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NICE National Institute for Health and Care Excellence

Atezolizumab for untreated PD-L1 positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF review TA492)

Lead team presentation

Lead team: Gary McVeigh, David Meads, Soo Fon Lim and Malcolm Oswald
ERG: Southampton Health Technology Assessments Centre (SHTAC)
Technical team: Elizabeth Bell, Sally Doss, Linda Landells
Company: Roche

CDF review committee meeting 12 August 2021

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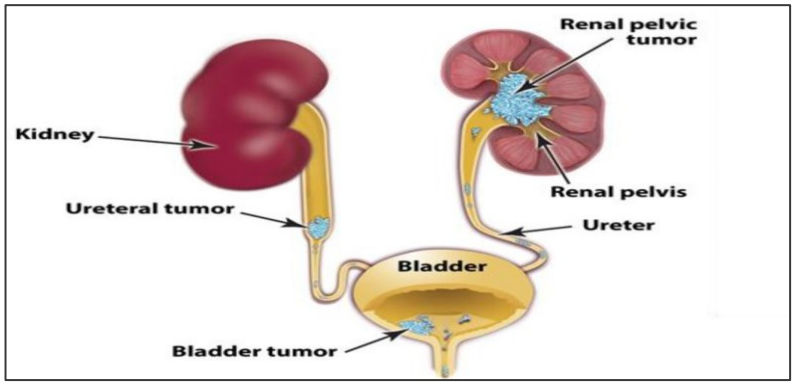
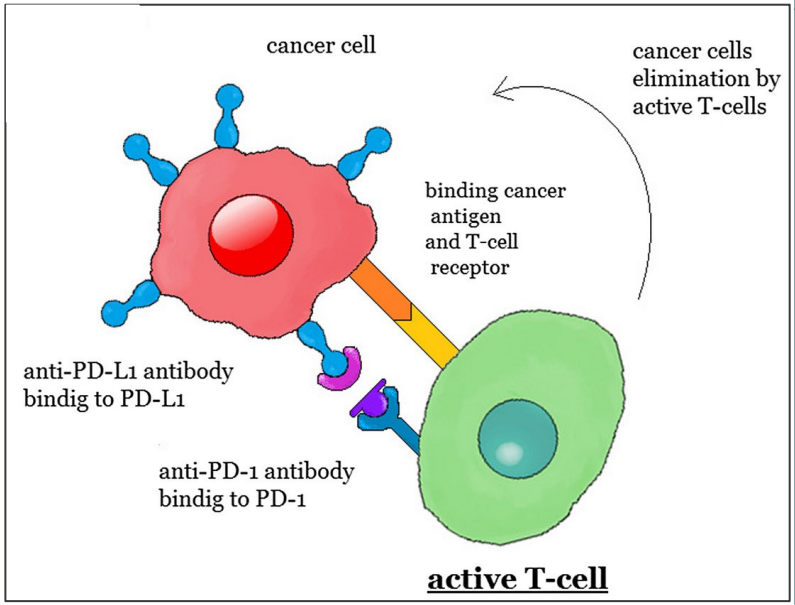
Disease background



Urothelial cancer

- Urothelial cancer is cancer of the transitional cells which form the inner lining of the bladder, urethra, ureter or renal pelvis
- Urothelial carcinoma is most common in the bladder
- Bladder cancer is the 9th most common cancer in the UK, with 12,434 people diagnosed with it in 2020.



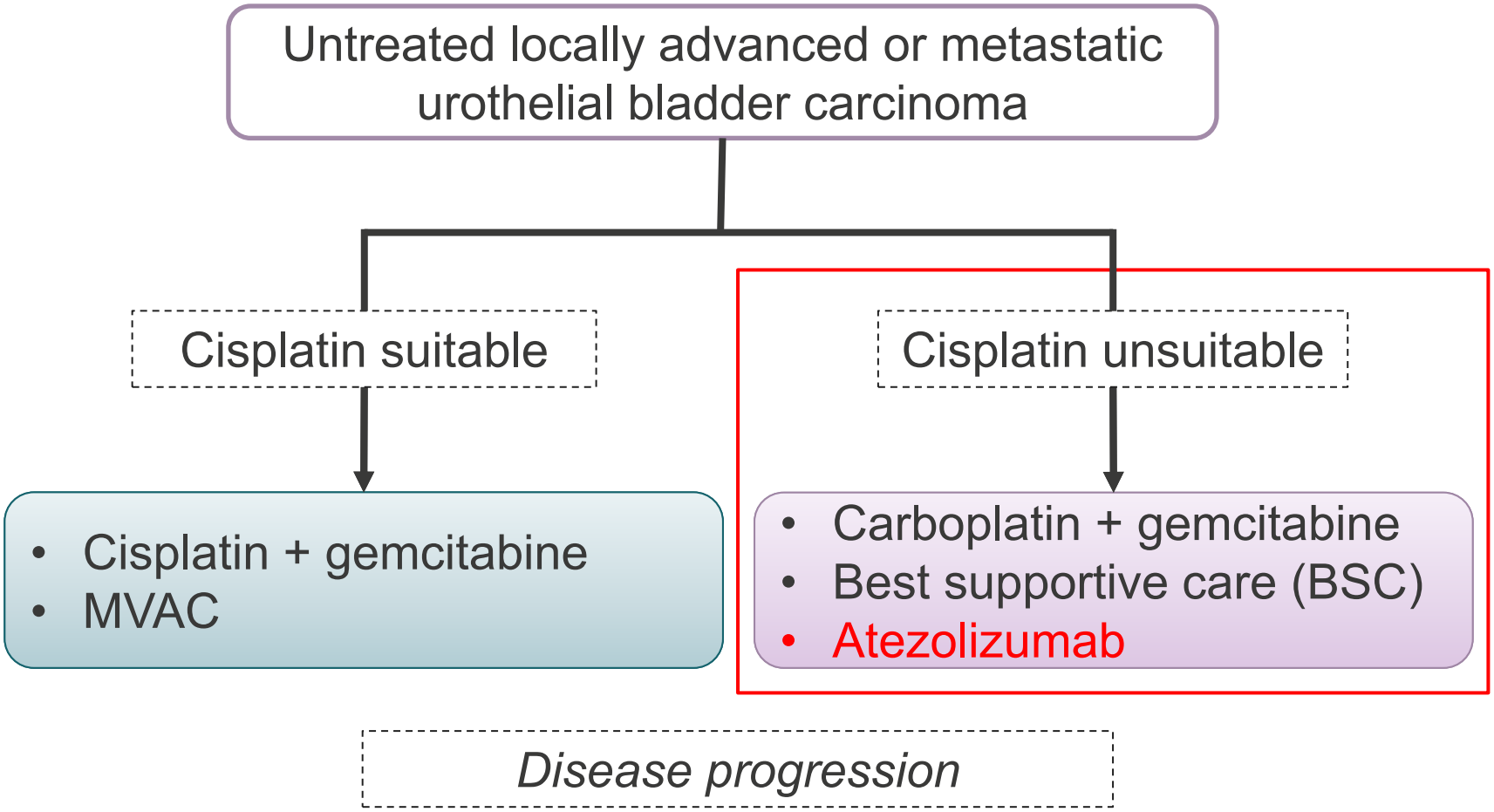
Treatments

- Patients with metastatic or advanced urothelial cancer may receive treatment with surgery and/or radiotherapy
- If the urothelial cancer is too advanced for surgery/radiotherapy or has recurred after these treatments, chemotherapy can be used to improve quality of life and survival
- Atezolizumab is an anti-programmed cell death ligand-1 (PD-L1) monoclonal antibody, involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells.

Source:
1. Urinary Tract Pathology: An Illustrated Practical Guide to Diagnosis, J Bernstein and J Churg. 1993.
2. Immunotherapies based on PD-1/PD-L1 pathway inhibitors in ovarian cancer treatment. Clin Exp Immunol, Accessed July 2021.

PD-L1: Programmed cell death ligand-1

Treatment pathway



BSC: Best supportive care; MVAC: Methotrexate, vinblastine, doxorubicin and cisplatin

Summary of original appraisal TA492

TA492 recommendation (published Dec 2017):
Atezolizumab is recommended in the Cancer Drugs Fund (CDF) as an option for **untreated locally advanced or metastatic urothelial carcinoma in adults, for whom cisplatin-based chemotherapy is unsuitable and whose tumours have a PD-L1 expression ≥5%,** only if the conditions in the managed access agreement are followed.

Uncertainties in TA492		Committee preference
Relative effect	Effectiveness of atezolizumab has only been studied in a single-arm study. All comparisons based on indirect methods.	Robust relative effectiveness measures, likely to be addressed by IMvigor 130.
Utilities	Appropriate health-related quality of life values (HRQoL).	Encouraged the company and NHS England to seek other ways to collect robust HRQoL data, as people in the trial whose disease progressed may only be followed for a short time.
Others	Duration of treatment with atezolizumab.	Alongside IMvigor 130 data, data from the systemic anti-cancer therapy (SACT) dataset would provide evidence to address the uncertainties in the clinical evidence.
	Effectiveness for PD-L1 subgroups.	

CDF: Cancer Drugs Fund; HRQoL: Health-related quality of life; PD-L1: Programmed cell death ligand-1; SACT: Systemic anti-cancer therapy

Atezolizumab (Tecentriq, Roche)

Marketing authorisation	Treatment of adults with locally advanced or metastatic urothelial carcinoma: • After prior platinum containing chemotherapy, or • who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥5%.
Administration & dose	• Intravenous infusion, 1,200 mg every 3 weeks.*
Cost	• List price: £3,807.69 per 1200-mg vial • Annual cost: ~£66,000 • Proposed simple discount patient access scheme (PAS)

*EMA summary of product characteristics (SmPC): IV infusion, 840 mg every 2 weeks, 1,200 mg every 3 weeks or 1,680 mg every 4 weeks. The SmPC was changed in 2019 following updated pharmacokinetic data.

PAS: Patient access scheme PD-L1: Programmed cell death ligand-1; SmPC: Summary of product characteristics

Appraisal summary

	Original appraisal (TA492)	Current CDF review (ID3777)
Population	• People with untreated disease for whom cisplatin-based chemotherapy is unsuitable, originally irrespective of PD-L1 status*	• People with untreated disease for whom cisplatin-based chemotherapy is unsuitable • Tumours with a PD-L1 expression of ≥5%
Data source	• Intention to treat population	• Subgroup data for the cisplatin-ineligible population
Clinical data	• IMvigor 210 (2016)	• IMvigor 130 (2020) • SACT data from 64 people (July 2018 to August 2020)

*In July 2018, during the CDF period, the EMA restricted the use of atezolizumab for people with high-levels of PD-L1.
PD-L1: Programmed cell death ligand-1; SACT: Systemic anti-cancer therapy

CDF review TA492 – Key clinical evidence

Outcome	TA492	CDF review		
	IMvigor 210 2016	IMvigor 130 2020		SACT 2020
	Atezolizumab (n=119)	Atezolizumab (n=50)	Chemo (n=43)	Atezolizumab (n=64)
	Intention to treat population	Cisplatin-ineligible PD-L1-positive subgroup		
Median overall survival (OS), months (95% CI)	15.9 (10.4 to NE)	18.6 (14.0 to NE)	10.0 (7.4 to 18.1)	12.4 (8.3 to 20.1)
Hazard ratio (HR) (95% CI)	NA	Stratified HR = 0.50 (0.29 to 0.87)		NA
Median progression-free survival (PFS), months (95% CI)	2.7 (2.1 to 4.2)	6.4 (4.2 to 12.5)	6.0 (4.2 to 7.4)	NR
HR (95% CI)	NA	Stratified HR = 0.56 (0.34 to 0.93)		NA
Median time to treatment discontinuation (TTD), months (95% CI)	NR	6.0 (3.5 to 12.6)	3.7 (2.6 to 3.9)	5.9 (3.4 to 8.5)

Source: Table 6 and 10 from the ERG report post-FAC and Section 4.11 TA492 company submission.
CDF: Cancer drugs fund; CI: Confidence interval; HR: Hazard ratio; NA: Not available; NE: Not evaluable; NR: Not reported; OS: Overall survival; PD-L1: Programmed cell death ligand-1; TTD: Time to treatment discontinuation

CDF review TA492 – Key considerations

	Committee preferred in TA492	Company base case in current CDF review
Comparator	Carboplatin plus gemcitabine*	Carboplatin plus gemcitabine
OS extrapolation	Kaplan Meier (KM) curve and exponential extrapolation	
PFS extrapolation	Weibull extrapolation over the whole period	
TTD	Extrapolated the observed duration of atezolizumab treatment from IMvigor 210 using the Weibull distribution	KM curve and exponential extrapolation
Utility values	Progressed disease plausible value is likely to be between 0.5 and 0.71	Progressed disease value is 0.611
PD-L1 subgroups	Unable to make recommendations for subgroups based on PD-L1 expression	EMA limited the use of atezolizumab to those with PD-L1 positive tumours
End of life	The end-of-life criteria were met	TBC

*The committee acknowledged the lack of data would make a comparison with BSC difficult in this indication.
BSC: Best supportive care; KM: Kaplan Meier; OS: Overall survival; PD-L1: Programmed cell death ligand-1 PFS: Progression-free survival; TTD: Time to treatment discontinuation

ID3777 – Patient expert perspectives

Responses from: Action Bladder Cancer UK, Fight Bladder Cancer and National Cancer Research Institute

Experience of the condition	• The diagnosis can come as a shock as bladder cancers are not always well known or understood and the prognosis can be poor • There has been little or no improvements in care for people with urothelial cancer in over 30 years • Pressure on the carers.
Current treatments	• Current treatments, which include chemotherapy and radiotherapy, are very invasive and can have significant side effects which reduce quality of life in the final months • Pembrolizumab has been removed from Cancer Drugs Fund • Existing treatments have limited effectiveness & there is an unmet need.
Advantages of atezolizumab	• It offers hope of a step change in treatment for this ignored cancer which has high recurrence rates • Atezolizumab has demonstrated durable response rates, survival and tolerability.
Disadvantages of atezolizumab	• While the treatment is life extending, for many it is not a cure • 75% of patients spoken to said the drug worked well, 25% said they didn't respond • Some reported side effects • Regular attendance for treatment could be a challenge.

"Atezolizumab is a walk in the park. And if it has a good and measurable efficacy, it should remain as part of treatment for cancer"

ID3777 – Clinical expert perspectives

Responses from: Professor Syed Hussain and Dr Selina Bhattarai

Experience of the condition	• There is a huge unmet need in this indication • Survival is low with chemotherapy (8 to 9 months) • Survival is higher with atezolizumab (12 to 18 months).
Current treatments	• There are limited treatment options in this setting, the use of anti PD-L1s is recommended in people who are cisplatin ineligible • Some clinicians may use gemcitabine plus carboplatin in younger patients with good performance status
Advantages of atezolizumab	• Drug is generally well tolerated, and clinically significant benefit can be seen • Studies show quality of life is more favourable compared with chemo • The toxicities are well managed by specialist hospitals in collaboration with other specialities.
Investment required to introduce atezolizumab	• Laboratory's input, where the test is validated, should be recognised and funded • Testing of PD-L1 should be made available in more centres with a centralised service to improve turnaround time and initiate treatment without delays.

PD-L1: Programmed cell death ligand-1

Issues resolved after technical engagement

Issue	Summary	ERG critique	Company base case?
Issue 5a	The company originally chose the KM curve with an exponential extrapolation to model PFS.	• Favours the use of a parametric function over the whole range of PFS rather than using KM directly for an initial period due to the low numbers of participants and associated uncertainty • The ERG favours the Weibull extrapolation.	✓
Issue 6	1. The company did not provide a detailed description of the approach used to estimate utility values 2. Value for the platinum-based chemotherapy progression-free heath state was lower than the pooled value for progressed disease.	• The company used a mixed-effects treatment model, using time, treatment arm and progression status as variables • The company provided updated base case health state utility values. The updated values presented by the company are similar to those seen in the original naïve utility values presented by the company but are still considerably lower than the naïve values. However, the ERG accepted the updated utility values as these are more conservative compared to the naïve utility values.	✓
Issue 7	The approach to estimate the duration of subsequent treatments.	• ERG estimated TTD duration was 7.9 months for atezolizumab, in contrast to the estimated 10.7 months by the company.	✓

KM: Kaplan Meier; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Issues unresolved after technical engagement

Issue	Summary	Impact	Slide
Issue 1	The IMvigor 130 trial treatment estimates are based on interim data analysis of a small subgroup of the trial's total population, comprising cisplatin-ineligible PD-L1 positive participants		13
Issue 2	There were baseline differences between trial arms in terms of gender and racial characteristics, and it is unclear if these differences could have biased the treatment effects		14
Issue 3	The OS estimates from the SACT dataset and the IMvigor 130 trial differ substantially		15
Issue 4	No comparison was made between atezolizumab and BSC in the company's base case		16
Issue 5b	The approach to modelling the long-term outcomes of OS and TTD		17 to 20

Key:
 Model driver;  Unknown impact;  Small/moderate impact

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BSC: Best supportive care; PD-L1: Programmed cell death ligand-1; OS: Overall survival; SACT: Systemic anti-cancer therapy; TTD: Time to treatment discontinuation

Issue 1: IMvigor 130 subgroup

Background

- The IMvigor 130 trial treatment effect estimates, including OS and PFS outcomes, are based on an interim data analysis of a small subgroup of the trial's total population, comprising cisplatin-ineligible PD-L1-positive participants (n=93).

ERG

- Inherent uncertainty in treatment effects due to the small sample subgroup
- OS and PFS HR CIs are wide, based on interim analyses
- Survival data are 87% mature, and the final results expected in Q2 to Q3 of 2022, may increase the precision of the effects.

Company

- Small sample size is a by-product of the restricted EMA marketing authorisation after CDF entry
- Despite the small sample size, the confidence intervals on the HR do not cross 1.

Clinical expert

- Best available data for a small sub-set of patient groups.

Is the trial data robust, despite the small patient population?

CDF: Cancer drugs fund; CI: Confidence intervals; EMA: European medicines agency; HR: Hazard ratio; OS: Overall survival; PD-L1: Programmed cell death ligand-1; PFS: Progression-free survival

Issue 2: IMvigor baseline differences between trial arms

Background

- Within the IMvigor 130 subgroup there were baseline differences between trial arms in terms of gender and racial characteristics, and it is unclear if these differences could have biased the treatment effects.

ERG

- Some of the imbalances are likely to bias treatment effects
- The direction and magnitude of bias is unclear.

Clinical expert

- Understanding the differences of baseline characteristics and the impact of immune checkpoint inhibitors on clinical outcomes and toxicities for clinical tumours remains an area of active research
- There is no reasonable hypothesis to suggest these imbalances would impact the conclusions.

Company

- Gender and racial characteristics may have bias in favour of atezolizumab
- Bajorin risk factor and Eastern Cooperative Oncology Group Performance Scores (ECOG PS) may have bias in favour of platinum-based chemotherapy
- The small sample size and opposing influences means it is not possible to determine the magnitude of direction of potential bias.

Are the differences in baseline characteristics between trial arms important?

ECOG PS: Eastern Cooperative Oncology Group Performance Scores

Issue 3: OS estimates between SACT dataset and IMvigor 130 trial

Background

- The median OS estimates for atezolizumab:
  - SACT dataset **12.4 months** (95% CI: 8.3 to 20.1)
  - IMvigor 130 trial: **18.6 months** (95% CI: 14.0 to NE).

Clinical expert

- Compared with the people in the IMvigor 130 trial, people included in the SACT dataset are:
  - Older
  - Have a poorer performance status
- The magnitude of difference is in line with previous differences in real world and trial populations
- Potential selection bias of good prognostic features for people enrolled in IMvigor 130, who could have received chemotherapy, compared to the SACT dataset.

ERG

- Consider the SACT dataset estimates of OS are more likely to be representative of people seen in clinical practice
- ERG scenario assumes the same treatment effect as in IMvigor 130 (HR = 0.5).

Company

- As per the Terms of Engagement, the primary source of evidence to inform OS for this submission is the IMvigor 130 trial
- The company have used the SACT dataset for validation in the curve selection in the company submission
- In the ERG scenario using SACT data, atezolizumab is considered more cost-effective against platinum-based compared to when the IMvigor 130 data are used.

Which estimates of OS are more representative?

CI: Confidence interval; HR: Hazard ratio; NE: Not evaluable; OS: Overall survival; SACT: Systemic anti-cancer therapy

Issue 4: No comparison was made between atezolizumab and BSC in the company's base case

Background and TA492

- No comparison was made between atezolizumab and BSC in the company's base case
- In TA492 the committee concluded that although BSC was an appropriate comparator, it acknowledged the lack of data would make a comparison difficult.

ERG

- Concurs that evidence on best supportive care is sparse, inconsistently defined and difficult to identify
- Expert clinical advice on typical BSC practice for this patient group may help inform further searches to identify potentially relevant BSC data
  - Two randomised trials not identified in the systematic review search by the company
  - However, these trials may not include the population in this appraisal and so indirect comparisons may not be feasible.

Company

- An extreme upper bound scenario analysis was conducted in order to address this issue
- Assuming BSC is equal in clinical efficacy to platinum-based chemotherapy
  - The incremental cost effectiveness-ratio (ICER) could still be considered cost-effective.

Patient expert

- ERG acknowledged the BSC data are sparse.

NICE technical team

- Collecting BSC data was not part of the managed access agreement.

Is the lack of data for BSC a limitation?

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio

Issue 5b: The approach to modelling the long-term outcomes of OS (1)

TA492

- The KM OS curve from the clinical trial was used and the tail was extrapolated using the exponential distribution
- This approach used more data and produced clinically plausible results.

	Company	ERG
Base case	KM curve (until 48% of patients are at risk) + exponential extrapolation.	Parametric function over the whole time period: exponential distribution.
Justification	• Good statistical fit • Conservative extrapolation • Alignment to SACT data • Doesn't use an unreasonably low number of patients at risk in the KM curve to model an endpoint, as per TA492 • Clinically plausible.	Parametric function: • There is uncertainty associated with the small sample size in the IMvigor 130 subgroup used Exponential: • Considers distributions with a long tail to be clinically implausible.

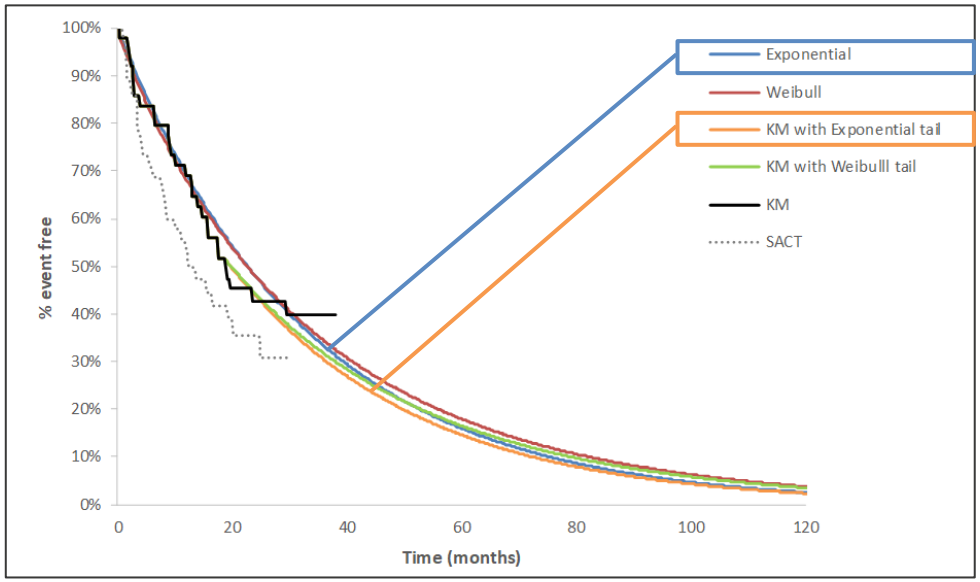
ERG critique

- KM curve until 48% discards almost half the observed data
- Unclear how the SACT dataset used to validate the curve choice.

KM: Kaplan Meier; SACT: Systemic anti-cancer therapy; OS: Overall survival

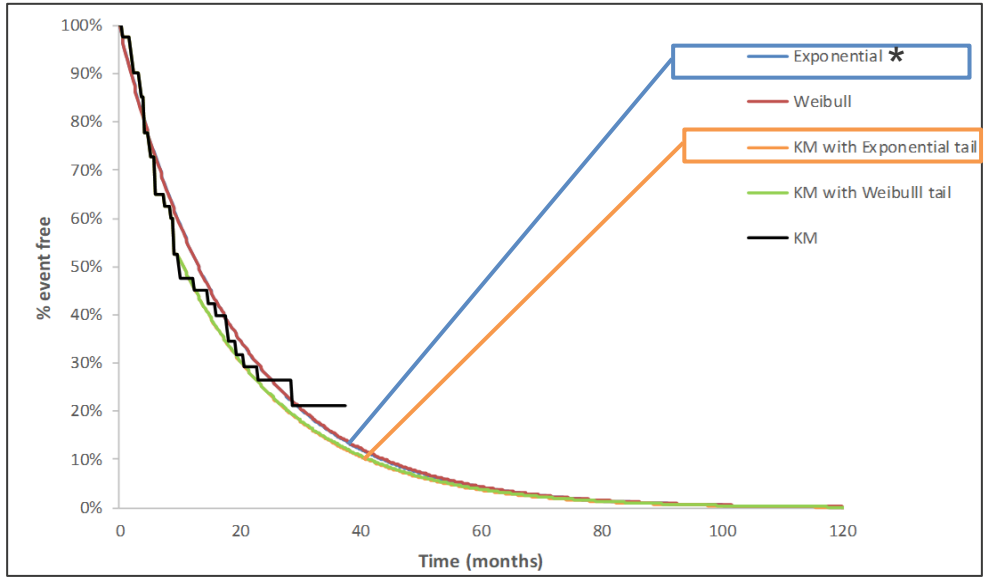
Issue 5b: The approach to modelling the long-term outcomes of OS (2)

Atezolizumab



Source	5-year OS Atezo*
Company clinical expert	5 to 30%
KM + exponential **(company)**	15%
KM + Weibull	17%
Exponential **(ERG)**	16%
Weibull	18%

Platinum-based chemotherapy



Source	5-year OS Chemo
Company clinical expert	1 to 5%
KM + exponential **(company)**	4%
KM + Weibull	4%
Exponential **(ERG)**	4%
Weibull	4%

What is the most appropriate method for extrapolating OS data?

*Exponential is close to the red line (Weibull)

Source: Figure 1 and 2 and Table 1 from the company technical engagement response appendix.

KM: Kaplan Meier; OS: Overall survival

Issue 5b: The approach to modelling the long-term outcomes of TTD to model atezolizumab (1)

TA492

- The observed duration of atezolizumab treatment was extrapolated
- The committee preferred the Weibull distribution because it fitted the data best.

	Company	ERG
Base case	KM curve (until 48% of patients are at risk) + exponential extrapolation.	Parametric function over the whole time period: Weibull extrapolation.
Justification	• Clinically plausible and good statistical fit • Conservative extrapolation to align with SACT data (Weibull predicts implausibly long TTD) • Doesn't use an unreasonably low number of patients at risk in the KM curve to model an endpoint, as per TA492 • Exponential displays a poor fit to the observed data and over-predicts survival in the first 18 months.	Parametric function: • There is uncertainty associated with the small sample size in the IMvigor 130 subgroup used. Weibull: • Hazard for TTD is decreasing over time • Good statistical fit.

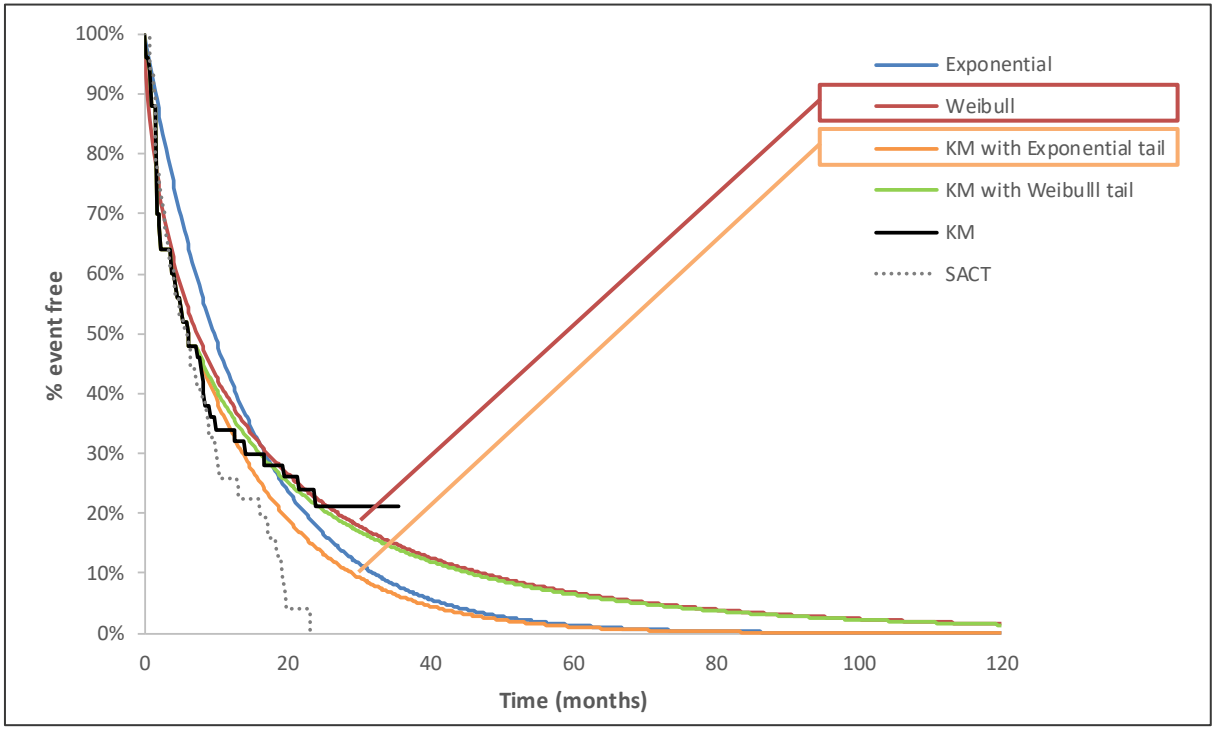
ERG critique

- KM data + exponential tail assumes a constant probability of treatment discontinuation over time, whereas this probability is decreasing in the trial KM data
  - This approach overestimates the probability of treatment discontinuation = underestimates costs
- Using the SACT data to inform the choice of TTD curve selection for IMvigor 130 is problematic as there are differences between the patient population characteristics.

KM: Kaplan Meier; SACT: Systemic anti-cancer therapy; TTD: Time to treatment discontinuation

Issue 5b: The approach to modelling the long-term outcomes of TTD to model atezolizumab (2)

Atezolizumab



Source	5-year TTD Atezolizumab
Company clinical expert	0 to 2%
SACT cohort study	0%
KM + exponential **(company)**	1%
KM+ Weibull	7%
Exponential	1%
Weibull **(ERG)**	7%

- 5-year PFS estimate is 5% for atezolizumab using the Weibull (as agreed by company and ERG)
- Using the ERG OS estimate and the ERG TTD estimate would lead to >40% of those alive on treatment at 5 years.

What is the most appropriate method for extrapolating TTD data?

Source: Figure 3 and Table 3 from the company technical engagement response appendix.
KM: Kaplan Meier; PFS: Progression-free survival; OS: Overall survival; SACT: Systemic anti-cancer therapy; TTD: Time to treatment discontinuation

End of life

TA492

Criterion	Committee considerations	Criterion met?
Short life expectancy: life expectancy less than 24 months for people having treatment with any standard care	• Data from the company's model and literature showed median survival was less than 24 months for people having treatment with any standard care.	✓
Extension to life: the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared to current NHS treatment	• Because of the lack of comparative data, it was difficult to draw conclusions about OS gain • Data from the company's model and from the literature suggested a difference in median survival of at least 7 months.	✓

Current CDF review (ID3777)

		Mean (months)
Short life expectancy	**Atezolizumab**	[redacted]
	Platinum-based chemotherapy	16.56
Extension to life		[redacted]

ERG

- Atezolizumab would still meet the criteria for end-of-of life treatments on the basis of the new evidence submitted.

Source: Table 15 from the ERG report.
OS: Overall survival

Innovation and equality

Innovation:

- First immunotherapy for locally advanced or metastatic urothelial carcinoma
  - pembrolizumab was not recommended for use in this indication.
- No additional benefits not captured in the quality-adjusted life years (QALYs) highlighted by company.

Equality:

- During technical engagement patient experts highlighted potential equality issues for the treatment:
  - Women tend to present later so are more likely to have advanced disease, experience difference in quality-of-life following treatment and suffer worse cancer specific mortality.

- **Is atezolizumab an innovative treatment for untreated PD-L1 positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable?**
- **Are there any additional benefits with atezolizumab that have not been captured adequately in the economic model?**
- **Are there any equality issues relevant to this appraisal?**

PD-L1: Programmed cell death ligand-1; QALY: Quality-adjusted life year

Key modelling assumptions

Assumption	Company base case	ERG base case
Atezolizumab OS estimate:	KM curve and exponential extrapolation	Exponential extrapolation
Chemotherapy OS estimate:		
PFS estimate	Weibull extrapolation over the whole period	
Atezolizumab TTD	KM curve and exponential extrapolation	Weibull extrapolation
Estimate of health state utility values	Mixed-effects model	

KM: Kaplan Meier; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Issues unresolved after technical engagement

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