario with subsequent atezolizumab in both arms

NICE

*published May 2022

Nivolumab (Opdivo, Bristol Myers Squibb)

Description of technology	Fully humanised monoclonal 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. It is administered intravenously.
Marketing authorisation	For the adjuvant treatment of adults with MIUC [Muscle invasive urothelial carcinoma] with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC Summary of product characteristics states that for adjuvant therapy, the maximum treatment duration is 12 months
Dosage and administration	240 mg intravenous infusion every 2 weeks over 30 minutes for a maximum of 12 months
List price	£2,633.00 per 240 mg (24 mL) vial Simple PAS discount approved

Slide updated following granting of GB marketing authorisation

Background

Comparators	NICE Scope: • Adjuvant chemotherapy (e.g. cisplatin-based regimen) • Best supportive care (monitoring and further treatment at recurrence) Note: company do not consider adjuvant chemotherapy to be a relevant comparator (see issue 1)
Subgroups	NICE scope: PD-L1 status. • Company provided updated clinical and cost-effectiveness results by PD-L1 ≥1, in line with the marketing authorisation (see issue 9)
Clinical trial	CheckMate 274 (on-going): Phase III, RCT comparing nivolumab v placebo
Key results	PD-L1 ≥1 population, Disease-free survival, median (95% CI), months: Nivolumab = not reached (22.1,N.E), Placebo = 8.4 (5.6, 20.0)
Indirect treatment comparison	Company provide an indirect comparison v adjuvant chemotherapy, but do not present cost-effectiveness results (see issue 1). ERG considers current analysis only relevant to cisplatin-ineligible population
Model	Markov model with 4 health states (initial disease-free, long-term disease-free, recurrence and death)

Abbreviations CI; Confidence interval, NE; not estimable, RCT: Randomised controlled trail

Evidence from CheckMate 274 (Intention-to-treat population)

Patients enrolled

- Adults who have undergone radical resection of MIUC originating in the bladder or upper urinary tract and are at high-risk^ of recurrence
- Patients who have not received prior neoadjuvant cisplatin chemotherapy must be ineligible for or refuse cisplatin-based adjuvant chemotherapy

Note: patients stratified by PD-L1 status (<1% and ≥ 1%*)

CheckMate 274

Phase 3, double blind, randomised, placebo controlled trial

Nivolumab (n=353, PD-L1≥ 1%* n=140):
240mg IV (30 minutes) at 2-week intervals for a **maximum of 1 year or until recurrence, unacceptable toxicity or discontinuation from study**

Placebo (n=356, PD-L1≥ 1%* n=142)
IV (30 minutes) at 2-week intervals for a maximum of 1 year or until unacceptable toxicity or discontinuation from the study

*:Marketing authorisation is for PD-L1≥ 1%

CheckMate 274 is ongoing.
A data cut from February 2021 (11 months min follow-up) informs this appraisal.
No OS data available at current data-cut

Outcomes

Primary
- Disease-free survival (DFS) ★

Secondary (Selected)
- Overall survival (OS)
- Disease-specific survival (DSS)
- non-urothelial tract recurrence free survival (NUTRFS)

Quality of life data
- EORTC QLQ-C30
- EuroQoL EQ-5D-3L ★

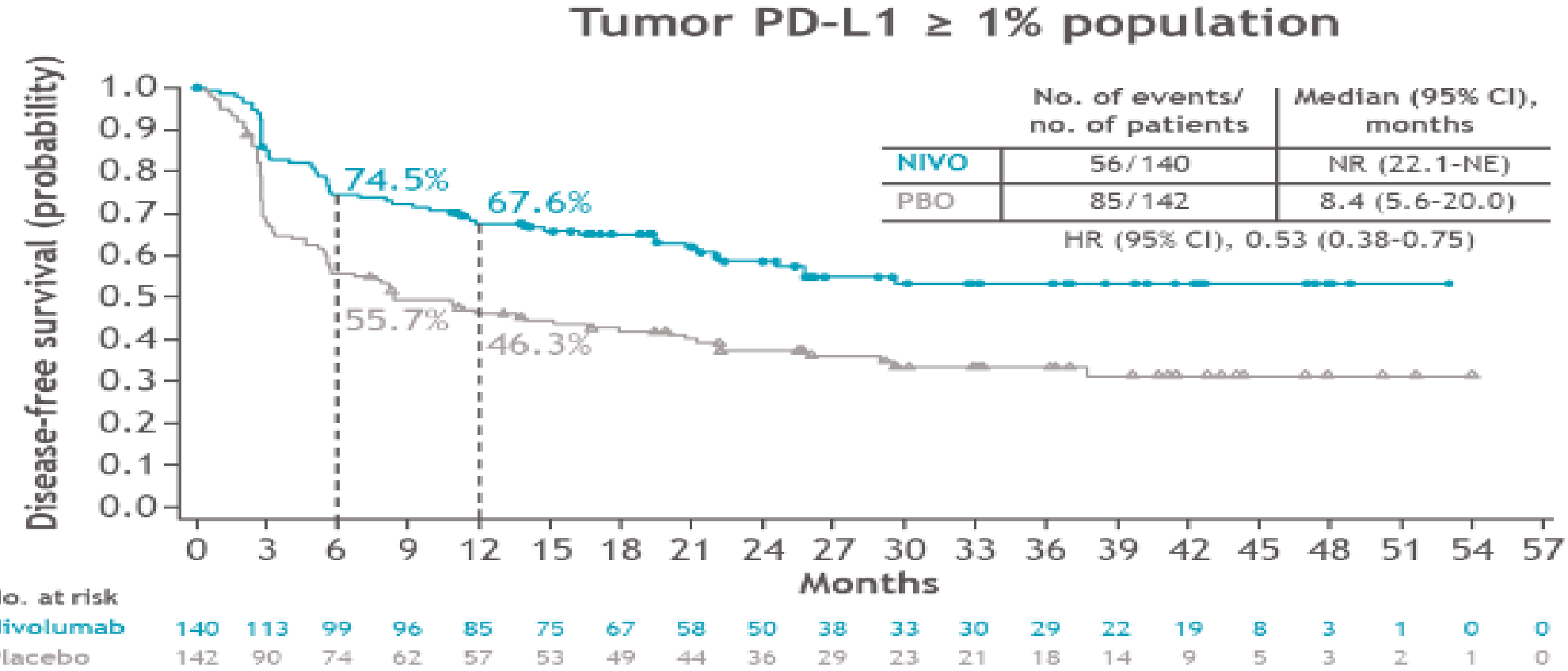
^High risk of recurrence was defined as:
- pathological stage of pT3, pT4a, or pN+ and ineligible or declined adjuvant cisplatin-based combination chemotherapy for patients who had not received neoadjuvant cisplatin-based chemotherapy.
- pathological stage of ypT2 to ypT4a or ypN+ for patients who received neoadjuvant cisplatin (*Bajorin et al*).

★Used in model

Abbreviations: ITT; intention to treat IV;: Intravenous, MIUC; Muscle invasive urothelial cancer, EORTC QLQ; European Organisation for Research and Treatment of Cancer quality of life questionnaire

Results from CheckMate 274 (PD-L1 ≥ 1%)

Kaplan-Meier Curve showing disease-free survival (PD-L1 ≥ 1%)
(Minimum follow-up was 11 months at latest data cut)



Randomised patients	Nivolumab (n=140)	Placebo (n=142)
DFS Events, n (%)	56 (40.0)	85 (59.9)
Median DFS (95% CI), months	Not reached (22.1, N.E.)	8.4 (5.6, 20.0)
Hazard Ratio (% CI)	0.53 (0.38, 0.75)	

Abbreviations N.E: not estimable, CI: confidence interval

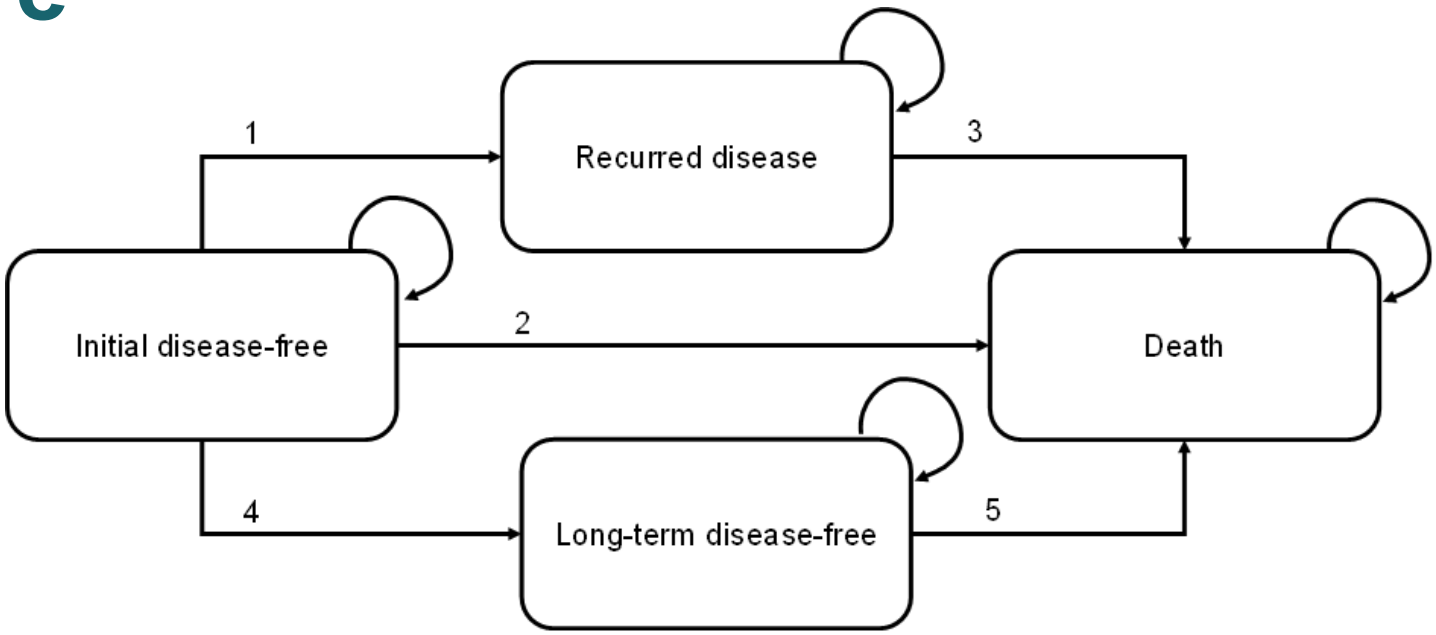
Model structure

Company model:

Markov model, 4 health states with lifetime horizon.

Utility values:

- **Disease-free:** [redacted]
- **Recurred disease disutility:** [redacted]



Modelled cohort of patients aged [redacted] years with [redacted]% male in the company base case. Maximum treatment with Nivolumab = 1 year

DFS state: event occurrence informed by models fitted to CheckMate 274 DFS data (see issue 2)

Long-term disease free state: company's base case assumes disease recurrence does not occur after 5 years post surgery. Uses same mortality rate as the general population (ERG notes clinical advice stating risk of recurrence lower but not zero after 5 years – see issue 8)

Recurred disease state: transitions from this state to death informed by published literature (Bellmunt et al and De Santis et al). (company base case: exponential function)

Abbreviations: DFS: disease-free survival

Post disease free survival modelling

Company's assumes 1 line of treatment after disease recurrence in its model

- After recurrence, probability of death in company model applied as a static probability (exponential extrapolation) in both treatment arms, assuming treatment of cisplatin + gemcitabine or carboplatin + gemcitabine (50/50 split assumed)
- Probability is sourced using data from Bellmunt et al. and De Santis et al: cisplatin (12.7 months median OS), and carboplatin (9.3 months median OS)
- Assumption tested in scenario analysis, where median OS arbitrarily doubled and halved
- Progression post-recurrence not modelled as the company assume treatment costs applied in post-recurrence health state represent any and all further lines of treatment
- Treatment costs/duration applied until death
- ERG correct company error by calculating the rate of exponential distribution and then converting to annual probability (company used linear approach)

Post-recurrence survival (without subsequent atezolizumab scenario) ERG corrected

NICE Source: ERG addendum

Note: ERG correct an error in transitions rates used in the model

Subsequent treatments

Atezolizumab (TA739) + Avelumab (TA788) are recently recommended by NICE. Company's model includes 1 line of treatment in disease recurrence state (see treatment pathway slide)

TA	Recommendations in disease recurrence state
TA788 (May 2022)	Maintenance treatment of locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy
TA739 (Oct 2021)	Untreated locally advanced/metastatic urothelial cancer in tumours express PD-L1 at 5% or more and cisplatin-containing chemotherapy is unsuitable
TA525 (Jun 2018)	Locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy

Company subsequent atezolizumab (TA739) scenario

- Company provide scenario analysis in which people with tumours that express PD-L1 at 5% or more receive atezolizumab following disease progression in BSC arm. Company highlight it is unclear if retreatment with immunotherapy would be permitted
- Median OS data from IMvigor 130 trial (atezolizumab) used to estimate fixed annual transitions assuming [redacted] in BSC arm would receive atezolizumab, based on % in CheckMate 274 whose tumours expressed PD-L1 ≥5% and were within licensed population
- TA788 (avelumab) and TA525 (atezolizumab) do not feature in company's model pathway

ERG correct company costing calculations in the subsequent atezolizumab scenario to match costs reported in TA739 – also include a scenario with atezolizumab in both treatment arms

Issue 1: Cisplatin comparison (1/3)

Company only present cost-effectiveness results for nivolumab vs best supportive care. The NICE scope included adjuvant chemotherapy and best supportive care as relevant comparators.

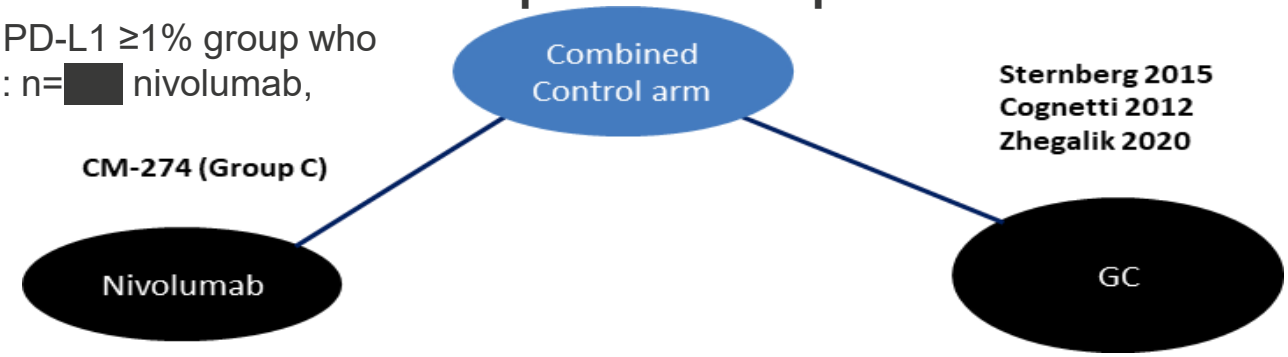
Cancer Drugs Fund Clinical lead comments: Adjuvant cisplatin is particularly likely to be used for upper tract urothelial cancer (UTUC) but use is low in other groups (lack of RCT data)

ERG report comments:

- A proportion of people are likely to be eligible for adjuvant chemotherapy
- Company's indirect treatment comparison shows nivolumab very likely associated with a high ICER or be dominated (more costly + less effective) vs adjuvant chemotherapy
- Current analysis only relevant to cisplatin-ineligible population

Company's indirect treatment comparison v cisplatin-based chemotherapy

CheckMate 274 PD-L1 ≥1% group who refused cisplatin: n=[redacted] nivolumab, n=[redacted] placebo



Combined control arm includes placebo, deferred chemotherapy and treatment (GC) on relapse

Results: HR of nivolumab vs placebo was [redacted] (UTUC patients included) and HR of nivolumab versus adjuvant chemotherapy from two gemcitabine studies (Cognetti 2012 and Zhegalik 2020) and Sternberg pooled was [redacted] (UTUC patients not included in comparator studies).

- Company notes ITC results are not robust enough for decision-making due to limitations such as small sample sizes (under-powered), methodological and design differences between studies

Abbreviations HR: Hazard ratio, CI: confidence interval, GC: Gemcitabine + cisplatin

Issue 1: Cisplatin comparison 2/3

	Comments
Company	• Exclude cisplatin comparison due to clinical relevance and lack of robust evidence base • CheckMate 274 excluded patients cisplatin eligible + willing to receive cisplatin • Trial included patients with a thoroughly documented reason for refusal • Adjuvant cisplatin use varies, from <5% to 30-40% (company clinical experts) • Some people refuse cisplatin: reasons include toxicity and efficacy uncertainty • no clear international consensus on effectiveness of cisplatin • European Association of Urology guidelines do recommend adjuvant chemotherapy for upper tract urothelial cancer (UTUC) • Updated ITC: considerable heterogeneity/limitations, not appropriate to use
NCRI-ACP-RCP-RCR (joint response)	• Exclusion of cisplatin unreasonable, standard of care for majority undergoing nephroureterectomy who have not received neoadjuvant chemotherapy. Adjuvant cisplatin is recommended in NICE guidelines if eligible • UK POUT trial demonstrated activity for carboplatin in place of cisplatin in patients unsuitable for cisplatin due to impaired renal function
Clinical expert 1	• Cisplatin can be considered a comparator for people who have not received neoadjuvant cisplatin and are fit to receive it • % receiving adjuvant cisplatin small (~10-15%) as most receive neoadjuvant cisplatin if fit • People with upper tract urothelial cancers do not get offered neoadjuvant chemotherapy - adjuvant chemotherapy should be a comparator for this group (based on POUT trial results)

Abbreviations NCRI-ACP-RCP-RCR: National Cancer Research Institute, Association of cancer physicians, Royal College of Physicians, Royal College of Radiologists

Issue 1: Cisplatin comparison 3/3

	Comments

Clinical expert 2	• Cisplatin should not be used a comparator:
	  • No RCTs demonstrating a benefit
	  • NICE guidelines state "consider" rather than recommending cisplatin
	  • Adjuvant therapy use variable and mostly confined to node positive cancers. Most at highest risk of recurrence receive no treatment

Action Bladder Cancer	• Including cisplatin as a comparator not meaningful - numbers are low, data is difficult to ascertain, and high dropout rate
Fight Bladder Cancer	• Cisplatin-based adjuvant chemotherapy is rarely used

ERG comments following technical engagement and updated submission:

- None of company sources state % receiving adjuvant chemotherapy is zero
- Acknowledge limitations of ITC, but onus on company to provide evidence showing that nivolumab is more clinically effective than adjuvant cisplatin given cost differences
- Inappropriate to obtain ITC estimate using a mixture of both conditional (from Checkmate274) and marginal effect (from comparator studies)
- UTUC patients included in nivolumab arm but excluded from comparator studies in ITC
- Maintain view that cisplatin-based chemotherapy is a relevant comparator for a small %
- ERG clinical advice states as cisplatin is only given for 6 cycles, it is less burdensome
- Highly likely nivolumab either dominated (more costly and less effective) or associated with an ICER above £30,000 per QALY gained vs cisplatin-based chemotherapy

◉ Is cisplatin a relevant comparator?
◉ If so, should any potential positive recommendation specify use in the cisplatin-ineligible population?

Issue 2: Disease-free survival (1/2)

Kaplan Meier functions from the updated database lock (11 months minimum follow-up) and fitted survival models using the Generalized gamma and Gompertz distributions (CheckMate 274; PD-L1 ≥ 1%)

ERG suggest the Gompertz distribution is informative however minimal impact on ICER.

The **company** uses a Generalized gamma distribution to model DFS for both treatment arms.

NICE Source ERG updated report figure 7

Abbreviations: DFS: disease-free survival

Issue 2: Disease-free survival (2/2)

ERG comments:

- Choice of Generalized gamma over Gompertz is subject to a number of limitations:
  - Generalized gamma distribution has 3 parameters, Gompertz has 2 parameters. Allows greater flexibility and better fit to protocol induced features
  - Fitting to these features may be undesirable if patterns not observed in clinical practice (if underlying hazard monotonically decreasing rather an increasing hazard which peaks at first tumour assessment and then declines)
  - B-spline versions of smoothed hazard are monotonically decreasing (more aligned with Gompertz distribution)
  - However, hazards for Gompertz fall below those of the general population at ~[redacted] in nivolumab arm, and ~[redacted] in placebo arm, which is implausible
  - Generalized gamma distribution has hazards higher than that of the general population at 5 years – which does not align with the company's 5-year cure assumption
- Small differences in estimated survival between distribution choices for PD-L1 ≥1% population explain minor impact of ICER on choice between Generalized gamma and Gompertz distributions

◉ Which extrapolation is the most appropriate to use to model disease-free survival?

NICE

Abbreviations: ICER: Incremental cost-effectiveness ratio

Issue 6: DFS utility values (1/2)

Company assumes people in DFS health states have the same health utility as those in general population (age and sex matched)

ERG report: Clinical advice to the ERG, and published evidence, states that having a history of urothelial cancer has a detrimental impact on quality of life. ERG apply a 0.02 decrement on general population utility values to assess impact on cost-effectiveness

Technical engagement responses

	Technical engagement comments
Company	• DFS utility values from CheckMate 274 exceed those of general population • ERG's 0.02 decrement is arbitrary and small (indicating ERG expect negligible disutility). Impact on ICER is minimal • Base case unchanged. 0.02 disutility scenario analysis provided
Clinical expert 1	• Impact of radical surgery on QoL well documented and there will be treatment related toxicities. These are short lived and patient adapt to surgical changes • We routinely see these patients enjoying a fully functional lifestyle and good quality of life
Clinical expert 2	• Patients living beyond BC have marginally worse QoL than general population • Some aspects are similar to general population (e.g EQ-5D) while others differ (disease-specific measures) and sexual issues are more common • Agree QoL similar but may be marginally worse than that of the general population (bladder cancer populations also have other co-morbidtiies)

Abbreviations: DFS: disease-free survival, QoL: quality of life, BC: bladder cancer

Issue 6: DFS utility values (2/2)

Technical engagement responses (continued)

	Technical engagement comments
NCRI-ACP-RCP-RCR	• Whilst many people have negative impacts from permanent changes in urinary and sexual function, the impact of these on overall utility are known to be short-lived as people adapt
Action Bladder Cancer	• Loss of function (or disability or dysfunction) does not of itself lead to a loss in QoL. Perfectly possible to have a high quality of life with a disability
Fight Bladder Cancer	• The quality of life for a person with resected high-risk urothelial cancer is similar to that of those who are disease-free

ERG comments following technical engagement and company updated submission:

- Acknowledge arbitrary nature of 0.02 utility decrement value, but consider it more plausible than no disutility (which is not aligned to clinical advice received by ERG)
- ERG maintains 0.02 utility decrement in base case until timepoint where no excess mortality is assumed (cure point – see issue 8).

◉ Should DFS health states be modelled with using a general population utility value or should a disutility be applied?

Abbreviations: DFS: disease-free survival, QoL: quality of life

Issue 7: Long term DFS life expectancy

Company assumes that people in long-term disease free health state have the same life expectancy as the matched general population

ERG report: Plausible that life expectancy in people with resected UC who have not had a DFS event within five years will be shorter than that who do not have resected UC.

Technical engagement responses

Company:

- Maintains base case assumption of matched general population mortality after 5 years disease free – which was informed by clinical expert input
- Standardised Mortality Rate (SMR) of 1.1 used by ERG is arbitrary (with minimal impact on the ICER) and no data to suggest an alternative value to use

	Technical engagement comments
Clinical expert (1)	• For people who are disease free from urothelial cancers after 5 years, the relapse rate remains extremely low. Most clinicians discharge patients from hospital follow up after 5 years
Clinical expert (2)	• Most cancer recurrences occur within 5 years of radical cystectomy • After this time, survival matches general population/normal life expectancy • For example, outcomes from the last 1,100 Cystectomies in Sheffield (*Eur Urol Focus. 2021*). Show after 5 years that bladder cancer recurrence rates are low and so patient survival matches that of general life expectancy

Abbreviations: UC: urothelial cancer

Issue 7: Long term DFS life expectancy (2)

Technical engagement responses (continued)

	Technical engagement comments
NCRI-ACP-RCP-RCR	• Most clinicians accept increased relapse or death from urothelial cancer in people who have remained alive and recurrence-free for 5 years is so low, that they are generally discharged from follow up for relapse
Action Bladder Cancer	• Strongly agree with company assumption • No evidence to support ERG assumptions

ERG comments following technical engagement and updated company submission:

- Data from *Sternberg et al.* shows hazard of death much higher at 5 years in the deferred arm (a population the company states is similar to that of this appraisal)
- Generalized gamma distribution for DFS also indicates a higher risk of death than that of the general population
- ERG estimated increased risk of death in long term DFS state:
  - ERG scenario analysis uses a standardised mortality rate (SMR) of [redacted] (hazard of DFS event at month 60 in model divided by all cause mortality for that time) for a period of 5 years

◉ what mortality rate should be applied to the long-term disease-free health state?

Issue 8: Cure point (1/2)

Company assume that after 5 years in DFS state, there will not be a disease recurrence

ERG report: Clinical advice to the ERG suggests that whilst the recurrence rate diminishes as the time since resected UC increases, it is not zero after 5 years.

Technical engagement responses and updated submission

Company:

- Retain 5-year cure timepoint, based on clinical opinion, published literature and trial data
  - CheckMate 274 trial hazards approach those of general population at 5 years
  - Clinical experts state recurrence after 5 years is rare
  - *Sternberg et al.* data shows a plateau of survival curves around 4 years
- ERG 10-year cure point based on Hautmann et al uses a dataset from 1986 to 2009 with people who did not have neoadjuvant chemotherapy. Survival therefore likely underestimated
- ERG alternative source (Soria et al): used data from 1998 to 2012, no neoadjuvant chemotherapy use and included high risk non-MIUC patients refractory to intravesical chemotherapy or immunotherapy.

	Technical engagement responses
Clinical expert (1)	• Relapse rate after 5 years is extremely low • There is never no risk of death from bladder cancer. Other co-morbidities may also exist, given the age of the population
Clinical expert (2)	• No fixed time at which chance of recurrence is zero with 100% certainty • Would use a 5-year timepoint as a cure, as the NHS guidelines are to discharge patients after 5 years

Abbreviations: MIUC: muscle invasive urothelial cancer

Issue 8: Cure point (2/2)

	Technical engagement comments
NCRI-ACP-RCP-RCR	• While clinicians usually discharge patients after 5 years disease-free, the risk of relapse is never zero • Note that ERG use data from a population who did not have neoadjuvant chemotherapy in their analysis
Action Bladder Cancer	• Possible that risk of recurrence after 5 years may be higher than some other cancers, but little evidence to show any particular significant alternative timepoint • Disease-free for 5 years is a meaningful turning point

Fight Bladder Cancer	• No clear consensus from the patient perspective, patient responses include:
	  • They are told after 5 years there are no check-ups
	  • Told not to use the term “cancer free”
	  • Told all clear after 10 years
	  • Not considered cancer free until 5 years
	  • Others feel like they would never consider themselves “cured” but rather having no evidence of disease

ERG comments following technical engagement and updated company submission:

- *Sternberg et al* study shows increased risk of death after 5 years for people with resected UC compared to general population
- ERG run exploratory analysis using a 10-year cure point

◉ what cure point should be used in the model?

Additional issue: Post DFS modelling

The company's model adopts a simplified approach to model post DFS outcomes, and does not include all potential treatment lines or treatment options

- There are several potential treatments available following disease recurrence
- Company's model includes only 1 line of treatment post-DFS and does not include NICE recommended treatment options TA525 (atezolizumab after platinum-based chemotherapy) or TA788 (avelumab for maintenance treatment after platinum-based chemotherapy)
- Company's model uses a simplified approach to model post-DFS outcomes, using constant hazards/exponential distribution (i.e. static transitions). A more robust approach with tunnel states could have been used, allowing transition probabilities and costs to vary over time.
- The committee lead team/NICE technical team, following discussions with the ERG, suggest that in general, the simplified approach taken by the company and omissions of some therapy options from the model are unlikely to impact on decision making (ICER would likely decrease if treatments that are priced at or close to the threshold are added into the model in the advanced stage)
- The committee lead team/NICE technical team note that, in this case, the company model is unlikely to bias results in favour of nivolumab in the post-DFS state, but note a more robust approach would have been preferred

◉ Is the committee satisfied that the post DFS modelling approach by the company does not bias results in favour of nivolumab?

Cost-effectiveness analysis

Summary of key cost-effectiveness scenarios

Company analysis →

Company base case	Issue no.
Generalized gamma distribution for DFS	2
Long-term DFS state same life expectancy and utility as general population	7
Cure point of 5 years	8

Key ERG analysis →

ERG analysis	Issue no.
Use of alternative DFS survival function (Gompertz)	2
Exploratory analysis with higher mortality than that of the general population in long-term DFS health state	7
Extending the cure point to 10 years	8

All ERG scenarios include a utility decrement of 0.02 until a full cure is assumed

Both the Company (BSC arm only) and ERG (BSC arm and both model arms) also provide exploratory analysis which incorporates subsequent atezolizumab treatment following disease progression based on TA739 recommendation (results presented in part 2)

Cost-effectiveness results

Company base case (deterministic) – ERG corrected*							
Generalized gamma distribution for DFS							
Cure point of 5 years							
Long-term DFS state same life expectancy and utility as general population							
Options	**LYGs**	**QALYs**	**Cost**	**Inc. LYGs**	**Inc QALYs**	**Inc Costs**	**ICER**
BSC	XXXX	XXXX	XXXX				
Nivolumab	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	**£11,361**

ERG scenario analysis

Scenario	Distribution used to model DFS	Cure time point (years)	Time point considered fully cured†	Utility decrement applied for DFS?
ERG Alternative Scenario 1	Generalized gamma	5	10	Yes
ERG Alternative Scenario 2	Gompertz	5	5	Yes
ERG Alternative Scenario 3	Generalized gamma	10	10	Yes

†At which point the risk of death and utility are assumed to be equal to the age- and sex-matched general population values.

NICE *Note: ERG identified an error in post DFS transitions rates used in the model and correct for this

All ICERs are deterministic – includes PAS for nivolumab

ERG Scenario analyses

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case (error corrected as per key issue 10)							
BSC	XXXX	XXXX	XXXX				
Nivolumab	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	£11,361
ERG ASA 1 ICER†							
BSC	XXXX	XXXX	XXXX				
Nivolumab	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	£13,758
ERG ASA 2 ICER†							
BSC	XXXX	XXXX	XXXX				
Nivolumab	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	£12,114
ERG ASA 3 ICER†							
BSC	XXXX	XXXX	XXXX				
Nivolumab	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	£11,259

Note: ERG identified an error in post DFS transitions rates used in the model and correct for this

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

† Assumed applicable only to those in whom cisplatin-based chemotherapy would not be an option (see Issue 1)

All ICERs are deterministic, includes PAS for Nivolumab

Equality considerations, innovation and end of life criteria

Innovation

Comments from submissions

- Company: MHRA promising innovative medicine (PIM) designation and first immunotherapy to demonstrate superior efficacy to placebo in adjuvant setting after radical surgery for MIUC
- Patient groups: Nivolumab offers prospect of a step change improvement in outcomes in a patient population with high unmet need

Equality issues

- Fight Bladder Cancer UK: Women often diagnosed much later with bladder cancer. Women are also more likely to die of bladder cancer

End of life criteria

- The company does not make a case for nivolumab meeting NICE's end of life criteria

◉ Is nivolumab considered innovative? Are there any potential equality issues?

Abbreviations: MIUC: muscle invasive urothelial cancer, MHRA: Medicines and Healthcare products Regulatory Agency

Cancer Drugs Fund

CheckMate 274 trial is currently ongoing.

Committee decision-making criteria:

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.