# Lead team presentation

## Atezolizumab for treating locally advanced or metastatic urothelial carcinoma– STA

**Clinical effectiveness**

1st Appraisal Committee Meeting: 26 April 2017
Committee D

Evidence Review Group: Southampton HTA Centre
Lead Team: Rebecca Harmston and Sumithra Maheswaran

# Metastatic urothelial carcinoma

## *Disease background*

- There are around 10,100 new cases of bladder cancer in the UK each year, resulting in 5,400 deaths
- 90% of bladder cancers are urothelial carcinomas
  - remainder are squamous cell bladder cancers (5%) and adenocarcinomas of bladder (1–2%)
- 90–95% of urothelial carcinomas develop in bladder
  - tumours can also originate in renal pelvis, urethra or ureter as these are also lined by urothelial cells
- 55% of new cases occur in people 75+, ~75% in men
- 5-year survival rate for metastatic disease ~6%

# Impact on patients and carers

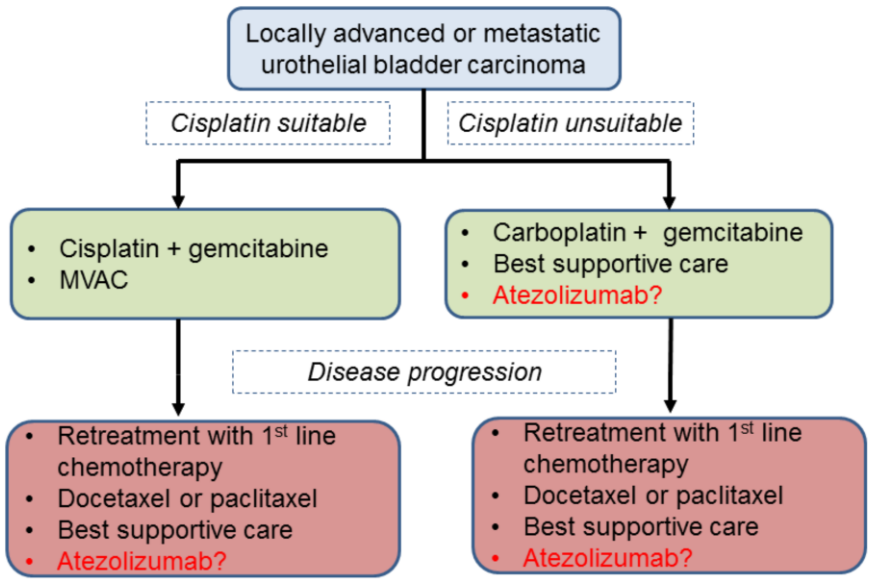
- Symptoms include: haematuria (blood in urine), pain at site of primary tumour or metastatic disease, increased frequency, urgency and pain associated with urination
- Awareness is low and surgical treatments such as urostomy can have a substantial impact on quality of life and daily activities
- Older age of diagnosis means many people have co-morbidities which can affect treatment decisions
- Current treatments for advanced disease have poor outcomes
- Cisplatin is unsuitable for some people as it can be very harmful for the kidneys; there is a need for alternative therapies
- Prolonging life, improved quality of life, minimal side effects and complete response are important outcomes
- As an immunotherapy atezolizumab may have fewer side effects than chemotherapy treatment which can cause neutropenic fever, nausea and diarrhoea and require in-patient treatment

# Atezolizumab (Tecentriq), Roche

| | |
|---|---|
| **Mechanism of action** | Monoclonal antibody that binds to and inactivates a protein called programmed death ligand 1 (PD-L1) leading to downstream activation of T cells that can detect and attack tumour cells |
| **Marketing authorisation** | • Anticipated marketing authorisation: [redacted]<br>• CHMP positive opinion expected [redacted]<br>• Full marketing authorisation expected [redacted]<br>• Has early access to medicines scheme status for use in people who have had platinum-based chemotherapy |
| **Administration and dose** | • 1,200 mg intravenous infusion every 3 weeks<br>• Treatment continues until loss of clinical benefit or unmanageable toxicity |
| **Cost** | • List price: [redacted] per 1200-mg vial<br>• Annual cost: [redacted] |

[a]The company has also applied for a marketing authorisation [redacted] This is being appraised separately.

# Clinical pathway of care



# Decision Problem - **population**

| NICE scope | Company submission | Company rationale |
|---|---|---|
| Adults with locally advanced or metastatic urothelial carcinoma:<br><br>• Whose disease has progressed after prior chemotherapy<br>• For whom cisplatin-based chemotherapy is unsuitable | • Populations based on IMvigor 210 trial:<br>– 1st line, cisplatin-based chemotherapy is unsuitable<br>– 2nd line, disease progression after platinum-based chemotherapy<br>• 2nd line population includes people for whom cisplatin is unsuitable and who have had platinum-based chemotherapy; they are separated in scope | • Treatment patterns and response rates for people having 2nd line therapy do not differ based on suitability of cisplatin<br>• Comparators are the same |

# Decision Problem - **comparators**

| NICE scope | Company rationale | ERG comment |
|---|---|---|
| 1. Cisplatin-based chemotherapy unsuitable:<br>• Gemcitabine + carboplatin<br>• ~~Best supportive care~~ | • People having BSC 1st line must be unable/unwilling to have any active therapy including atezolizumab<br>• No data; no comparison possible | • Atezolizumab likely to have better safety profile than chemotherapy and may be option for some people unable/unwilling to have chemotherapy |
| 2. Disease progressed after platinum-based chemo; 3. Cisplatin-based chemotherapy unsuitable, disease progressed after platinum-based therapy:<br>• ~~Retreatment with 1st line platinum-based therapy~~<br>• Docetaxel, paclitaxel<br>• Best supportive care | • Retreatment with 1st line therapy is an option for a small number of people and not standard care in England<br>• No data; no comparison possible | • Reasonable approach given limited evidence base |
| **~~Red~~ = in scope but not in company's submission** | | |

# Trial evidence – IMvigor 210, single-arm trial

| | IMvigor 210 |
|---|---|
| **Description** | • Multicentre (3 UK), open-label, single-arm, phase II<br>• Cohort 1: previously untreated, unsuitable for cisplatin-based chemotherapy (n=119)<br>• Cohort 2: disease progression after platinum-based chemotherapy (n=310) |
| **Eligibility criteria** | • People with locally advanced or metastatic urothelial carcinoma<br><u>Cohort 1:</u><br>• ECOG≤2<br>• No prior chemotherapy, unsuitable for cisplatin<br><u>Cohort 2:</u><br>• ECOG≤1<br>• Disease progression following treatment with at least 1 platinum containing regimen (≥2 cycles) |
| **Outcomes** | 1º: Independent review-facility assessed objective response rate (ORR), according to RECIST criteria<br>2º: Overall survival, progression-free survival, duration of response |

# IMvigor 210 – Baseline characteristics

| | | Cisplatin unsuitable (1st line) | Previous chemotherapy (2nd line) |
|---|---|---|---|
| **Male** | | 81% | 78% |
| **Age: median (range)** | | 73 (51–92) | 66 (32–91) |
| **≥80 years** | | 21% | 7.7% |
| **ECOG performance status score** | | 0 = 38%<br>1 = 42%<br>2 = 20% | 0 =38%<br>1 = 62% |
| **Visceral metastasis** | | 66% | 78% |
| **Tumour site** | **Bladder/urethra** | 71% | 77% |
| | **Renal pelvis/ureter** | 28% | 22% |
| **Prior therapy** | **Cisplatin-based** | 15% | 73% |
| | **Carboplatin-based** | 1% | 26% |
| | **Number of prior therapies (for metastatic disease)** | 0 = 98%<br>1 = 2% | 0 = 18%<br>1 = 39%<br>2 = 21%<br>≥3 = 22% |

# ERG comment on baseline characteristics

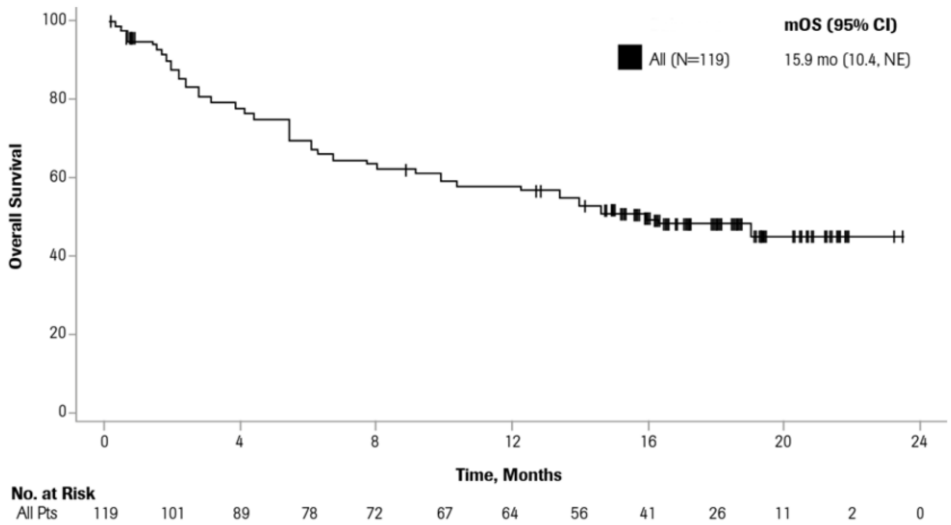
- 20% of patients for whom cisplatin is unsuitable (1st line population) had ECOG = 2, 66% visceral metastases and 21% liver metastases
  - reflects population with poor prognostic factors
- 43% of patients who had previous chemotherapy (2nd line population) had ≥2 regimens for metastatic disease
  - heavily pre-treated population
- High proportion primary tumour site renal pelvis or ureter (28% and 22%) compared with 5–10% in clinical practice
  - more likely to be invasive at diagnosis and have worse prognosis than those in the bladder
- Few UK patients (n=22), but ERG's clinical adviser believes trial population generalisable to those with advanced or metastatic bladder cancer in England

# IMvigor 210 – results

| | Cisplatin unsuitable (1st line) n=119 | Previous chemotherapy (2nd line) n=310 |
|---|---|---|
| **Primary analysis** | **6 month follow-up** | **6 month follow-up** |
| **Objective response rate, % (95% CI)** | 19.3 (12.66 – 27.58) | 15.1 (11.3-19.6) |
| **Updated analysis** | **15 month follow-up** | **20 month follow-up** |
| **Objective response rate, % (95% CI)** | 22.7 (15.52 – 31.27) | 15.8 (11.9 – 20.4) |
| ***-historical controls ORR*** | *10.0* | *10.0* |
| **Median PFS, months (95% CI)** | 2.7 (2.1 – 4.2) | 2.1 (2.1 – 2.1) |
| **Median OS, months (95% CI)** | 15.9 (10.4 – not estimable) | 7.9 (6.7 – 9.3) |
| **12 month survival, % (95% CI)** | 57.2 (48.2 – 66.3) | 36.9 (31.4 – 42.3) |
| **Median treatment duration (range)** | 15 weeks (0 – 102 weeks) | 12 weeks (0 – 104 weeks) |

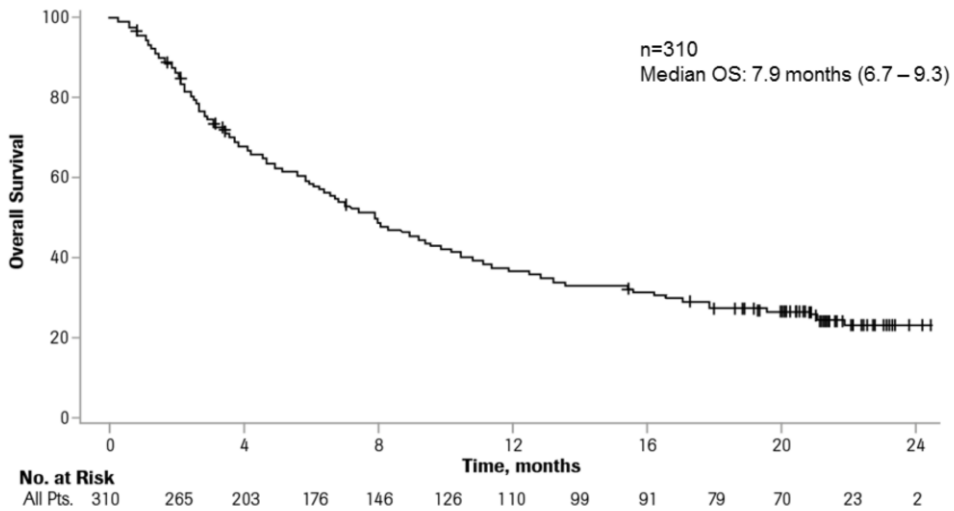
# IMvigor 210 – overall survival

## *Cisplatin unsuitable (1st line)*



# IMvigor 210 – overall survival

## *Previous chemotherapy (2nd line)*



# IMvigor 210 – PD-L1 subgroups

| Cisplatin unsuitable (1st line) – 6 month follow-up | | | |
|---|---|---|---|
| | **All patients (n=119)** | **PD-L1 expression ≥5% (n=32)** | **PD-L1 expression ≥1% (n=80)** |
| **ORR % (95% CI)** | 19.3 (12.66 – 27.58) | 21.9 (9.28 – 39.97) | 18.8 (10.89 – 29.03) |
| **Complete response % (95% CI)** | 5.0 (1.87 – 10.65) | 3.1 (0.08 – 16.22) | 3.8 (0.78 – 10.57) |

| Previous chemotherapy (2nd line) – 6 month follow-up | | | |
|---|---|---|---|
| | **All patients (n=311)** | **PD-L1 expression ≥5% (n=100)** | **PD-L1 expression ≥1% (n=208)** |
| **ORR % (95% CI)** | 15.1 (11.3 – 19.6) | 27.0 (18.6 – 36.8) | 18.3 (13.3 – 24.2) |
| **Complete response % (95% CI)** | 3.9 (2.0 – 6.6) | 8.0 (3.5 – 15.2) | 5.3 (2.7 – 9.3) |

# Indirect treatment comparison

- No comparative efficacy data for atezolizumab
- Company conducted simulated treatment comparison using cox regression
  - key prognostic factors identified and atezolizumab individual patient data was adjusted and used to predict atezolizumab outcomes for comparator trials
  - effectively building an atezolizumab 'arm' into each trial
- Network meta-analysis constructed linked together through atezolizumab 'arms'
- Network meta-analysis used fractional polynomial model
  - allows analysis of outcomes at multiple time-points
  - company believes proportional hazards assumption likely to be violated (based on appraisals of immunotherapies in melanoma and lung cancer) so traditional survival models not appropriate

# Indirect treatment comparison

## *Prognostic factors*

- Company identified 4 characteristics which predict clinical outcomes:
  - age (≥65 years)
  - gender (male)
  - performance status (ECOG≥1 or Karnofsky ≤90%)
  - presence of liver metastases at baseline
- Comparator studies all reported ≥3 factors
  - for missing data, company imputed values by generating random values

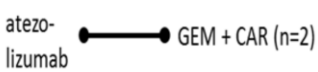
# ERG comment on simulated treatment comparison

- Fundamental assumption: all prognostic factors have been included in the analysis
  - company only included up to 4 which may limit how well the simulated atezolizumab arms match the comparator arms
  - re-treatment interval could have been considered
  - age and performance status important but correlated
- Selection of the prognostic factors is not well-justified
  - e.g. no empirical evidence for age cut-off at ≥65 years
- Method of imputing missing data and multiple errors and inconsistencies add to uncertainty

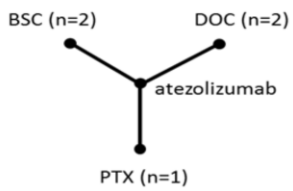
# Network meta-analysis (NMA)

- Outcomes: overall survival, 12-month survival, objective response rate, progression-free survival
  - only overall survival used in the economic model

Network for overall survival
Cisplatin unsuitable (1st line)




Network for overall survival
Previous chemotherapy
(2nd line)



# Included studies

## *Cisplatin unsuitable (1st line)*

| | Bamias et al. | De Santis et al. | IMvigor 210 |
|---|---|---|---|
| **Description** | Single arm, phase II, n=34 | RCT, n=119 | Single arm, phase II, n=119 |
| **Intervention of interest** | Gemcitabine + carboplatin | Gemcitabine + carboplatin | Atezolizumab |
| **Age ≥65 years** | 94% | 65% | 83% |
| **Gender (male)** | 82% | 76% | 81% |
| **Performance status** | ECOG ≥2: 68% | ECOG ≥1: 83% | ECOG ≥1: 62% |
| **Liver metastases** | - | 17% | 21% |
| **Study results** | | | |
| **Median PFS** | 4.4 months | 5.8 months | 2.7 months |
| **Median OS** | 9.8 months | 9.3 months | 15.9 months |

- Not reported

# Included studies

## *Previous chemotherapy (2nd line)*

| | Bellmunt et al. | Choueiri et al. | Kim | Lee et al. | Noguchi et al. | IMvigor 210 |
|---|---|---|---|---|---|---|
| **Description** | RCT, n=117 | RCT, n=75 | Single-arm, n=31 | Single-arm, n=37 | RCT, n=41 | Single-arm, n=310 |
| **Intervention of interest** | BSC | Docetaxel + placebo | Docetaxel | Paclitaxel* | BSC | Atezolizu-mab |
| **Age ≥65** | 44% | 46% | 46% | 17% | 50% | 59% |
| **Gender** | 78% | 68% | 77% | 78% | 80% | 78% |
| **Performance status ≥1** | 69% | 53% | 100% | 62% | 20% | 62% |
| **Liver mets.** | - | 38% | 32% | 30% | - | 31% |
| **Study results** | | | | | | |
| **Median PFS** | - | 1.6 months | 1.4 months | 2.7 months | 1.8 months | 2.1 months |
| **Median OS** | 4.6 months | 7.0 months | 8.3 months | 6.5 months | 4.1 months | 7.9 months |

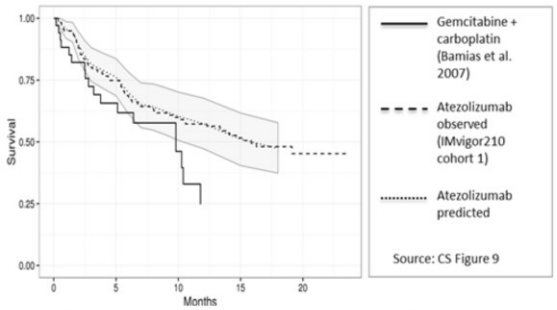
- Not reported
* Polyethoxylated caster oil-free, polymeric micelle formulation

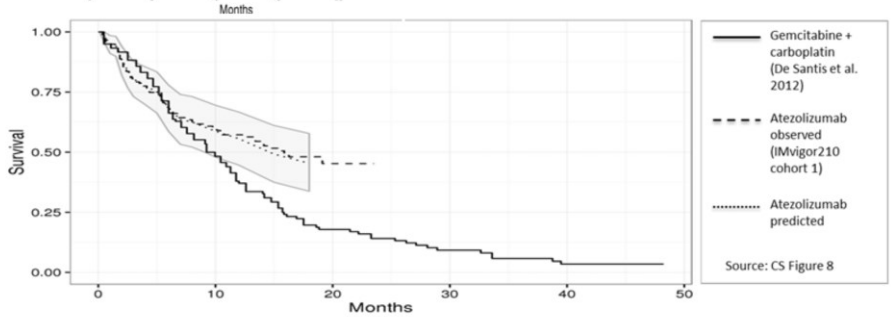
# ERG comment on network meta-analysis

- Hard to assess heterogeneity of included studies (e.g. prior therapies not consistently reported)
- Results are presented as log-hazard function curves and their intercept and slope because hazard ratio varies over time
  - company provides no guidance on clinical interpretation of these parameters or discussion of clinical effectiveness results from the NMA
- The NMA produced clinically implausible results: PFS not used in model and the company caps hazard ratios for overall survival to obtain plausible results
- No sensitivity analyses to test robustness of the simulated treatment comparison or NMA methods, adding to uncertainty

# NMA results – cisplatin unsuitable (1st line)

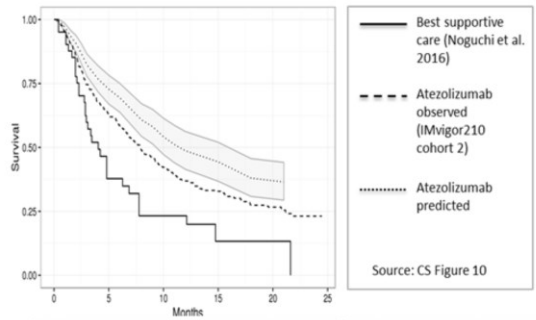
## *gemcitabine + carboplatin, overall survival*

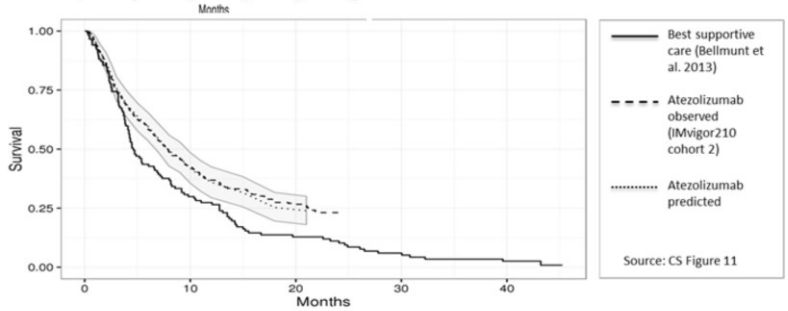


# NMA results – previous chemotherapy (2nd line)

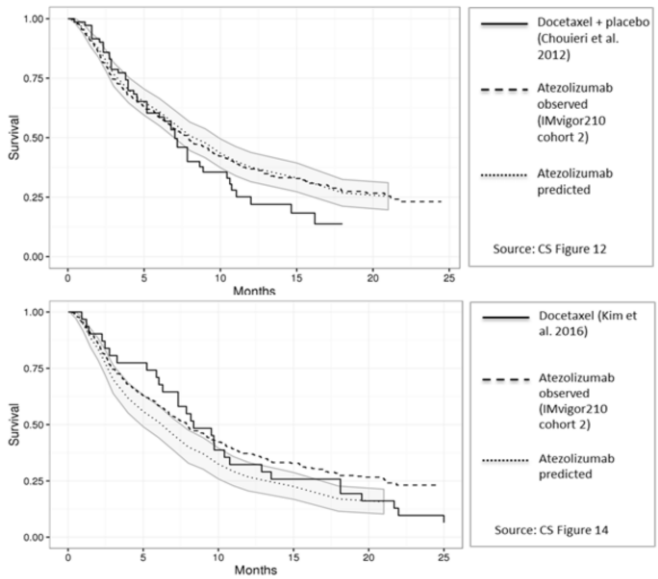
## *BSC, overall survival*



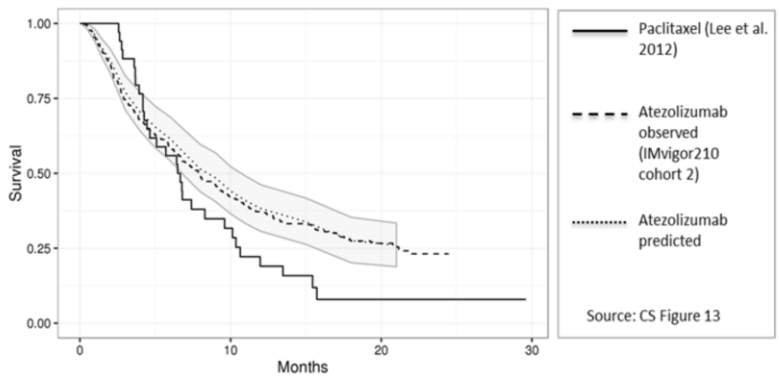



# NMA results – previous chemotherapy (2nd line)

*docetaxel, overall survival*



# NMA results – previous chemotherapy (2nd line)
*paclitaxel, overall survival*



# Adverse events

- Most commonly reported treatment-related adverse events in IMvigor 210 were
  - cisplatin unsuitable: fatigue (30%), diarrhoea (12%) and pruritus (11%)
  - previous platinum-based chemotherapy: fatigue (31%), nausea (27%), pyrexia (22%), vomiting (19%), arthralgia (18%), pruritus (12%), rash (12%), decreased appetite (11%) and chills (11%).

# On-going trials

- IMvigor 211
  - phase III, open-label RCT (n=932)
  - previously treated metastatic urothelial carcinoma
  - atezolizumab compared with investigator's choice of vinflunine, docetaxel or paclitaxel
  - estimated completion date: November 2017
- IMvigor 130
  - phase III, double-blind RCT (n=1,200)
  - previously untreated metastatic urothelial carcinoma
  - Arm A: atezolizumab monotherapy
  - Arm B: atezolizumab + gemcitabine + carboplatin
  - Arm C: gemcitabine + carboplatin
  - estimated completion date: July 2020

# Key issues – clinical effectiveness

- Decision problem:
  - Is BSC a comparator for people for whom cisplatin is unsuitable?
  - Is re-treatment with 1st line chemotherapy a comparator for the 2nd line population?
  - Is it appropriate to consider only one 2nd line population, regardless of whether people could have cisplatin as 1st line therapy?
- Quality of evidence
  - No comparative atezolizumab trial data
  - How reliable is the simulated treatment comparison? Does the company account for all of the important prognostic factors?
  - How reliable is the network meta-analysis? Are the included studies sufficiently homogeneous?
- How effective is atezolizumab?

# Lead team presentation

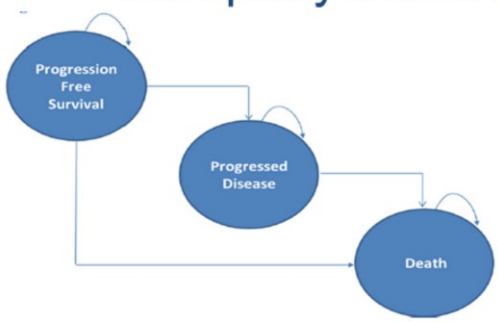
## Atezolizumab for treating locally advanced or metastatic urothelial carcinoma– STA

**Cost effectiveness**

1st Appraisal Committee Meeting: 26 April 2017
Committee D

Evidence Review Group: Southampton HTA Centre
Lead Team: David Meads

# Company's economic model




| Populations modelled |
| --- |
| People for whom cisplatin is unsuitable and have had no previous treatment |
| People whose disease has progressed after previous platinum-based chemotherapy |

- 20 year time horizon, NHS/PSS perspective, 3.5% discount rate
- Weekly cycle length with half-cycle correction
- Treatment with paclitaxel and docetaxel continues until disease progression and with atezolizumab until loss of clinical efficacy or discontinuation due to adverse events
- Treatment with gemcitabine + carboplatin is given for the number of cycles specified in the summary of product characteristics

# Overview of sources of clinical inputs

| Outcome | Intervention | Comparators | | |
|---|---|---|---|---|
| **1st line** | **Atezolizumab** | **Gemcitabine + carboplatin** | | |
| PFS | Extrapolation from IMvigor 210 | Assumption: PFS of gemcitabine + carboplatin = PFS of atezolizumab | | |
| OS | Mix cure rate model (data from IMvigor 210 and Life tables) | Results from NMA with capped HR | | |
| **2nd line** | **Atezolizumab** | **BSC** | **Docetaxel** | **Paclitaxel** |
| PFS | Extrapolation from IMvigor 210 | Use of proportional hazards model (HR from NMA) | Assumption: PFS of docetaxel and paclitaxel = PFS of atezolizumab | |
| OS | Mix cure rate model (data from IMvigor 210 and Life tables) | Results from NMA with capped HR | | |

# Clinical inputs: progression-free survival

- Atezolizumab: PFS extrapolated from IMvigor 210 by fitting generalised gamma distribution to Kaplan–Meier curves for both populations
- Gemcitabine + carboplatin: PFS assumed to be equivalent to atezolizumab
- Docetaxel and paclitaxel: PFS assumed to be equivalent to atezolizumab
  - Company rationale: KEYNOTE-045 trial reported non-significant hazard ratio of 0.98 for PFS, pembrolizumab vs. blended comparison docetaxel, paclitaxel, vinflunine for metastatic urothelial carcinoma
- BSC: proportional hazard ratio of 1.12 vs. atezolizumab from company network meta-analysis

# ERG comments on PFS modelling

- Generalised gamma appears to fit the atezolizumab data well
- Company explores alternative distributions, but these had little effect on the ICER
- Assuming equal efficacy of atezolizumab and comparators for PFS (company approach) vs. using hazard ratios from network meta-analysis produces similar ICERs

# Clinical inputs: overall survival

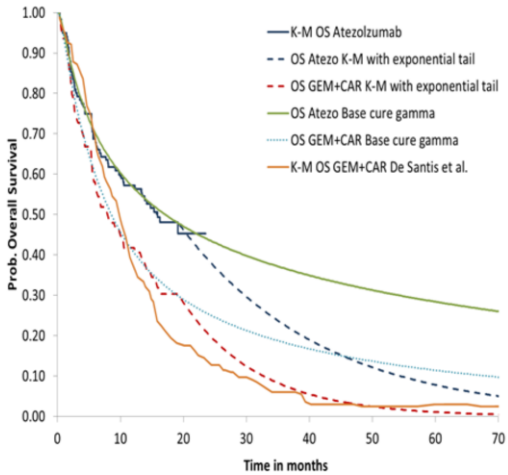
- Atezolizumab: observed survival in IMvigor 210 adjusted for background mortality and extrapolated using generalised gamma distribution
- Gemcitabine + carboplatin: hazard ratio from NMA
  - company noted that this increased linearly over time, producing clinically implausible results
  - hazard ratio capped at 8 months (median follow-up in the Bamias et al. study), with proportional hazards assumed beyond this point
- Docetaxel, paclitaxel and BSC: hazard ratios from NMA capped at 21.16 months (median follow-up in atezolizumab study), proportional hazards assumed beyond this point

# ERG comments on OS modelling

- Atezolizumab extrapolation corresponds well with observed data
- Company does not provide any sensitivity analyses for the choice of parametric distribution
- Inconsistent time points used for capping hazard ratios
- Using capped network meta-analysis results in model adds to uncertainty
- No sensitivity analyses varying atezolizumab treatment effect
- ERG exploratory analyses assess
  - the effect of equalised time points for capping the hazard ratios
  - varying the change in hazard ratio over time (to avoid the need to cap the hazard ratios)
  - varying the atezolizumab treatment effect (using the upper and lower bounds of the confidence interval for the hazard ratio intercept)

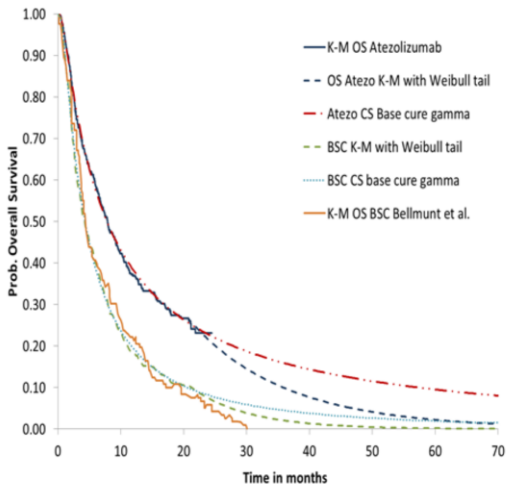
# ERG exploratory analyses: OS extrapolation
## *Cisplatin unsuitable (1st line)*

- Company uses gamma distribution for atezolizumab and comparator extrapolations, as it fits atezolizumab data well
- Follow-up in gemcitabine + carboplatin trial (De Santis) longer than atezolizumab
  - exponential distribution fits De Santis better than gamma
- ERG: more reasonable to use individual Kaplan–Meier curves from atezolizumab and comparator trials with tails extrapolated using exponential function

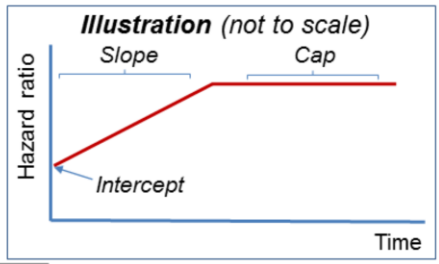


# ERG exploratory analyses: OS extrapolation
## *Previous chemotherapy (2nd line)*

- Company uses gamma distribution for atezolizumab and comparator extrapolations as it fits atezolizumab data well
- Of comparator trials, BSC (Bellmunt) has largest number of patients and longest follow-up
  - Weibull distribution fits BSC data better than gamma
- ERG: more reasonable to use individual Kaplan–Meier curves from atezolizumab and comparator trials with tails extrapolated using Weibull function



# ERG exploratory analyses: treatment effect




- Starting treatment effect
  - Varied initial hazard ratio ('intercept') using upper and lower bounds of confidence interval
  - Large effect on ICER
  - Significant uncertainty

  e.g. using lower bound, ICER increases by [redacted] for 1st line population and [redacted] for BSC for 2nd line population. Atezolizumab is [redacted] for other 2nd line comparisons
- Capping of hazard ratios
  - Equalised time points at which the hazard ratios were capped
  - Large effect on ICER [redacted] vs docetaxel, small effect [redacted] in all other comparisons
- Change in hazard ratio over time
  - Varied change in hazard ratio over time ('slope') to avoid need to cap
  - Large effect on ICER [redacted] vs docetaxel, small effect [redacted] in all other comparisons
- These scenarios were not included in the ERG's preferred analysis

# Clinical inputs: time to treatment discontinuation

- Company used data from IMvigor 210 for atezolizumab, extrapolated using generalised gamma function as trial still on-going
- Gemcitabine + carboplatin given for 6 cycles (as detailed in summary of product characteristics)
- For docetaxel and paclitaxel, progression-free survival used as a proxy for time on treatment
- ERG comments:
  - same distribution used to extrapolate atezolizumab discontinuation for both populations, but Weibull for 1st line and log-logistic for 2nd line provide a better fit

# Health-related quality of life

- No health-related quality of life data collected in IMvigor 210
- Company used values from an Australian HTA of vinflunine
- ERG comment:
  - same utility value on-treatment for atezolizumab and comparators counter-intuitive due to adverse events of chemo
  - people off-treatment after atezolizumab would not have a lower utility than on-treatment because of treatment related adverse events

| | Company choice | | ERG choice | |
|---|---|---|---|---|
| | **Atezolizumab** | **Comparators** | **Atezolizumab** | **Comparators** |
| **On-treatment** | 0.75 | 0.75 | 0.75 | 0.71 |
| **Off-treatment** | 0.71 | 0.75 | 0.75 | 0.75 |

- No adverse event disutility included in model

# Company's cost-effectiveness results
## *with PAS, deterministic analyses*

| Cisplatin unsuitable (1st line) | | | | | |
|---|---|---|---|---|---|
| | Total | | Incremental | | ICER |
| | Costs | QALYs | Costs | QALYs | |
| Gemcitabine + carboplatin | [redacted] | 1.35 | [redacted] | 1.34 | [redacted] |
| Atezolizumab | [redacted] | 2.69 | | | |

| Previous chemotherapy (2nd line) | | | | | | |
|---|---|---|---|---|---|---|
| | Total | | Pairwise vs. Atezolizumab | | | ICER: incremental |
| | Costs | QALYs | Inc. costs | Inc. QALYs | ICER | |
| BSC | [redacted] | 0.55 | [redacted] | 0.68 | [redacted] | - |
| Docetaxel | [redacted] | 0.76 | [redacted] | 0.47 | [redacted] | [redacted] |
| Paclitaxel | [redacted] | 0.71 | [redacted] | 0.53 | [redacted] | [redacted] |
| Atezolizumab | [redacted] | 1.23 | - | - | - | [redacted] |

# Company base case probabilistic analysis (1st line) - **with PAS**

# Company base case probabilistic analysis (2nd line) - **with PAS**

# Company's sensitivity and scenario analyses

- Company: probabilistic results unlikely to be reliable due to high level of uncertainty in fractional polynomial and prediction models
- Deterministic sensitivity analyses: ICER most sensitive to atezolizumab cost, on- and off-treatment utility values
- Scenario analyses:
  - atezolizumab PFS as proxy for time on treatment increases ICER for 1st line population and decreases ICERs for the 2nd line population
  - decreasing atezolizumab off-treatment utility value from 0.71 to 0.5 increases ICERs for both populations

| With-PAS analyses | ICER vs. gem+carbo | ICER vs BSC | ICER vs. docetaxel | ICER vs. paclitaxel |
|---|---|---|---|---|
| Base case | [redacted] | [redacted] | [redacted] | [redacted] |
| Atez. time on treatment = PFS | [redacted] | [redacted] | [redacted] | [redacted] |
| Off-treatment utility value: 0.5 | [redacted] | [redacted] | [redacted] | [redacted] |

# ERG exploratory analyses and preferred analysis
## ***with PAS**, deterministic analyses*

| | Cisplatin unsuitable | Previous chemotherapy (2nd line) | | |
|---|---|---|---|---|
| | ICER vs. gem + carbo | ICER vs BSC | ICER vs. docetaxel | ICER vs. paclitaxel |
| Company base case | [redacted] | [redacted] | [redacted] | [redacted] |
| OS: K-M + exponential tail | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD: Weibull | [redacted] | [redacted] | [redacted] | [redacted] |
| OS: K-M + Weibull tail | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD: log-logistic | [redacted] | [redacted] | [redacted] | [redacted] |
| ERG preferred utility values | [redacted] | [redacted] | [redacted] | [redacted] |
| ERG preferred analysis | [redacted] | [redacted] | [redacted] | [redacted] |
| | | [redacted] | | |

# ERG preferred analysis probabilistic analysis (1st line) - **with PAS**

# ERG preferred analysis probabilistic analysis (2nd line) - **with PAS**

# End of life criteria

| | | From company's base-case modelling | | From literature |
|---|---|---|---|---|
| | | Mean (months) | Median (months) | Median (months) |
| **Cisplatin unsuitable (1st line)** | | | | |
| **Short life expectancy** | **Atezolizumab** | 55.3 | 17.1 | 15.9 |
| | **Gem + carboplatin** | 25.1 | 8.5 | 9 – 10 |
| **Extension to life** | | 30.2 | 8.6 | >7 |
| **Previous chemotherapy (2nd line)** | | | | |
| **Short life expectancy** | **Atezolizumab** | 22.7 | 7.9 | 7.9 |
| | **Docetaxel** | 12.9 | 7.6 | 7 – 8 |
| | **Paclitaxel** | 12.2 | 5.3 | 6.5 |
| | **BSC** | 9.4 | 4.4 | 4 – 5 |
| **Extension to life** | | 9.8 – 13.3 | 0.3 – 3.5 | 0 – 4 |

green = end of life criterion is met, red = end of life criterion is not met

# Innovation and equality

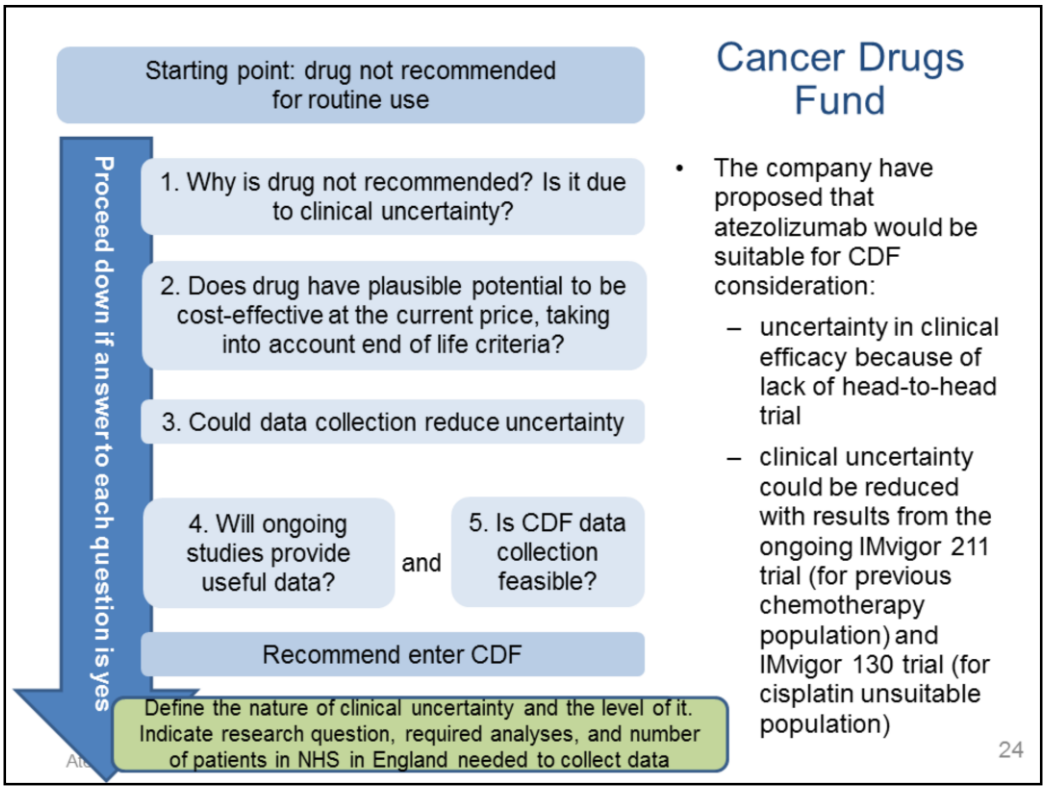
- First immunotherapy for locally advanced or metastatic urothelial carcinoma
  - pembrolizumab also being assessed by NICE for same indication (does not yet have marketing authorisation)
- Early access to medicine scheme designation
  - (for population 2: previous platinum-based chemotherapy only)
- No additional benefits not captured in the QALY highlighted by company
- No equality issues identified during scoping or in submissions

# Key issues – cost effectiveness (1)

- Which overall survival extrapolations are most appropriate?
  - Company: gamma distribution for atezolizumab and all comparators
  - ERG: Individual Kaplan-Meier curves for all therapies with exponential tail (cisplatin unsuitable population) and Weibull tail (previous platinum-based chemotherapy population)
- Are the hazard ratios from the network meta-analysis suitable for decision-making, given that they had to be capped to provide plausible results?
- Which distribution should be used for time to treatment discontinuation?
  - Company: gamma for both populations
  - ERG: Weibull (cisplatin unsuitable population), log-logistic (previous platinum-based chemotherapy population)

# Key issues – cost effectiveness (2)

- Which utility values should be used?
  - Company lower value for atezolizumab off-treatment than on-treatment
  - ERG lower value for comparators on-treatment than atezolizumab
- Are the end-of-life criteria met?
  - Difference between mean and median overall survival
- What are the most plausible ICERs?


Starting point: drug not recommended for routine use
Proceed down if answer to each question is yes
1. Why is drug not recommended? Is it due to clinical uncertainty?
2. Does drug have plausible potential to be cost-effective at the current price, taking into account end of life criteria?
3. Could data collection reduce uncertainty
4. Will ongoing studies provide useful data?
and
5. Is CDF data collection feasible?
Recommend enter CDF
Define the nature of clinical uncertainty and the level of it. Indicate research question, required analyses, and number of patients in NHS in England needed to collect data
Cancer Drugs Fund
The company have proposed that atezolizumab would be suitable for CDF consideration:
uncertainty in clinical efficacy because of lack of head-to-head trial
clinical uncertainty could be reduced with results from the ongoing IMvigor 211 trial (for previous chemotherapy population) and IMvigor 130 trial (for cisplatin unsuitable population)
24