NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Roche

2. **Company response to NICE's request for clarification**
   a. Main response
   b. Appendix

3. **Patient group, professional group and NHS organisation submission** from:
   a. Action Bladder Cancer UK
   b. Fight Bladder Cancer
   c. Royal College of Pathologists

4. **Evidence Review Group report** prepared by Southampton Health Technology Assessment Centre

5. **Evidence Review Group – factual accuracy check**

6. **Public Health England Study Report**

7. **Technical engagement response** from Roche
   a. Response form
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8. **Expert personal perspectives and technical engagement responses from:**
   a. Dr Selina Bhattarai, Consultant Histopathologist – clinical expert, nominated by Royal College of Pathologists
   b. Professor Syed A Hussain, Professor of Medical Oncology and Honorary Consultant – clinical expert, nominated by Roche
   c. Mr Allen Knight, Chair – patient expert, nominated by Action Bladder Cancer UK
   d. Dr Lydia Makaroff, Chief Executive – patient expert, nominated by Fight Bladder Cancer

9. **Technical engagement responses from consultees and commentators:**
   a. NCRI-ACP-RCP-RCR

10. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessment Centre

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA492

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) ID3777

Company evidence submission for committee

May 2021

File name	Version	Contains confidential information	Date
ID3777_NICE_Atezolizumab_Company_Submission_1LmUC	V1	Yes	14th May 2021

Contents

Tables and Figures

Abbreviations

AIC	Akaike information criteria
ALK	anaplastic lymphoma kinase
AUC	area under the curve
BIC	Bayesian information criteria
BNF	British National Formulary
BSA	body surface area
BSC	best supportive care
CI	confidence interval
CDF	Cancer Drugs Fund
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ERG	Evidence Review Group
HCC	hepatocellular carcinoma
HRQoL	Health related quality of life
ICER	incremental cost effectiveness ratio
ITT	intent-to-treat
LYG	life years gained
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	objective response rate
PAS	patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PFS	progression-free survival
PSA	partitioned survival analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
RCT	randomised-controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours.
SACT	systemic anti-cancer therapy
SCLC	small cell lung cancer
SLR	systematic literature review
TNBC	triple negative breast cancer
TTD	time to treatment discontinuation
UC	urothelial carcinoma

Cancer Drugs Fund review submission Background

- Atezolizumab is recommended for use within the Cancer Drugs Fund (CDF) as an option for untreated locally advanced or metastatic urothelial carcinoma (mUC) in adults when cisplatin-containing chemotherapy is unsuitable, only if:
    - their tumours express PD-L1 at a level of 5% or more, and;
    - the conditions of the managed access agreement for atezolizumab are followed.
- Incremental cost-effectiveness ratios (ICER) presented to the committee at the time included a patient access scheme (PAS) simple discount of [redacted].
- The committee originally made a recommendation irrespective of programmed death ligand 1 (PD-L1) status. The committee was unable to make a recommendation based on PD-L1 status, as the company had not provided cost-effectiveness analyses for these subgroups. The committee stated that it would have liked to have seen these analyses. In July 2018 (during the CDF period), the European Medicines Agency (EMA) restricted the use of atezolizumab for untreated urothelial carcinoma (UC) to adults with high levels of PD-L1. As a result, the National Institute for Health and Care Excellence (NICE) guidance was updated, in line with the EMA license.
- The committee noted that the company presented two base-case ICERs varying the progressed disease (PD) utility value. The ICERs (with the PAS applied) for atezolizumab vs. carboplatin plus gemcitabine were [redacted] per quality adjusted life year (QALY) (PD utility value = 0.71) and [redacted] per QALY (PD utility value = 0.50). The committee agreed with the evidence review group's (ERG) corresponding ICERs vs. carboplatin plus gemcitabine, which were [redacted] and [redacted] per QALY respectively. The committee concluded that the most plausible ICER lay between these values.
- The committee's key uncertainty was the relative effectiveness of atezolizumab because the evidence presented was from IMvigor210, a phase II, single arm trial. The indirect comparisons suggested that atezolizumab may improve survival but the committee was concerned by the robustness of the data.
    - Additional data from IMvigor130, an ongoing phase III, randomised controlled trial (RCT) comparing atezolizumab with carboplatin plus gemcitabine, would help resolve the uncertainty and provide data on other uncertainties: the duration of treatment with atezolizumab, quality of life and effectiveness for PD-L1 subgroups.

- The committee noted that its preferred ICERs were above the range normally considered cost-effective, but that the overall survival (OS) extrapolation drives the model and there is currently uncertainty around this element. The committee concluded that there was plausible potential for atezolizumab to be cost-effective, pending results from IMvigor130.

A.2 Key committee assumptions

- Unless otherwise stated, the committee preferred assumptions refer to the originally appraised population that is irrespective of PD-L1 status. The EMA restricted the use of atezolizumab for untreated UC to adults with high levels of PD-L1 after the original guidance was produced. No cost-effectiveness analyses for the cisplatin-ineligible PD-L1-positive subgroups were provided at the original appraisal.

Table 1 Key committee assumptions

Area	Committee preferred assumptions
Population	The population for the original appraisal were people with untreated PD-L1 positive locally advanced or metastatic UC who cannot have cisplatin. In July 2018 (during the CDF period), the EMA restricted the use of atezolizumab for untreated UC to adults with high levels of PD-L1. **Adults with untreated locally advanced or metastatic UC whose tumours express PD-L1 at a level of 5% or more and cannot have cisplatin is the relevant population for the CDF review.**
Comparators	The company submitted clinical- and cost-effectiveness analyses comparing atezolizumab with carboplatin plus gemcitabine, but not comparing to BSC despite this being listed in the scope. The company stated that BSC would not be offered to those well enough to have atezolizumab. Committee understood that carboplatin plus gemcitabine may not be suitable for a significant proportion of people for whom cisplatin is unsuitable and therefore for this group BSC would be the appropriate comparator, though committee acknowledged the lack of data would make a comparison difficult. **Carboplatin plus gemcitabine and best supportive care should be the relevant comparators within the CDF review.**
Comparative effectiveness	The clinical trial data underpinning the economic model was from IMvigor210, a single arm trial that required a simulated treatment comparison and network meta-analysis to obtain comparative effectiveness evidence. The committee did not consider the results of either the simulated treatment comparison or the network meta-analysis to be robust. The committee was aware that the ongoing IMvigor130 trial would provide direct comparative evidence, and considered that this trial data should be used to inform the relative effectiveness of atezolizumab.

	The company should use data from IMvigor130 to inform the relative effectiveness of atezolizumab.
Survival data	The company used a generalised gamma distribution to model atezolizumab OS but this led to 5-year survival estimates that the committee deemed implausibly high for both atezolizumab (28%) and the comparator (12%). The ERG used the trial OS KM data for atezolizumab and extrapolated with an exponential distribution. They used the De Santis trial for the comparator (1). This provided 5-year survival estimates of 10% for atezolizumab and 1% for the comparator. The committee concluded that these were more plausible and consistent with the data. The company stated that the ERG's approach is implausible because the PFS and OS curves cross. The ERG addressed this by adjusting the PFS extrapolation, which they considered to be less robust because it was based on the uncertain assumption that PFS would be the same for both treatment and comparator arms. The ERG explained that a Weibull distribution fits the PFS data well and the OS curves do not cross. The committee acknowledged that extrapolation of the survival data was highly uncertain but preferred the ERG's approach for decision-making because it used more data and produced more clinically plausible results. **The company should use survival data from the IMvigor130 trial and fully explore the most appropriate modelling.**
Treatment duration	The committee noted that patients in the IMvigor210 trial continued to take atezolizumab until unmanageable toxicity or lack of clinical efficacy. This meant that some people continued to take atezolizumab after disease progression. Clinical experts explained that in practice treatment with atezolizumab would only continue after disease progression for people who have had previous chemotherapy, not for those who were previously untreated. The company chose a generalised gamma distribution to extrapolate treatment duration. The ERG noted that the Weibull distribution provided a better statistical fit. The committee agreed with the ERG but noted that the choice of distribution had only a small effect on the cost-effectiveness results. **The company should use updated time-on-treatment data from the IMvigor130 trial and validate the generalisability of this assumption using the data collected within the SACT dataset.**

Utilities	IMvigor210 did not collect quality-of-life data and the company used utility values from an Australian appraisal of vinflunine for metastatic urothelial bladder cancer (2). The committee was concerned that the value of 0.71 for the progressed state was too high as this is the same as the value for the age-matched general population. The company ranged the utility value 0.50 to 0.71 in a sensitivity analysis, which had a large impact on the ICER. The committee considered that a value of 0.50 might be too low but that post-progression utility is an important driver of the model. The committee was aware that EQ-5D data would be collected within the IMvigor130 trial and this would provide directly comparable health-related quality of life evidence. **The company should use EQ-5D data from the IMvigor130 trial to inform the economic model.**
Most plausible ICER	No cost-effectiveness analyses were provided by the company for those with high PD-L1 status, the relevant population of the CDF review.
End of life	Atezolizumab meets the end-of-life criteria.

BSC, best supportive care; CDF, Cancer Drugs Fund; EMA, European Medicines Agency; ERG, evidence review group; EQ-5D, EuroQol- 5 Dimension; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; UC, urothelial carcinoma

A.3 Other agreed changes

- **Subsequent treatments:** After consultation in the terms of engagement meeting, due to changes in the treatment landscape, subsequent treatments were included in the economic model. Further detail is included in Section A.8.7 .

- **Best supportive care (BSC):** As per Table 1, a systematic literature review (SLR) was conducted in order to identify potential studies with a view to incorporating BSC as a comparator into the analysis via a network meta-analysis. The SLR was conducted in September 2020 and looked to identify studies of atezolizumab and comparator treatments in patients with untreated locally advanced or mUC. No trials that identified BSC in mUC were identified. Further details on the SLR are provided in Appendix A. Therefore, as in the original company submission, BSC was not included in the submission due to lack of available evidence.

A.4 The technology

Table 2 Technology being reviewed

UK approved name and brand name	Atezolizumab (Tecentriq®)

Mechanism of action	Atezolizumab is a monoclonal antibody that binds to and inactivates a protein called PD-L1, which leads to downstream activation of T cells that can detect and attack tumour cells.
Marketing authorisation/CE mark status	It should be highlighted that the indication for this CDF review differs from the original company submission (TA492, Section 1.2 page 27 (3)) owing to a restricted EMA marketing authorisation. Following the original submission, the EMA provided the following marketing authorisation for atezolizumab (July 2018): *"Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%"*

Indications and any restriction(s) as described in the summary of product characteristics	• Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:
	  ○ after prior platinum-containing chemotherapy, or
	  ○ who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%
	• Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies
	• Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq
	• Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC
	• Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with ES-SCLC
	• Tecentriq, in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease
	• Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy

	• Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% tumour cells or ≥ 10% tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC.
Method of administration and dosage	1,200 mg administered intravenously Q3W. Initial dose is administered over 60 minutes. If tolerated all subsequent infusions may be administered over 30 minutes. It is recommended patients are treated with atezolizumab until loss of clinical benefit, or unmanageable toxicity.
Additional tests or investigations	Only PDL1-positive patients receive atezolizumab in this indication, therefore PD-L1 testing is required. As validated with clinical experts, clinicians either test PD-L1 in all mUC patients or only those who are cisplatin-ineligible. The majority of cisplatin-ineligible patients will receive PD-L1 testing.
List price and average cost of a course of treatment	The list price for atezolizumab is £3,807.69. The average (undiscounted) cost of a course of treatment is £71,114 as per the cost of treatment multiplied by the mean treatment duration (12.9 months).
Commercial arrangement (if applicable)	A simple PAS is in place for atezolizumab representing a [redacted] discount from the list price £3,807.69 per 1,200 mg vial.
Date technology was recommended for use in the CDF	October 2017
Data collection end date	August 2020

ALK, anaplastic lymphoma kinase; CDF, Cancer Drugs Fund; EGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; ES-SCLC, extensive-stage small cell lung cancer; HCC, hepatocellular carcinoma; mUC, metastatic urothelial carcinoma; NSCLC, non-small cell lung cancer; PAS, patient access scheme; PD-L1, programmed death ligand 1; TNBC, triple-negative breast cancer; UC, urothelial carcinoma

A.5 Clinical effectiveness evidence

A.5.1 *IMvigor130*

Table 3 provides an overview of IMvigor130, the study that provides the primary evidence base for this CDF review (4, 5). The data cut used for this submission was 14th June 2020. Further information on IMvigor130 such as methodology, demographics and baseline characteristics, intention to treat (ITT) results and safety information are provided in Appendix C.

Table 3 Primary source of clinical effectiveness evidence

Study title	**IMvigor130 (NCT02807636)**
Study design	A phase III, multicentre, randomized, double-blind placebo-controlled study
Population	Patients with untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable
Intervention(s)	Atezolizumab 1,200 mg administered by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1
Comparator(s)	• Carboplatin will be administered at doses to achieve AUC of 4.5 mg/mL per min by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity • Gemcitabine will be administered at a dose of 1000 mg/m^2 by IV infusion on Day 1 and Day 8 of each 21-day cycle, until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity
Outcomes collected that address committee's key uncertainties	• OS • PFS • TTD • Health state utility values (All outcomes included in the economic model base-case)
Reference to section in appendix	Appendix C

AUC, area under the concentration-time curve; IV, intravenous; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTD, time to treatment discontinuation

The patient population in the original submission (TA492, Section 1.2 page 27 (3)) represented cisplatin-ineligible patients with locally advanced or metastatic UC regardless of their PD-L1 expression. Following this, the EMA issued a restricted marketing authorisation for atezolizumab to:

> *"Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced metastatic UC who are considered cisplatin-ineligible, and whose tumours have a PD-L1 expression ≥ 5%."*

Data presented in this CDF review submission from the IMvigor130 clinical trial represent the cisplatin-ineligible PD-L1-positive subgroup that corresponds to the EMA marketing authorisation for this indication.

Cisplatin-ineligibility was defined as per the Galsky criteria (6) (Appendix C). This matches the eligibility criteria for IMvigor210 (which provided the main evidence base for the original submission) and the EMA marketing authorisation. PD-L1-positive was defined as patients whose tumours have a PD-L1 expression ≥ 5% as per the licenced indication. PD-L1 expression was an IMvigor130 trial stratification factor. Further information on the definition of PD-L1-positive in IMvigor130 is outlined in Appendix C.

In the IMvigor130 trial, the pragmatic approach was taken to allow physicians to choose whether patients received cisplatin or carboplatin (outside of the Galsky criteria (6)) in order to reflect real-world practice. Therefore, a small number of subjects in the 'cisplatin-ineligible' subgroup (n=5, 12%) were defined as cisplatin-ineligible as per the Galsky criteria but continued to received cisplatin based on physician assessment. Despite receiving cisplatin, these patients can still be considered cisplatin-ineligible as per the Galsky criteria and EMA marketing authorisation and are therefore within the licenced population. This patient population was chosen for this appraisal as alignment with the original submission population and EMA marketing authorisation population, both of which defined cisplatin ineligibility as per the Galsky criteria, was seen as the top priority. In the economic model, a decision was taken not to include the costs of cisplatin and only assume the costs of carboplatin as the number of patients this impacted is small and the differences in costs between carboplatin and cisplatin is minor and has a negligible impact on results. For the avoidance of confusion, the comparator arm was labelled the "platinum-based chemotherapy" arm.

Appendix C also outlines the statistical testing methodology for IMvigor130, which was designed before the EMA marketing authorisation restriction. Because statistical significance was not met in the A vs C comparison (atezolizumab + chemotherapy vs. placebo + chemo) no conclusions regarding statistical significance are able to be drawn regarding the atezolizumab vs. placebo + chemotherapy comparison which is relevant to this submission. This can be considered an exploratory analysis.

A.5.2 *Systemic-Anti-Cancer Therapy (SACT)*

The SACT data cohort study comprises real world evidence for this indication collected whilst atezolizumab was in the CDF. Table 4 displays an overview of the SACT data cohort study. Results from the SACT data cohort study were not used directly in the economic model but were used to validate efficacy observed in IMvigor130 (Section A.8.2 and Section A.8.4).

Table 4 Secondary source of clinical effectiveness evidence

Study title	**SACT data cohort study**
Study design	SACT data cohort study
Population	Patients with untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable
Intervention(s)	Atezolizumab 1,200 mg administered by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1
Comparator(s)	Not applicable
Outcomes collected that address committee's key uncertainties	• OS • TTD
Reference to section in appendix	N/A

OS, overall survival; PD-L1, programmed death ligand 1; SACT, Systemic-Anti-Cancer Therapy, TTD, time to treatment discontinuation

A.6 Key results of the data collection

The original company submission included efficacy of IMvigor210 outcomes against an indirect treatment comparison (TA492 Section 5.3, pages 151-165 (3)). Given the difference in patient populations, direct comparisons of OS, PFS, TTD and ORR between the original submission and the updated IMvigor130 data for this review are of limited relevance. Comparisons are provided in the sections below for demonstrative purposes only.

A.6.1 *IMvigor130*

Overall survival

Table 5 represents the OS trial results, demonstrating that atezolizumab improves survival compared to platinum-based chemotherapy. At the time of the latest data cut, 56% (28/50) of patients in the atezolizumab arm and 70% (30/43) of patients in the platinum-based chemotherapy arm had an event (5). Median OS was 18.6m in

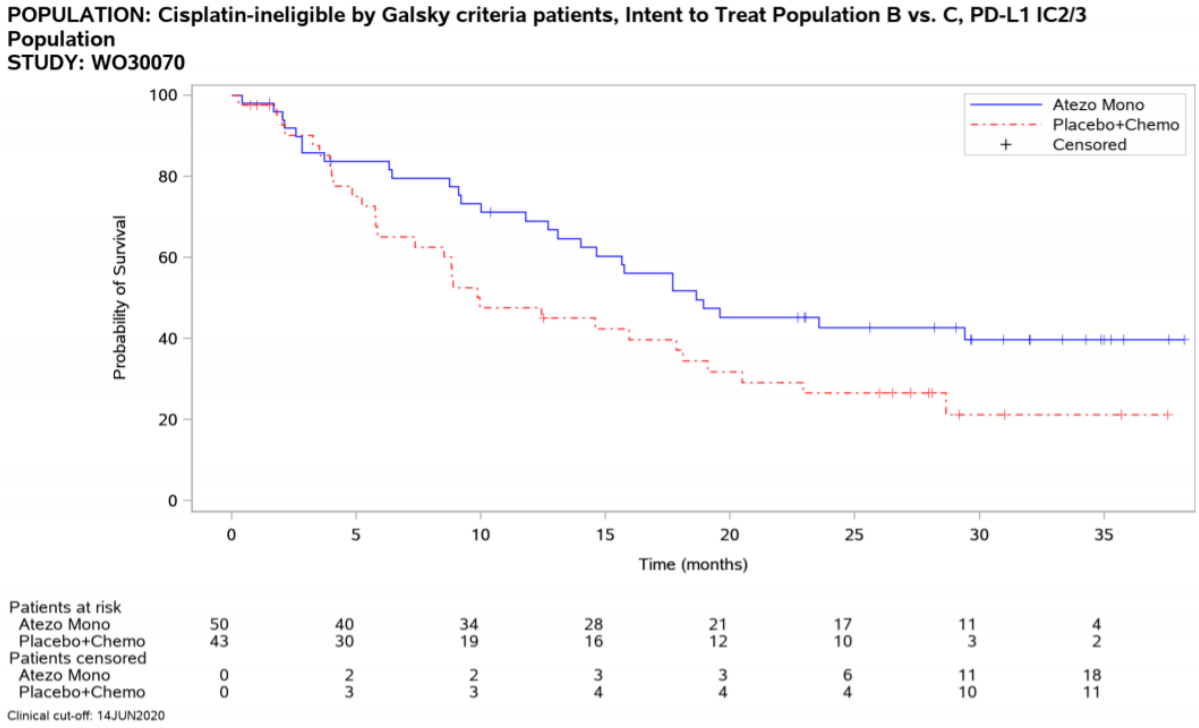
the atezolizumab arm and 10.0m in the platinum-based chemotherapy arm (vs. 17.1m and 8.5m respectively in the original company submission economic model ITT population, TA492, Section 4.13.3, page 144 (3)). These results can be considered clinically meaningful.

Table 5 IMvigor130 OS atezolizumab vs. platinum-based chemotherapy

	Atezolizumab (n=50)	Platinum-based chemotherapy (n=43)
Patients with event, n (%)	28 (56%)	30 (70%)
Median OS, months (95% CI)	18.6 (14.0,NE)	10.0 (7.4 ,18.1)
Stratified hazard ratio (95% CI) p value (log-rank)	0.50 (0.29, 0.87) p=0.0125	

CI, confidence intervals; NE, not evaluable; OS, overall survival

Figure 1 Kaplan-Meier plot of IMvigor130 OS atezolizumab vs. platinum-based chemotherapy



OS, overall survival; PD-L1, programmed death ligand 1

Progression-free survival

Table 6 represents the PFS trial results. At the time of the latest data cut, 72% (36/50) of patients in the atezolizumab arm and 86% (37/43) of patients in the platinum-based chemotherapy arm had progressed (4). Median PFS was 6.4m in the atezolizumab arm and 6.0m in the platinum-based chemotherapy arm (vs. 3.9m and

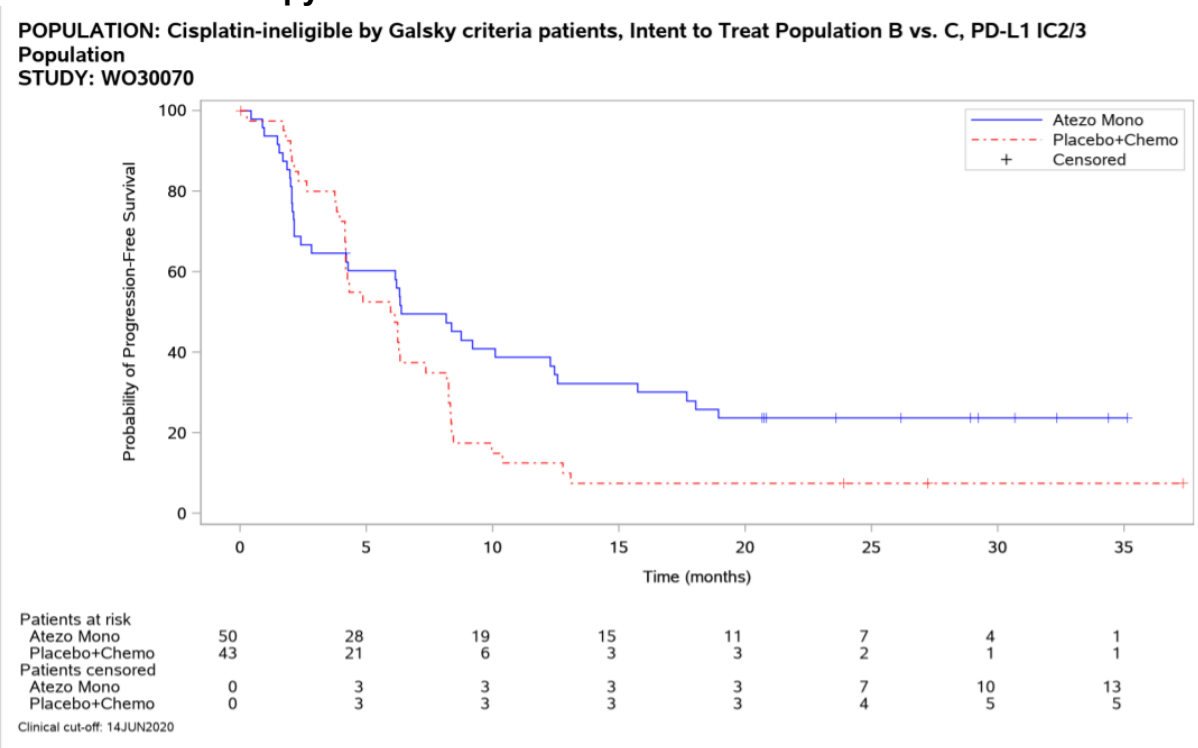
assumed 3.9m respectively in the original company submission economic model ITT population, TA492, Section 5.3.3, page 155 (3)). These results can be considered clinically meaningful.

Table 6 IMvigor130 PFS atezolizumab vs. platinum-based chemotherapy

	Atezolizumab (n=50)	Platinum-based chemotherapy (n=43)
Patients with event, n (%)	36 (72%)	37 (86%)
Median PFS, months (95% CI)	6.4 (4.2, 12.5)	6.0 (4.2, 7.4)
Stratified hazard ratio (95% CI) p value (log-rank)	0.56 (0.34, 0.93) p= 0.0235	

CI, confidence intervals; PFS, progression-free survival

Figure 2 Kaplan-Meier plot of IMvigor130 PFS atezolizumab vs. platinum-based chemotherapy



PFS, progression-free survival; PD-L1, programmed death ligand 1

Treatment duration

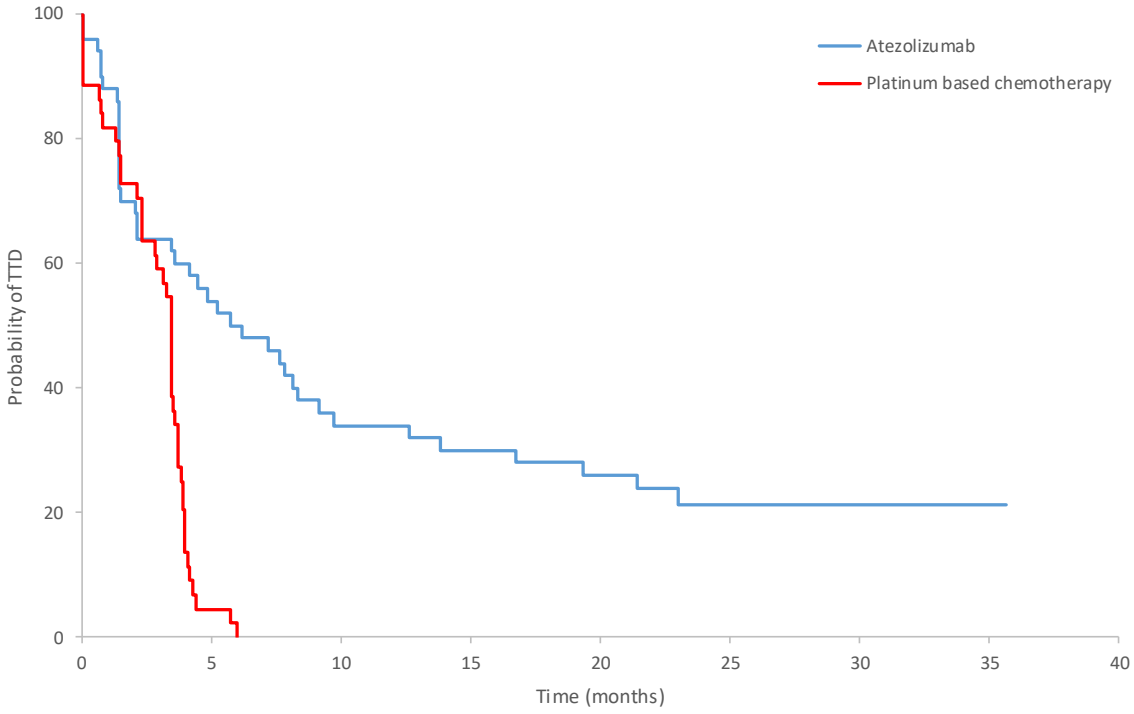
Table 7 represents the TTD trial results. At the time of the latest data cut, 78% (39/50) of patients in the atezolizumab arm and 100% (43/43) of patients in the platinum-based chemotherapy arm had discontinued treatment (4). Median TTD was 6.0m in the atezolizumab arm and 3.7m in the platinum-based chemotherapy arm (vs. 3.4m and assumed 3.9m respectively in the original company submission economic model ITT population, TA492, Section 5.5.5, page 191 (3)).

Table 7 IMvigor130 TTD atezolizumab vs. platinum-based chemotherapy

	Atezolizumab (n=50)	Platinum-based chemotherapy (n=43)
Patients with event, n (%)	39 (78%)	43 (100%)
Median TTD, months (95% CI)	6.0 (3.5, 12.6)	3.7 (2.6, 3.9)

CI, confidence intervals; TTD, time to treatment discontinuation

Figure 3 Kaplan-Meier plot of IMvigor130 TTD atezolizumab vs. platinum-based chemotherapy



PD-L1, programmed death ligand 1; TTD, time to treatment discontinuation

Overall Response Rate (ORR)

Table 8 represents the ORR trial results. At the time of the latest data cut, 40% (20/50) of patients in the atezolizumab arm and 33% (14/43) of patients in the platinum-based chemotherapy arm had responded (4). This compares to 19.3% for atezolizumab in the original company submission (ITT population, TA492, Section 4.11.10.2, page 115 (3)).

Table 8 IMvigor130 response rate atezolizumab vs. platinum-based chemotherapy

	Atezolizumab (n=50)	Platinum-based chemotherapy (n=43)

Responders Non-Responders Response rate 95% CI	20 (40.0%) 30 (60.0%) (26.41, 54.82)	14 (32.6%) 29 (67.4%) (19.08, 48.54)
Complete Response 95% CI	5 (10.0%) (3.33, 21.81)	4 (9.3%) (2.59, 22.14)
Partial Response 95% CI	15 (30.0%) (17.86, 44.61)	10 (23.3%) (11.76, 38.63)
Stable Disease 95% CI	11 (22.0%) (11.53, 35.96)	19 (44.2%) (29.08, 60.12)
Progressive Disease 95% CI	14 (28.0%) (16.23, 42.49)	4 (9.3%) (2.59, 22.14)
Not Evaluable	0	0
Missing	5 (10.0%)	6 (14.0%)

CI, confidence interval

Duration of follow-up

Median duration of follow up was 17.7m (min 0.4, max 38.2) in the atezolizumab arm and 8.9m (min 0.3, max 37.6) in the platinum based chemotherapy arm (vs. 17.2m and in the original company submission ITT population, TA492, Section 4, page 51 (3)).

Health state utility values

Health-related quality-of-life (HRQoL) data were collected in the IMvigor130 study directly from mUC subjects via the EQ-5D-5L questionnaire. Measurement and valuation of HRQoL using EQ-5D-5L directly from subjects is consistent with the NICE reference case (7). EQ-5D-5L data were completed on Cycle 1, Day 1 (first healthcare interaction); on Day 1 of each subsequent cycle; at the treatment discontinuation visit, which was within 30 days after the last treatment dose; and at any visits after disease progression and/or when OS was evaluated. The EQ-5D-5L results were mapped to EQ-5D-3L, using the van Hout algorithm (8). The EQ-5D utility weights per visit for each treatment arm were calculated using the UK Tariff from Dolan et al. and the Van Hout Crosswalk (8),(9).

Table 9 displays the health state utility data from IMvigor130. Atezolizumab displays a statistically significant HRQoL benefit over platinum-based chemotherapy in PF (0.642 vs. 0.527 $p<0.01$) and PD (0.625 vs. 0.510 $p<0.01$) health states.

The PF health state utilities for atezolizumab and platinum-based chemotherapy (0.642 and 0.527) are lower than those used in the original submission (0.75, TA492, Section 5.4.6, page 179 (3)) which had been identified as an area of concern by the committee (Committee discussion TA492, 3.12 (3)). The overall PD health state utility (0.567) falls within and towards the lower end of the 0.71–0.5 range that the committee considered plausible (Committee discussion TA492, 3.12 (3)).

Table 9 Health state utility data from IMvigor130

Treatment arm (n patient)	Health state	Mean utility	SD	CI	N. Obs
Pooled (91)	PF	0.584	0.043	(0.499, 0.670)	1,097
Pooled (45)	PD	0.567	0.043	(0.481, 0.653)	177
Atezolizumab monotherapy (49)	PF	0.642	0.054	(0.534, 0.750)	757
Atezolizumab monotherapy (21)	PD	0.625	0.055	(0.515, 0.734)	112
Platinum-based chemotherapy (42)	PF	0.527	0.062	(0.404, 0.649)	340
Platinum-based chemotherapy (24)	PD	0.510	0.061	(0.388, 0.631)	65

CI, confidence intervals; PD, progressed disease; PF, progression-free; SD, standard deviation

Subsequent treatments

Information on subsequent treatments were also collected in IMvigor130 (4). In total, subjects received 38 treatments after receiving atezolizumab and 34 treatments after platinum-based chemotherapy. The frequency of subsequent treatments received by subjects is displayed in Table 10. Some of the subsequent treatments shown are used in combination as part of a regimen.

Table 10 Subsequent treatments from IMVigor130

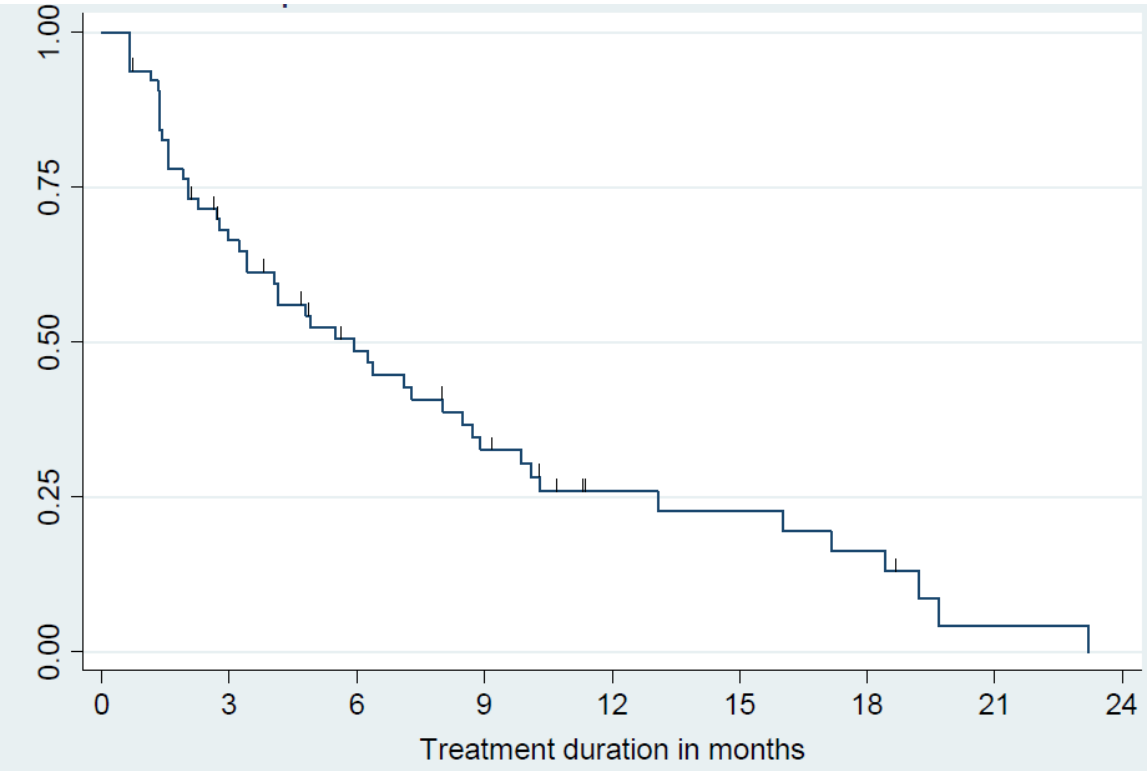
Subsequent treatment	Atezolizumab		Platinum-based chemotherapy	
	Number of patients, n (%)	Mean treatment duration (months)	Number of patients, n (%)	Mean treatment duration (months)
Atezolizumab	0 (0)	0.0	4 (9)	2.1
Vofatamab	0 (0)	0.0	2 (5)	5.1

Carboplatin	12 (24)	3.7	3 (7)	3.0
Cisplatin	4 (8)	2.3	2 (5)	1.1
Doxorubicin	0 (0)	0.0	1 (2)	2.0
Gemcitabine	16 (32)	2.7	3 (7)	2.9
Gemcitabine hydrochloride	2 (4)	7.7	0 (0)	0.0
Methotrexate	0 (0)	0.0	3 (7)	2.0
Nivolumab	0 (0)	0.0	4 (9)	1.7
Paclitaxel	2 (4)	5.3	10 (23)	3.1
Pembrolizumab	0 (0)	0.0	1 (2)	3.5
Vinblastine	0 (0)	0.0	1 (2)	2.0
Vinflunine	2 (4)	14.6	0 (0)	0.0

A.6.2 *SACT*

Median treatment duration was 5.9 months [95% confidence interval (CI): 3.4, 8.5] (179 days). Forty-eight percent (95% CI: 35%, 60%) of patients were receiving treatment at 6 months and 26% (95% CI: 15%, 38%) of patients were receiving treatment at 12 months. The SACT TTD Kaplan-Meier is shown in Figure 4.

Figure 4 Kaplan-Meier plot of SACT dataset TTD atezolizumab (n=64)

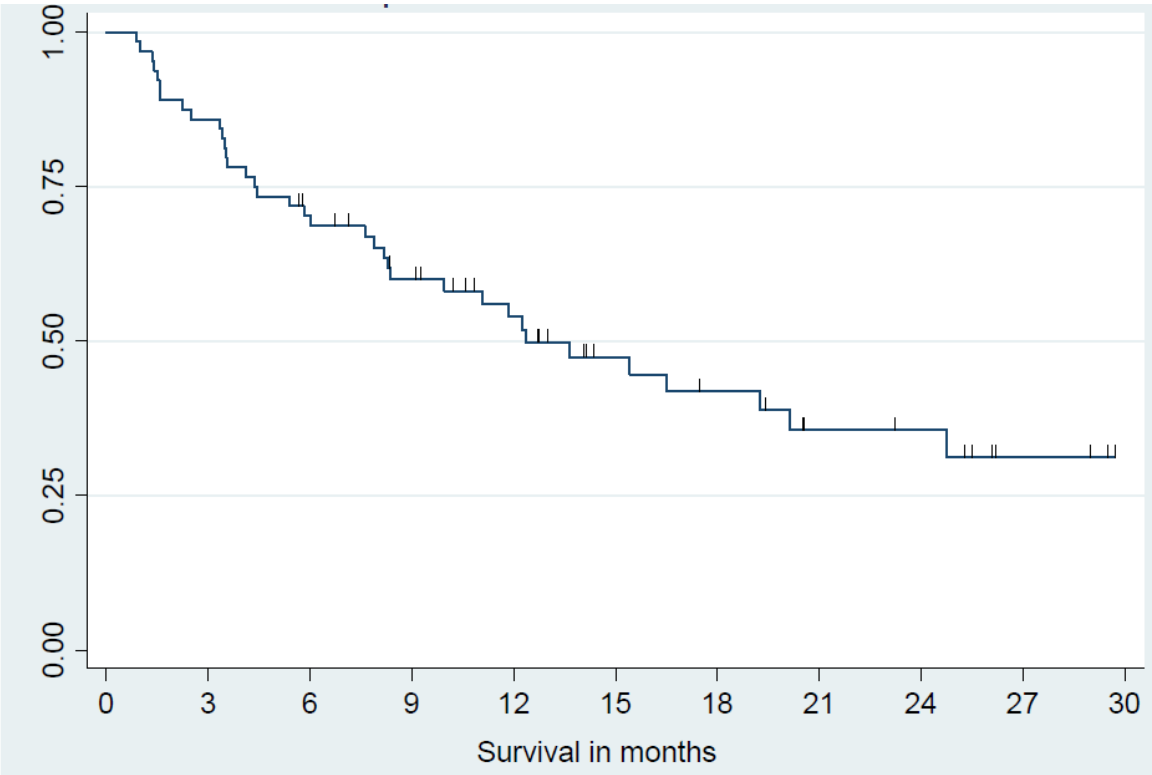


SACT, Systemic-Anti-Cancer Therapy, TTD, time to treatment discontinuation

The median OS was 12.4 months [95% CI: 8.3, 20.1] (377 days). OS at 6 months was 70% [95% CI: 57%, 80%], while OS at 12 months was 54% [95% CI: 41%, 66%]. The SACT OS Kaplan-Meier is shown in Figure 5.

Median OS in the SACT data set is comparable to the corresponding patient population in the IMvigor210 clinical trial (12.4m vs 12.3m).(10) The sample size in this population in IMvigor210 was 32. Further details on the SACT dataset are provided in Appendix B.

Figure 5 Kaplan-Meier plot of SACT dataset OS atezolizumab (n=64)



OS, overall survival; SACT, Systemic-Anti-Cancer Therapy

A.7 Evidence synthesis

Not applicable for this review.

A.8 Incorporating collected data into the model

A.8.1 *Extrapolation methods*

OS, PFS and TTD results from IMvigor130 were extrapolated to the time-horizon of the model as lifetime results are not available for subjects in the IMvigor130 study. Curve selection guidance from the NICE Decision Support Unit (DSU) was followed to identify base-case parametric survival models for OS, PFS and TTD (7, 11).

The validity of the proportional hazards assumption between treatments was assessed. This was tested using the proportional hazards Schoenfeld residual test and via visual inspection of the log-cumulative hazard plots. All parametric models were assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data. Curves were visually inspected and validated against relevant long-term data sources available to help identify the most plausible survival model. Clinical expert opinion was also

utilised to validate the extrapolation approach taken. Further details of the consultations are provided in Appendix D. More detailed information on OS, PFS and TTD curve choices are provided in Appendices E.1-3.

A.8.2 *Overall survival*

The log-cumulative hazard plot and the Schoenfeld residual test indicate that the proportional hazards assumption cannot be rejected (Appendix E.1). Independent models were used to model OS but the same functional form was used to account for proportional hazards between the two treatment arms (11).

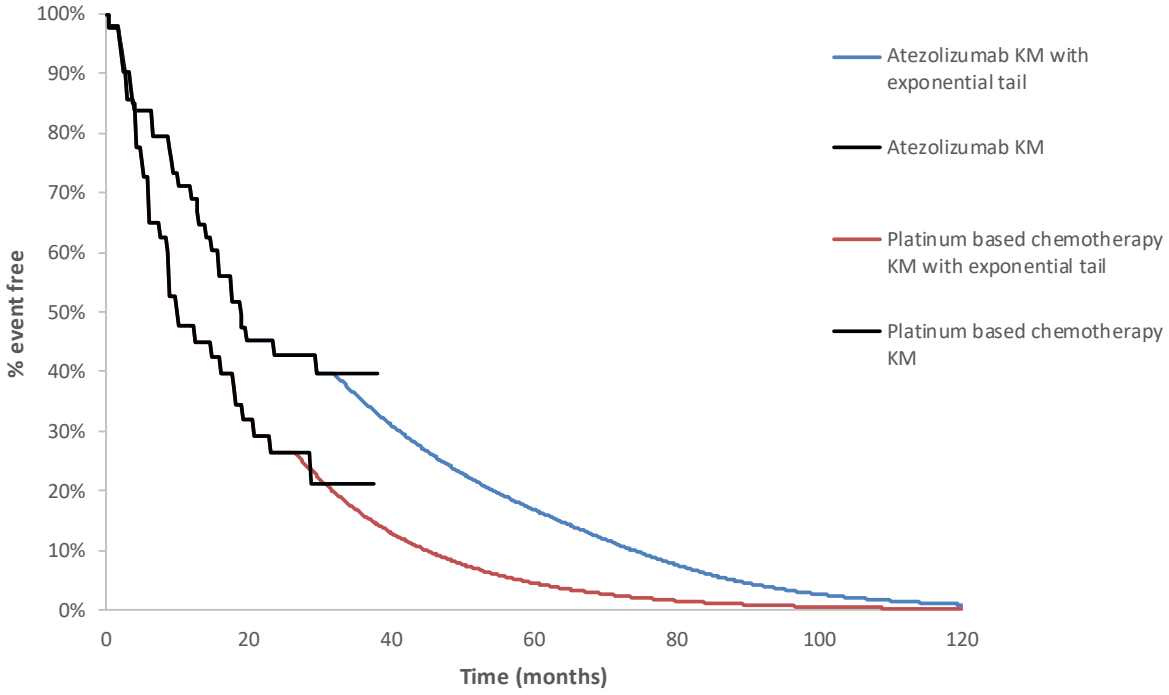
The distributions with the best statistical fit to the observed atezolizumab and platinum-based chemotherapy OS data were the exponential and log-logistic curves respectively (Appendix E.1).

In order to maintain consistency with the scenario that provided entry into the CDF, the KM model was used for the early part of the model with a parametric extrapolation used for the tail of the curve. The exponential curve was selected to model the tail of the atezolizumab and platinum-based chemotherapy OS curves as this was considered to give the most plausible long-term survival. The exponential curve represents the best statistical fit, for atezolizumab, the most conservative extrapolation, the extrapolation that most closely aligned with the SACT dataset (Appendix B), and was the preferred curve choice based on feedback from clinical experts. The KM curve with a log-logistic tail was used as a scenario analysis (Scenario 1).

The KM curve with exponential extrapolation chosen for the base-case analysis gives an estimated 5-year OS of 17% and 5% in the atezolizumab and platinum-based chemotherapy arms respectively. In both instances, this sits within the range considered plausible by the committee (10–28% in the atezolizumab arm, 1-12% in the carboplatin plus gemcitabine arm) (Committee discussion TA492, 3.9, 3.23 (12)). The 5-year OS of patients in the atezolizumab arm of 17% is less than the proportion of patients responding to treatment, 40%. This is in comparison to 28% and 23% respectively in the original submission, a relationship the committee considered infeasible. However, it should be noted that due to the addition of PD-L1-positive patients to the licenced indication, direct comparisons are of limited relevance and are provided here for reference only.

Figure 6 displays the OS KM curves + exponential tail used in the cost-effectiveness model to represent OS for atezolizumab and platinum-based chemotherapy. This evidence addresses a key uncertainty identified by the committee (Section A.2) and demonstrates the OS benefit of atezolizumab.

Figure 6 Kaplan-Meier plot of IMvigor130 OS atezolizumab vs. platinum-based chemotherapy and curves used in the economic model (Figure 23, TA492, Section 5.3.3 p154 (3))



KM, Kaplan-Meier; OS, overall survival

A.8.3 *Progression-free survival*

The log-cumulative hazard plot and the Schoenfeld residual test indicate that the proportional hazards assumption can be rejected (Appendix E.2). Therefore, independent models were used to model PFS. In line with NICE guidance, the same distribution was used in both treatment arms (11).

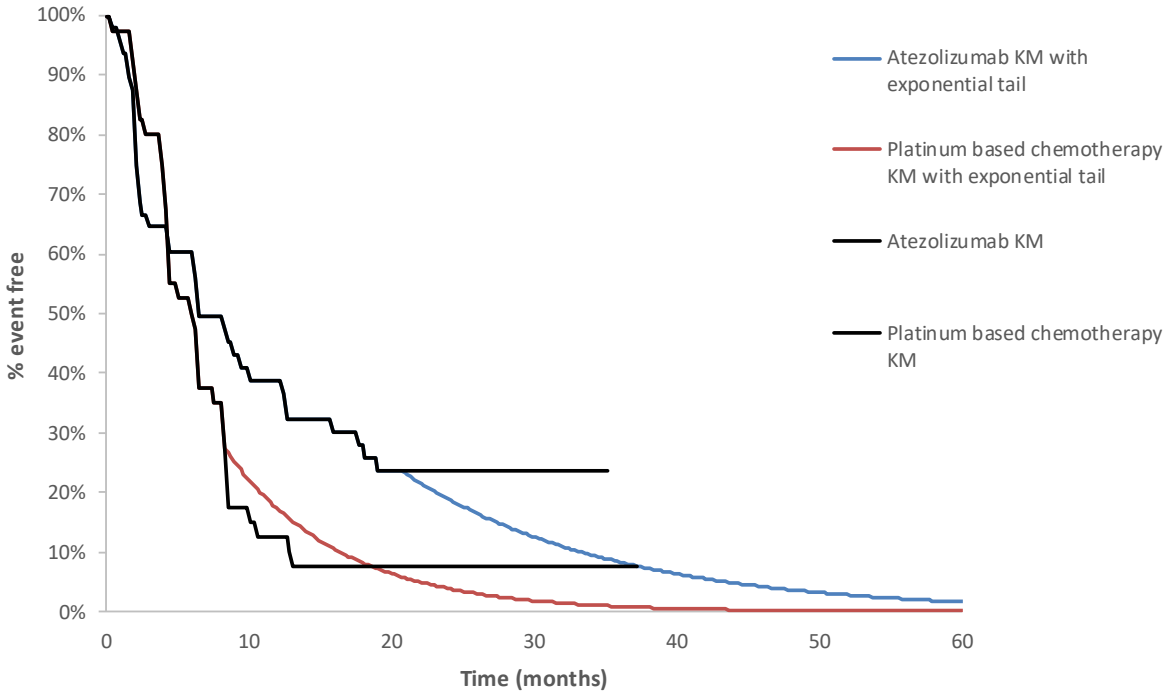
The distributions with the best statistical fit to the observed atezolizumab and platinum-based chemotherapy PFS data were the generalised gamma and log-logistic curves respectively (Appendix E.2).

In order to maintain consistency with the scenario that provided entry into the CDF, the KM model was used for the early part of the model with a parametric extrapolation used for the tail of the curve. Based on feedback from clinical experts, the more conservative exponential curve was selected to model the tail of the

atezolizumab and platinum-based chemotherapy PFS curves as this was considered to give the most plausible long-term estimates. The KM curve with a log-logistic tail was used as a scenario analysis (Scenario 2).

Figure 7 displays the PFS KM curves + exponential tail used in the cost-effectiveness model to represent PFS for atezolizumab and platinum-based chemotherapy. This evidence has addressed a key uncertainty identified by the committee (Section A.2) and demonstrates the PFS benefit of atezolizumab.

Figure 7 Kaplan-Meier plot of IMvigor130 PFS atezolizumab vs. platinum-based chemotherapy and curves used in the economic model (Figure 29, TA492, Section 5.3.6 p165 (3))



KM, Kaplan-Meier; PFS, progression-free survival

A.8.4 *Treatment duration*

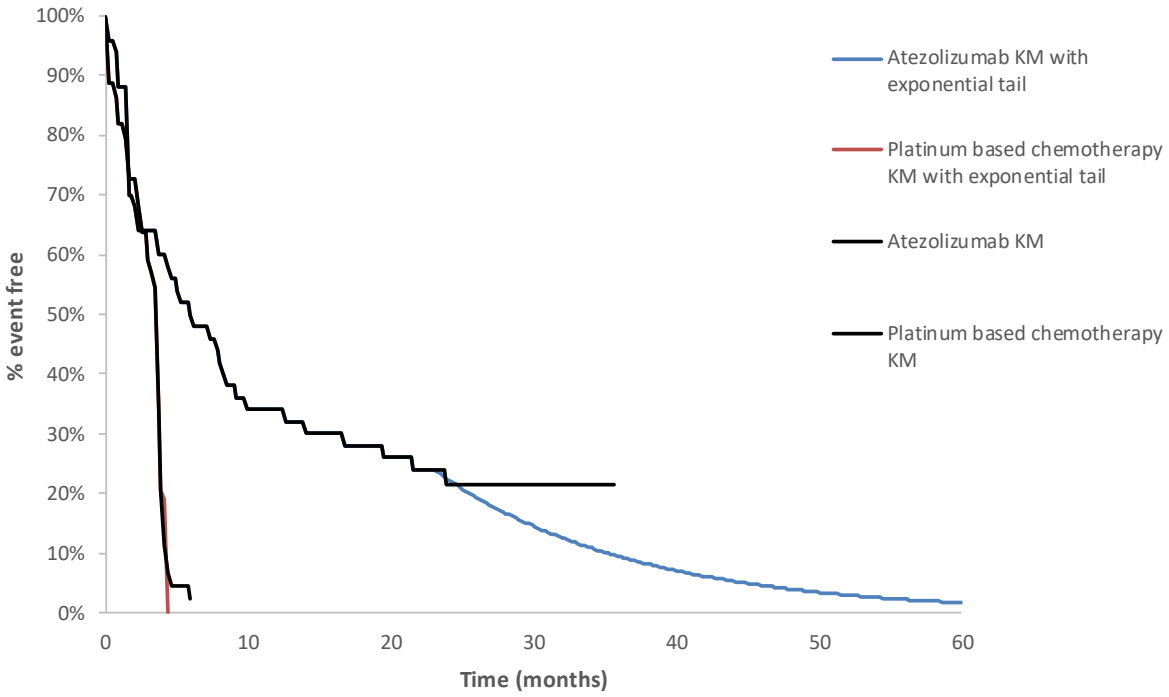
Given that treatment in the platinum-based chemotherapy arm was restricted to six cycles, no proportional hazards testing was conducted on TTD between atezolizumab and platinum-based chemotherapy. Independent models were used to model TTD. In line with NICE guidance, the same distribution was used in both treatment arms (11).

The distributions with the best statistical fit to the observed atezolizumab and platinum-based chemotherapy TTD data were the Gompertz distribution in both cases (Appendix E.3).

Based on NICE guidance and feedback from clinical experts, the exponential curve was selected to model atezolizumab and platinum-based chemotherapy TTD curves as this was considered to give the most plausible long-term estimates. Given a poor fit to the observed data, the KM curve was used to model a closer fit in the observed trial period. The Weibull curve was used as a scenario analysis (Scenario 3).

Figure 8 displays the KM curves + exponential tail used in the cost-effectiveness model to represent TTD for atezolizumab and platinum-based chemotherapy. This evidence has addressed a key uncertainty identified by the committee (Section A.2).

Figure 8 Kaplan-Meier plot of IMvigor130 TTD atezolizumab vs. platinum-based chemotherapy and curves used in the economic model (Figure 32, TA492, Section 5.5.5 p194 (3))



KM, Kaplan-Meier; TTD, time to treatment discontinuation

A.8.5 *Duration of treatment effect*

In the original company submission (TA492 (3)), no cap on the OS treatment effect was included in the economic model, although both the committee and the company recognised that the duration of the OS treatment effect is a potential source of uncertainty.

Roche sought consultation on the potential duration of treatment effect from three clinical experts in mUC (Appendix D). The feedback was consistent in that they all

expected the potential treatment benefit on survival of atezolizumab over platinum-based chemotherapy to last longer than the observed data from IMvigor130, and will persist past the end of treatment. It is plausible that some patients in the atezolizumab arm, likely to be younger and respond to treatment, demonstrate longer-term survival and therefore long-term survival plateaus with their risk of death moving in the direction of general population mortality as the risk of death from mUC decreases and increases from other comorbidities. Clinical experts suggested they expected a long-term treatment benefit of atezolizumab over platinum-based chemotherapy with a best estimate of 5–7 years after the start of treatment.

The base case in the original company submission (TA492 (3)) did not include a cap on the duration of the OS treatment effect. Based on clinical expert advice, the treatment effect of atezolizumab over platinum-based chemotherapy was said to last for 5 years from the start of treatment with the treatment effect waning for a further 2 years (up to 7 years from the start of treatment), with no treatment effect thereafter. To explore the impact of potential uncertainty around the duration of the OS treatment effect on results, the following scenario analyses were provided (Appendix I):

- No cap on treatment effect
- 7-year cap on OS treatment effect
- OS treatment effect cap wanes from 5 years to 7 years (base case)
- 5-year cap on treatment effect

A.8.6 *Health state utility values*

A summary of utility values used in the economic model is provided in Table 11. Health state utilities are aligned to pre/post progression. Atezolizumab displays a statistically significant HRQoL benefit over platinum-based chemotherapy in both the PF and PD health state. The HRQoL benefit in the PF health state was validated by clinical experts (Appendix D). Clinical experts also suggested that the HRQoL benefit might continue after patients have discontinued treatment. However, given the small number of observations (n=177) leading to uncertainty in the benefit, the base case PD health state was combined across both treatment arms. This aligns with the approach in the original company submission (TA492, Section 5.4.6, pages 179–180 (3)) where the health state utility value for PD was combined across both treatment

arms. Scenario analyses were conducted to explore the impact of utility values being applied on/off treatment and for other approaches to PD health state utilities (Scenario 4 and Appendix I). This evidence has addressed a key uncertainty identified by the committee (Section A.2) and demonstrates the HRQoL benefit of atezolizumab.

Table 11 Summary of utility values for cost-effectiveness analysis (Table 62, TA492, Section 5.4.6 p180 (3))

	Atezolizumab (95% CI)	Platinum-based chemotherapy (95% CI)
PF	0.642 (0.534, 0.750)	0.527 (0.404, 0.649)
PD	0.567 (0.481, 0.653)	

CI, confidence intervals; PD, progressed disease; PF, progression-free

A.8.7 *Subsequent treatments*

Subsequent treatments were not previously included in the original company submission (TA492 (3)) as at the time of submission there was a limited difference in the incremental costs between the potential subsequent treatments, leading to a negligible impact on results.

In June 2018, atezolizumab for treating locally advanced or metastatic UC after platinum-containing chemotherapy was recommended by NICE (13). Patients who receive atezolizumab in the first-line setting are unlikely to receive further immunotherapy in second-line; however, patients who receive first-line platinum-based chemotherapy commonly receive immunotherapy in the second-line. This is significant as immunotherapies incur a non-negligible cost to the healthcare system. Therefore, as per the Terms of Engagement meeting, subsequent therapies were included in this CDF review and the costs of subsequent treatments have been included in the economic model.

The distribution of subsequent treatments is multiplied by the acquisition and administration costs of each subsequent treatment and applied as a one-off cost in the economic model when patients enter the PD health state. Those patients who are not modelled to receive a subsequent treatment are modelled to receive best supportive care, which is not associated with additional cost.

Distribution of subsequent treatments

Data on the treatment and duration of subsequent treatments was collected in IMvigor130 (Section A.6.1). A high proportion of subjects in the clinical trial went on to receive treatments that are unlicensed, not recommended by NICE, or not standard practice in the UK. After consultation with key clinical experts (Appendix D), it was deemed inappropriate to use IMvigor130 subsequent treatments in the economic model to reflect UK practice. Therefore, the distribution of subsequent treatments that accurately reflects UK practice was estimated via expert opinion and used in the economic model base case (Table 12). It was estimated that 55% of patients in each treatment arm go on to receive second-line subsequent treatment. In the platinum-based chemotherapy arm, the majority (50%) would receive immunotherapy. Third-line subsequent treatment was not included in the model as there is a negligible difference in the incremental costs between the two treatment arms.

In IMvigor130, 21% of patients in the platinum-based chemotherapy arm received subsequent immunotherapy. A potential limitation of aligning subsequent treatment costs with UK practice is that, due to the survival benefit of immunotherapy, it may not be suitable to include the costs of subsequent immunotherapy if the impact on survival outcomes were not also included. The disparity of subsequent treatment usage between IMvigor130 and UK practice (21% vs 50%) might lead to an underestimation of OS in the comparator arm. Therefore, a scenario analysis was undertaken assuming the subsequent treatment distribution from IMvigor130 (Table 13; Scenario 5). Further subsequent treatment scenarios were explored in Appendix I.

For treatment durations, the IMvigor130 trial data contained too few observations to calculate duration on treatment for each individual subsequent treatment. Therefore, the mean treatment durations were pooled across treatments. Typically, patients receiving immunotherapy as a subsequent treatment have a longer time on treatment than non-immunotherapy patients (14),(15). Therefore, mean treatment duration for immunotherapies were taken from the respective NICE appraisal (14),(15).

Table 12 Subsequent therapies after discontinuation from atezolizumab and platinum-based chemotherapy as per expert opinion (base case)

Subsequent treatment	Atezolizumab		Platinum-based chemotherapy	
	Number of patients (%)	Mean treatment duration (months)	Number of patients (%)	Mean treatment duration (months)
Atezolizumab	0	--	50	10.7
Carboplatin + gemcitabine	44	4.0	0	--
Paclitaxel	11	4.0	6	2.8
Total	55		55	

Table 13 Subsequent treatments used in economic model as per IMvigor130 (Scenario 5)

Subsequent treatment	Atezolizumab		Platinum-based chemotherapy	
	Number of patients	Mean treatment duration (months)	Number of patients	Mean treatment duration (months)
Atezolizumab	--	--	9	10.7
Vofatamab	--	--	5	2.8
Carboplatin	24	4.0	7	2.8
Cisplatin	8	4.0	5	2.8
Doxorubicin	--	--	2	2.8
Gemcitabine	32	4.0	7	2.8
Gemcitabine hydrochloride	4	4.0	--	--
Methotrexate	--	--	7	2.8
Nivolumab	--	--	9	10.5
Paclitaxel	4	4.0	23	2.8
Pembrolizumab	--	--	2	10.5
Vinblastine	--	--	2	2.8
Vinflunine	4	4.0	--	--

Vofatamab is not available in the UK and therefore no cost was assumed.
Time on treatment for nivolumab was not reported publically in TA530 and therefore was assumed equal to pembrolizumab.

Subsequent treatment costs

Drug acquisition costs for the subsequent treatments included in the economic model are summarised in Table 14. For medicines available to the National Health Service (NHS) as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a generic medicine for the last period (16). For medicines only available to the NHS as proprietary medicines, prices are taken as

the list price stated in the British National Formulary (BNF) (17). A PAS of [redacted] was used for atezolizumab. Administration costs were sourced from 2018-19 NHS reference costs (18).

Table 14 Subsequent treatment acquisition and administration costs

Drug	Dose	List price cost (£)	Source	Unit (mg)	Admin. Cost (£)	Source
Atezolizumab	1,200mg Q3W	3,807.69	BNF	1,200	199	NHS ref.
Vofatamab	--	--	--	--	--	--
Carboplatin	400mg/m^2 Q3W	3.28	eMIT	200	199	NHS ref.
Cisplatin	70mg/m^2 Q3W	6.66	eMIT	100	199	NHS ref.
Doxorubicin	75mg/m^2 Q3W	17.21	eMIT	200	199	NHS ref.
Gemcitabine	1,000mg/m^2 Q3W	3.75	eMIT	50	199	NHS ref.
Gemcitabine hydrochloride	1,000mg/m^2 Q3W	3.75	eMIT	50	199	NHS ref.
Methotrexate	30mg/m^2 Q3W	8.70	eMIT	500	199	NHS ref.
Nivolumab	240mg Q2W	2,633.00	BNF	240	199	NHS ref.
Paclitaxel	175mg/m^2 Q3W	39.32	eMIT	300	199	NHS ref.
Pembrolizumab	200mg Q3W	2,633.00	BNF	200	199	NHS ref.
Vinblastine	100mg/m^2 Q3W	85.00	BNF	10	199	NHS ref.
Vinflunine	320mg/m^2 Q3W	212.50	BNF	50	199	NHS ref.

BNF, British National Formulary; eMIT, electronic market information tool; NHS, National Health Service

A.9 Key model assumptions and inputs

Table 15 Key model assumptions and inputs (Table 72, TA492, Section 5.6.2 p202 (3))

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification

Primary study used for clinical efficacy data (OS, PFS, TTD)	IMvigor210 data cut-off Jul 2016, cohort 1 (cisplatin-ineligible)	IMvigor130 data cut-off June 2020, cisplatin-ineligible (as per the Galsky criteria) PD-L1-positive subgroup	IMvigor210 represents a single-arm trial and therefore leads to uncertainties regarding the treatment effect of atezolizumab compared to platinum-based chemotherapy. IMvigor130 represents a randomised phase III trial between the two treatments and therefore reduces the uncertainty of the treatment effect, as per the terms of the CDF. The population has been updated to reflect the updated EMA licence
BSA	1.93m^2 as per IMvigor210 cohort 1	1.77m^2 as per IMvigor130 cisplatin-ineligible, PD-L1-positive subgroup	The BSA has been updated to reflect the different baseline patient characteristics between IMvigor210 and IMvigor130
Modelling of OS (Section, 5.3.5 page 159)	Atezolizumab modelled with IMvigor210 KM curve with exponential tail. Platinum-based chemotherapy modelled using results of fractional polynomial modelled	Atezolizumab and platinum-based chemotherapy modelled using respective IMvigor130 KM curves with exponential tail	IMvigor130 represents a Phase III trial which allows comparison of relative efficacy from trial data as per NICE's preferred method and addressing a key committee uncertainty from the original appraisal. Curve selections were made following NICE guidance (7)
Treatment effect on OS (Committee discussion, TA492, 3.12 (3))	Treatment effect is maintained	Treatment effect wanes from 5-7 years	Both the committee and the company recognised that the duration of the OS treatment effect is a potential source of uncertainty. A cap on treatment effect was introduced to align with the best estimates of clinical experts
Modelling of PFS curve selection (Section 5.3.3, page 152)	Atezolizumab modelled with IMvigor210 KM curve with Weibull tail. Platinum-based chemotherapy modelled assuming identical to atezolizumab	Atezolizumab and platinum-based chemotherapy modelled using respective IMvigor130 KM curves with Weibull tail	IMvigor130 represents a Phase III trial which allows comparison of relative efficacy from trial data as per NICE's preferred method and addressing a key committee uncertainty from the original appraisal. Curve selections were made following NICE guidance (7)
TTD curve selection (Section 5.5.5, page 191)	Atezolizumab modelled with IMvigor210 Weibull curve. Platinum-	Atezolizumab and platinum-based chemotherapy modelled using respective	IMvigor130 represents a Phase III trial which allows comparison of relative efficacy from trial data as per NICE's preferred method and addressing a key committee uncertainty from the original

	based chemotherapy modelled assuming identical to PFS	IMvigor130 Weibull curves	appraisal. Curve selections were made following NICE guidance (7)
Utility (Section 5.4.6, page 179)	PF health state utilities taken directly from vinflunine PBAC submission (PF: 0.75), PD health state arbitrarily assumed as 0.5	PF and PD health state utility values taken from IMvigor130 (atezolizumab PF: 0.642, platinum-based chemotherapy PF:0.527, PD: 0.567)	Utility values collected directly from trial as per NICE's preferred method and addressing a key committee uncertainty from the original appraisal
Year of costs	2016	2020	Drug costs, administration costs, adverse event costs and supportive care costs were updated to reflect current prices with the latest versions of eMIT, NHS reference costs and inflated using the PSSRU inflation index where necessary
Subsequent treatments (Section 5.2.2, page 149)	Subsequent treatments were excluded from the economic model	Subsequent treatments were included in the model with the distributions of treatments received aligned to UK practice based on clinical expert opinion	Following entry into the CDF, immunotherapies, which have a non-negligible cost and a potentially significant impact on the results, were approved for use and became standard of care for 2L UK patients
Atezolizumab PAS (Section 5.5.4, page 189)	[redacted]	[redacted]	[redacted]

2L, second-line; BNF, British National Formulary; BSA, body surface area; CDF, Cancer Drugs Fund; EMA, European Medicines Agency; eMIT, electronic market information tool; KM, Kaplan-Meier; NICE, National Institute for Health and Care Excellence; OS, Overall survival; PAS, patient access scheme; PBAC, Pharmaceutical Benefits Advisory Committee; PD-L1, programmed death ligand 1; PD, progressed disease; PF, progression-free, PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; TTD, time to treatment discontinuation, UK, United Kingdom

A.10 Cost-effectiveness results (deterministic)

Table 16 shows the deterministic results for the three CDF results criteria.

- Cost-effectiveness analysis 1 shows results from the original submission (Committee discussion TA492, 3.13 (12).
- Cost-effectiveness analysis 2 shows those results replicated but with IMvigor130 data replacing IMvigor210.
- Cost-effectiveness analysis 3 represents the new company base case with assumptions amended to reflect best practice with the updated clinical trial data and to reflect the present day conditions.

All analyses include a PAS for atezolizumab.

[redacted] Appendix F outlines the different assumptions used in each of these scenarios. For disaggregated and list price results, see Appendices H and J respectively.

By comparing the analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cost-effectiveness analysis 1) with the identical analysis but incorporating the updated clinical evidence (cost-effectiveness analysis 2), we observe that atezolizumab demonstrates a higher incremental outcome benefit in the updated analysis [inc. life years gained (LYG) [redacted] vs [redacted], inc. QALYs [redacted] vs. [redacted]. This demonstrates the improved survival in the IMvigor130 data and the updated patient population.

In the new company base case (cost-effectiveness analysis 3), atezolizumab provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted] in comparison to platinum-based chemotherapy. This represents an ICER of £21,838 per LYG and an ICER of £32,708 per QALY gained. As per the original appraisal and Terms of Engagement document, atezolizumab meets the end-of-life criteria.

Table 16 Cost-effectiveness results (deterministic, Table 73, TA492, Section 5.7.1 p204 (3))

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,065	66,735

Platinum-based chemotherapy	12,397	1.10	0.65	--	--	--	--	--
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,658	84,967
Platinum-based chemotherapy	14,110	1.47	0.82	--	--	--	--	--
Cost-effectiveness analysis 3: New company base-case								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,838	32,708
Platinum-based chemotherapy	22,085	1.47	0.82	--	--	--	--	--

CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A.11 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. All parameters and distributions used in the PSA are outlined in Appendix G. A Monte-Carlo simulation was conducted, where 1,000 iterations were used to ensure convergence. For list price results, see Appendix J.

The results of the new company base case PSA are presented in Table 17. In the new company base case (cost-effectiveness analysis 3), atezolizumab provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted] in comparison to platinum-based chemotherapy. This represents an ICER of £22,480 per LYG and an ICER of £33,602 per QALY gained. In 93.2% of iterations, the ICER was lower than £50,000. The PSA demonstrates the reduction in uncertainty in the model associated with the updated data and that results are robust to probabilistically varying assumptions.

Table 17 PSA results (new company base case, Table 90, TA492, Section 5.8.1 p216 (3))

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,480	33,602
Platinum-based chemotherapy	22,554	1.48	0.82	--	--	--	--	--

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Error! Reference source not found. displays the cost-effectiveness plane for the new company base case based on 1,000 iterations.

Figure 9 Cost-effectiveness plane results of atezolizumab and platinum-based chemotherapy (new company base case, Figure 42, TA492, Section 5.8.1 p217 (3))

QALYs, quality-adjusted life years

A.12 Key sensitivity and scenario analyses

A.12.1 *Deterministic sensitivity analysis*

A deterministic sensitivity analysis (DSA) was performed to investigate key drivers of the base-case results. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. The base-case parameter values were varied across their 95% CI where possible. The parameter values used in the DSA are displayed in Table 18. The tornado diagram for atezolizumab versus platinum-based chemotherapy is presented in Figure 10 with the six most influential parameters shown. The DSA highlighted that the PD supportive care costs for atezolizumab and the PF health state utility value for atezolizumab had the greatest impact on the cost-effectiveness results. The ICER

remained below £50,000/QALY in all analyses. Results with the atezolizumab list price are included in Appendix J.

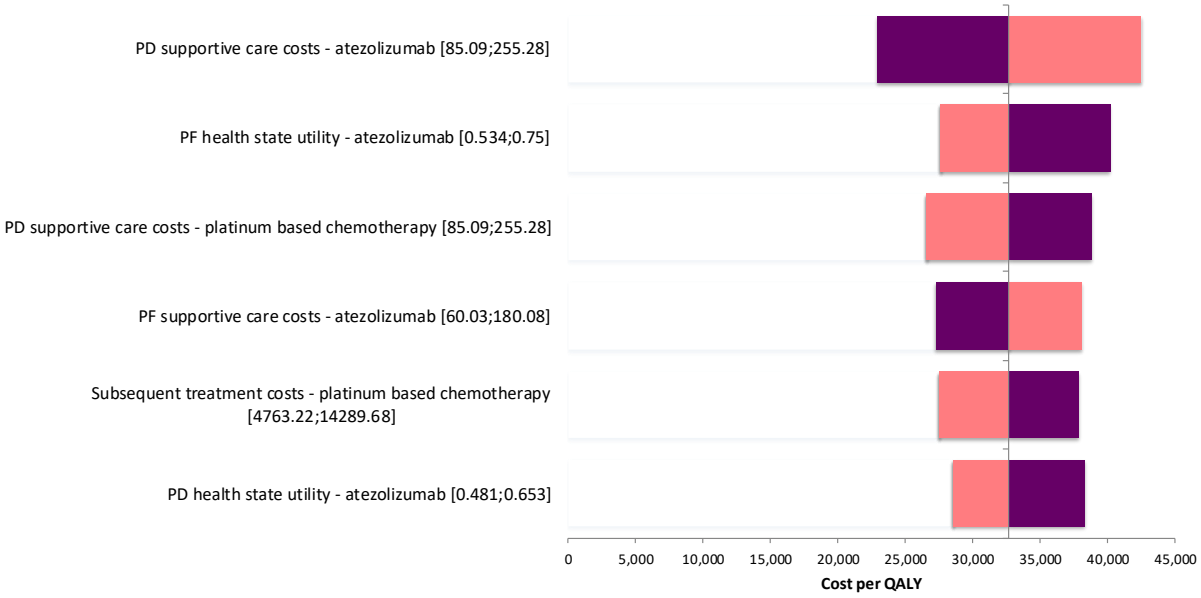
Table 18 Parameter values used for DSA and results (new company base case, Table 92, TA492, Section 5.8.2 p219 (3))

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	1.77	1.42	32,649	2.13	32,696	+/-20%
First admin cost - atezolizumab	183.54	146.83	32,649	220.25	32,696	+/-20%
First admin cost – platinum-based chemotherapy	259.08	207.27	32,948	310.90	32,756	+/-20%
Subsequent admin cost - atezolizumab	183.54	146.83	31,668	220.25	32,500	+/-20%
Subsequent admin cost – platinum-based chemotherapy	259.08	207.27	33,560	310.90	32,878	+/-20%
PF supportive care costs - atezolizumab	120.06	60.03	27,313	180.08	38,102	+/-50%
PF supportive care costs – platinum-based chemotherapy	120.06	60.03	35,953	180.08	29,462	+/-50%
PD supportive care costs - atezolizumab	170.19	85.09	22,985	255.28	42,431	+/-50%
PD supportive care costs – platinum-based chemotherapy	170.19	85.09	38,827	255.28	26,589	+/-50%

Subsequent treatment costs - atezolizumab	1,360.18	680.09	32,042	2,040.28	33,374	+/-50%
Subsequent treatment costs – platinum-based chemotherapy	[redacted]	[redacted]	37,851	[redacted]	27,564	+/-50%
PF health state utility - atezolizumab	0.642	0.534	40,182	0.75	27,578	95% CI
PF health state utility - platinum-based chemotherapy	0.527	0.404	30,671	0.649	35,014	95% CI
PD health state utility - atezolizumab	0.567	0.481	38,283	0.653	28,550	95% CI
PD health state utility – platinum-based chemotherapy	0.567	0.481	29,242	0.653	37,105	95% CI

BSA, body surface area; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PD, progressed disease; PF, progression-free

Figure 10 Tornado plot (new company base case, Figure 46, TA492, Section 5.8.2 p220 (3))



PD, progressed disease; PF, progression-free

A.12.2 *Scenario analyses*

Scenario analyses were conducted to assess uncertainty around structural assumptions of the new company base case. Results for five key scenario analyses are presented in Table 19. Results with the atezolizumab list price are included in Appendix J and full scenario results are presented in Appendix I. In every scenario in the analysis, the ICER remains under £50,000, demonstrating robustness of results.

Table 19 Key scenario analysis (new company base case, Table 93, TA492, Section 5.8.3 p222 (3))

No.	Parameter and cross reference	Base-case	Scenario	Brief rationale	Inc. costs	Inc. QALYs	ICER/ QALY
Base-case					[redacted]	[redacted]	32,708
Scenarios							
1.	OS curve selection for atezolizumab and platinum-based chemotherapy	KM curve with exponential tail	KM curve with log-logistic tail	Deemed alternative plausible curve choice	[redacted]	[redacted]	28,129
2.	PFS curve selection for atezolizumab and platinum-based chemotherapy	KM curve with exponential tail	KM curve with log-logistic tail	Deemed alternative plausible curve choice	[redacted]	[redacted]	30,116
3.	TTD curve selection for atezolizumab and platinum-based chemotherapy	KM curve with exponential tail	Weibull	Deemed alternative plausible curve choice	[redacted]	[redacted]	45,383
4.	PD health state utility values	Atezolizumab and platinum-based chemotherapy PD: 0.567	Atezolizumab and platinum-based chemotherapy PD: 0.500	To align with the most conservative scenario demonstrated in Committee discussion (TA492, 3.12 (3))	[redacted]	[redacted]	33,413
5.	Subsequent treatment distribution	UK standard practice based on clinical expert opinion	IMvigor130	For costs to reflect the IMvigor130 efficacy data	[redacted]	[redacted]	32,676

KM, Kaplan-Meier; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation; UK, United Kingdom

A.13 Key issues and conclusions based on the data collected during the CDF review period

During the original appraisal (November 2017) the committee indicated that atezolizumab had the potential to be cost-effective for the treatment of cisplatin-ineligible patients (Committee discussion TA492, 3.12 (12)), however the appraisal was characterised by key uncertainties. Therefore, the committee recommended atezolizumab for inclusion in the CDF for people with untreated locally advanced or metastatic UC for whom cisplatin is unsuitable. This temporarily addressed the high-unmet need for mUC patients. The committee concluded that the IMvigor130 trial and data from the SACT dataset would provide evidence to address most of the uncertainties in the clinical evidence:

- The relative effectiveness of atezolizumab on PFS and OS (Committee discussion TA492, 3.11, 3.25 (3))
- The duration of treatment with atezolizumab (Committee discussion TA492, 3.10, 3.25 (3))
- The appropriate health-related quality-of-life/health state utility values (Committee discussion TA492, 3.15, 3.25 (3))
- The effectiveness for PD-L1 subgroups (Committee discussion TA492, 3.16, 3.25 (3)).

Following the collection of IMvigor130 and SACT data to address these uncertainties, atezolizumab will exit the CDF in 2021 with an updated appraisal to review the reimbursement status. After the original appraisal, atezolizumab received EMA marketing authorisation, which restricted the licence to the PD-L1-positive population. The population of this CDF review was updated to reflect this licence and the cisplatin-ineligible PD-L1 positive subgroup of IMvigor130 was used. Due to this change in population, direct comparisons of efficacy evidence between the original company submission and this CDF review are of limited use.

Evidence has been provided to address each of the key uncertainties identified by the committee. Subjects in IMvigor130 receiving atezolizumab were associated with increased OS (median OS 18.6m vs. 10.0m, HR 0.50, CI 0.29, 0.87, p=0.0125), increased PFS (median PFS 6.4m vs. 6.0m, HR 0.56, CI 0.34, 0.93, p=0.0235) and a statistically significant HRQoL benefit (PF health state utility value 0.642 vs. 0.527)

versus platinum-based chemotherapy (4, 5). Due to the IMvigor130 statistical testing hierarchy, conclusions on statistical significance are unable be drawn on these comparisons. However, they do represent clinically meaningful results.

With this updated data from IMvigor130 and real-world evidence validation from SACT, the economic model from the original company submission has been updated and the uncertainties identified by the committee have been addressed. OS, PFS, TTD, health state utility values and subsequent treatments have been updated. The model remains a three health-state partitioned survival model with a 20-year time horizon from a NHS and Personal Social Services perspective. This document has outlined the changes as part of the CDF review.

The results of the economic model suggest that atezolizumab represents a cost-effective treatment option with an ICER/QALY gained of £32,708 (inc. cost [redacted], inc. QALYs [redacted], with [redacted] of the inc. QALY gain in the PF health state). As per the original appraisal and Terms of Engagement document, atezolizumab meets the end-of-life criteria. Results are robust to deterministic and probabilistic sensitivity analysis and extreme scenario analysis, which demonstrate the reduction in uncertainty in the model associated with the updated data.

Strengths

- Data in the economic model is taken directly from IMvigor130, a Phase III randomised trial that indicates atezolizumab is associated with increased OS and PFS compared to platinum-based chemotherapy. This reduces a key uncertainty identified by the committee (Section A.2).
- Health state utility values for PF and PD were collected directly from IMvigor130. This reduces a key uncertainty identified by the committee (Section A.2).
- All new inputs and changes to the model have been validated by clinical experts in mUC.

Uncertainties

- A restricted licence leading to an amended patient population meant that the relevant subgroup in IMvigor130 had a small sample size. Furthermore, due to the trial design in IMvigor130, statistical significance was unable to be

claimed for the comparison relevant to this submission. However, despite a small sample size, the IMvigor130 OS and PFS results provide evidence of a strong treatment effect, which can still be considered clinically meaningful.

- An SLR was conducted in an attempt to identify available evidence with a view to conducting a comparison vs. BSC (Appendix A). No relevant studies were identified and therefore, due a lack of evidence to inform the comparator arm, an analysis comparing atezolizumab to BSC could not be conducted.
- There is uncertainty over the long-term treatment effect of atezolizumab vs. platinum-based chemotherapy. This is an uncertainty that is common across immunotherapy appraisals. A treatment effect cap of 5-7 years (and further scenarios) were included in this appraisal based on clinical expert feedback to mitigate this.
- IMvigor130 was a multi-national trial and therefore subsequent treatments received by patients may not represent UK standard of care. Notably 20.9% of subjects in the platinum-based chemotherapy arm received immunotherapy vs. 49.5% expected in UK standard-of-care. This could underestimate survival in the comparator arm but it was not possible to adjust for this. The impact of a potential underestimation of comparator OS on results is mitigated by a cap on the treatment effect of atezolizumab on OS. Scenario analyses were conducted with a range of different assumptions on subsequent treatments demonstrating that the result of cost-effectiveness are not sensitive to these assumptions.

Atezolizumab represents a cost-effective treatment option for cisplatin-ineligible PD-L1-positive patients with untreated locally advanced or metastatic UC and should be recommended by NICE for routine use in England. Critically, for responding patients, atezolizumab has the potential to deliver a long lasting treatment effect not seen with conventional chemotherapy combinations. This would address the high-unmet need in mUC.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Clarification Questions Response

June 2021

File name	Version	Contains confidential information	Date
ID3777_NICE_Atezolizumab_Clarification_Questions_1LmUC_CIC	**V2**	**Yes**	**4th June 2021**

Section A: Clarification on effectiveness data

IMvigor130 trial

A1. Priority question. Selected baseline characteristics for the cisplatin-ineligible programmed death-ligand 1 (PD-L1) population in IMvigor130 are provided in Table 18, page 49, of the company submission (CS), Appendix C, Section C.2.7.3. Please also provide the baseline data for this population for the following characteristics: prior adjuvant or neoadjuvant regimen; site of primary bladder tumour; age-adjusted charlson comorbidity; site of metastatic disease; number of metastatic sites at enrolment; histology at initial diagnosis; impaired renal function and prior peripheral neuropathy grade >=2.

The baseline characteristics are displayed in Table 1.

Table 1: IMvigor130 additional baseline characteristics for the cisplatin-ineligible PD-L1-positive population

	Atezolizumab (n=50)	Platinum based chemotherapy (n=43)
Prior adjuvant or neoadjuvant regimen (%)		
Yes	4 (8.0)	4 (9.3)
No	46 (92.0)	39 (90.7)
Site of primary bladder tumour (%)		
Bladder	33 (66.0)	34 (79.1)
Renal pelvis	10 (20.0)	7 (16.3)
Ureter	7 (14.0)	2 (4.7)
Age-adjusted charlson comorbidity (%)		
0	0 (0.0)	1 (2.3)
1	2 (4.0)	1 (2.3)
2	1 (2.0)	1 (2.3)
3	1 (2.0)	3 (7.0)
4	6 (12.0)	0 (0.0)
5	1 (2.0)	0 (0.0)
6	1 (2.0)	5 (11.6)
7	3 (6.0)	3 (7.0)
8	8 (16.0)	7 (16.3)
9	7 (14.0)	4 (9.3)

10	4 (8.0)	2 (4.7)
11	8 (16.0)	5 (11.6)
12	1 (2.0)	4 (9.3)
13	3 (6.0)	5 (11.6)
14	0 (0.0)	2 (4.7)
17	1 (2.0)	0 (0.0)
18	1 (2.0)	0 (0.0)
19	1 (2.0)	0 (0.0)
Missing	1 (2.0)	0 (0.0)
Site of metastatic disease (%)		
Lung	18 (36.0)	11 (25.6)
Mediastinum	1 (2.0)	0 (0.0)
Liver	12 (24.0)	5 (11.6)
Bone	4 (8.0)	5 (11.6)
Visceral	26 (52.0)	15 (34.9)
Non-liver visceral	21 (42.0)	14 (32.6)
Non-bone visceral	24 (48.0)	13 (30.2)
Adrenal	1 (2.0)	1 (2.3)
Lymph node only disease	10 (20.0)	14 (32.6)
Pelvis	7 (14.0)	1 (2.3)
Peritoneum	5 (10.0)	1 (2.3)
Soft tissue	2 (4.0)	4 (9.3)
Spleen	0 (0.0)	1 (2.3)
Number of metastatic sites at enrolment		
0	6 (12.0)	7 (16.3)
1	17 (34.0)	20 (46.5)
2	17 (34.0)	9 (20.9)
3	7 (14.0)	5 (11.6)
>=4	3 (6.0)	2 (4.7)
Histology at initial diagnosis (%)		
Clinical	13 (26.0)	9 (20.9)
Pathological	37 (74.0)	34 (79.1)
Impaired renal function by calculated creatine clearance (%)		
<60	44 (88.0)	40 (93.0)
>=60	6 (12.0)	3 (7.0)
Prior peripheral neuropathy grade >=2 (%)		
Yes	1 (2.0)	1 (2.3)
No	49 (98.0)	42 (97.7)

PD-L1, programmed death-ligand 1

A2. Priority question. The updated clinical study report (CSR), based on the June 14, 2020 cut off, cites a primary CSR, which reports further details about the study design and results of co-primary endpoint (INV-PF) assessed at an earlier cut off. Please can this primary CSR be supplied to the evidence review group (ERG) (in advance of the response to the clarification questions if possible). Likewise, please provide the Statistical Analysis Plan (also cited in the update CSR).

The Primary CSR and Statistical Analysis Plan were uploaded to National Institute for Health and Care Excellence (NICE) Docs on 01/06/2021.

A3. Please provide a risk of bias/quality assessment of the IMvigor130 trial. CS, Appendix A, Section A.3, page 17, mentions that randomised controlled trials (RCTs) in the company's systematic literature review (SLR) were critically appraised using criteria based on guidance provided by the Centre for Reviews and Dissemination.

Table 2 displays the critical appraisal of clinical trials using criteria based on guidance provided by the Centre for Reviews and Dissemination.

Table 2 Clinical trials critically appraised using criteria based on guidance provided by the Centre for Reviews and Dissemination

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Any other sources of bias
EORTC study 30987 (1)	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lorusso 2005 (2)	Unclear	Unclear	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
EORTC Study 30924 (3, 4)	Low risk of bias	Low risk of bias	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
von der Maase 2000/2005 (5, 6)	Low risk of bias	Low risk of bias	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
IMvigor130 (7)	Low risk of bias*	Low risk of bias*	High risk of bias**	Low risk of bias***	Low risk of bias	Low risk of bias	Low risk of bias

* Patients were randomly assigned patients (1:1:1) with a stratified permuted block method (fixed block size) and an interactive voice–web response system

** Patients receive blinded atezolizumab plus open-label platinum-based chemotherapy (group A), open-label atezolizumab monotherapy (group B), or masked placebo plus open-label platinum-based chemotherapy (group C).

*** Progression-free survival (according to RECIST 1.1) determined by blinded independent central review. Protocol states: The Sponsor will remain blinded to the results until the analysis of the co-primary endpoint of PFS occurs.

A4. Would any of the IMvigor130 trial inclusion criteria have precluded patients from entry into the Cancer Drugs Fund (CDF)/ systemic anticancer treatment (SACT) data cohort study? In other words, would all 50 cisplatin-ineligible PD-L1-positive patients receiving atezolizumab in IMvigor130 have been eligible to receive atezolizumab via the CDF?

Overall, the SACT inclusion criteria is broadly in line with the IMvigor130 inclusion criteria. There are two small differences between the IMvigor130 trial's and SACT data cohort study's inclusion criteria (7, 8):

- In IMvigor130, patients with mixed histologies are required to have a dominant transitional cell pattern. There is no differentiation between complete transitional cell and mixed cell histologies in the SACT study.

- Prior local intravesical chemotherapy or immunotherapy was also allowed if completed at least 4 weeks prior to the initiation of study treatment in IMvigor130. In regards to the 50 patients, data is not available to determine whether any of the 50 patients had been treated with intravesical therapy or whether they had mixed histology.

A5. The clinical cut-off date for the second interim analysis (2IA) of overall survival (OS) presented in the CS is June 14, 2020. We note from the update IMvigor130 trial CSR, page 55, that a total of 579 deaths were reported up to this cut off, 86.8% of the 667 deaths required for the final analysis. Please can you indicate when the final OS analysis is likely to be reported/available?

The final analysis is estimated to be available Q2-3 2022.

Real world data

A6. Priority question. CS, Appendix A, page 5, reports the methods used to conduct a SLR to identify clinical evidence for best supportive care (BSC) "with a view to including BSC as a comparator in the economic analysis". The search terms used and the inclusion criteria are broad, and included studies of a range of treatments for patients with locally advanced or metastatic urothelial carcinoma (mUC) with no prior chemotherapy. However, it is not

evident to the ERG how evidence for BSC specifically was sought in this review, other than "*Prospective RCTs (phase 2-4) with active or placebo or BSC controls with no restriction on blinding"* being listed as a study design criterion in the CS, Appendix A, Section A.3, Table 7, page 19. The conclusion stated in the CS, Appendix A, Section A.5, page 26, "*No studies were identified. Therefore, as in the original submission, BSC was not able to be included."* does not appear to be completely supported by the methods presented.

a. **Please can you elaborate on the methods used to identify and screen evidence for BSC. In particular, was there a search to identify real world evidence for BSC in this patient group (or similar group)?**

Treatments included in the SLR were cross-referenced against all previous meta-analyses (9-13) and all possible treatments in first-line mUC were included and searched for. Therefore, any studies that contained a BSC arm would have been identified in search results. While the search was not specifically designed to identify real world evidence, any relevant clinical studies (RCTs and non-RCTs) which had a BSC arm would have been identified and considered for inclusion.

b. **In the absence of any randomised trial evidence of BSC, was consideration given to conducting an indirect comparison between atezolizumab and any BSC real world evidence, using a method such matched adjusted indirect comparison?**

<u>Feasibility of real world evidence comparison</u>

Roche have considered the possibility of using real world evidence from the Flatiron dataset to conduct an indirect comparison of atezolizumab vs. BSC in the target patient population. The BSC population from a real world evidence study would not lead to an accurate representation of the true treatment effect in relation to this decision problem as the patient population identified would be small, incomplete (risking bias) and the eligibility criteria would not be representative of the true patient population.

Small and incomplete data set

The Flatiron dataset is a United States (US) electronic health record that contains de-identified real world data on patient's treatments and outcomes. The Flatiron dataset contains data on oncology drugs from the following categories: anti-infective, antianemic, antidepressant, antiemetic, antineoplastic, bone therapy agent, cytoprotective, G-CSF/GM-CSF, glucocorticoid, hematological agent, analgesic, solution-fluid, and steroids. However, information in Flatiron on oral medications which might be associated with BSC is difficult to capture and is incomplete for multiple reasons:

- Physicians documentation of "less important" drugs is very poor
- At best, the medication order is documented but this doesn't mean that the patient took the drug (or for how long)
- Over-the-counter drug use is not captured.

Therefore, the patient population would be small and incomplete which could lead to bias in the comparative analysis making it unsuitable for decision-making.

Eligibility criteria not representative of the true patient population

The patient population of interest in relation to the decision problem is the small number of cisplatin-ineligible, PD-L1-positive patients who would have previously received BSC but would now receive atezolizumab due to the reduced toxicity associated with atezolizumab.

- It is not feasible to identify only the patients who would previously have received BSC care but now receive atezolizumab in the Flatiron or any real world data set
- Cisplatin-eligibility and PD-L1 status are not available for these patients in the Flatiron dataset.

Extreme upper bound scenario analysis

It is not feasible to estimate the true cost-effectiveness of atezolizumab vs. BSC given the absence of a reliable estimation of treatment effect. However, it is possible to conduct an extreme conservative scenario analysis assuming that BSC is equal in clinical efficacy to platinum-based chemotherapy whilst assuming no acquisition costs, administration costs and adverse event costs in the comparator arm and no subsequent treatment costs in either arm. Subsequent treatment costs were not included in the atezolizumab arm as it was assumed that if the patients who would have originally received BSC would not be suitable for further subsequent treatment. It should be noted this scenario in no way represents the true cost-effectiveness of atezolizumab vs. BSC as patients on BSC likely demonstrate much shorter progression-free survival (PFS) and OS than patients treated with platinum-based chemotherapy. Regardless, this scenario demonstrates an extreme upper bound on the incremental cost-effectiveness ratio (ICER) with the true ICER likely to be much lower than this.

Table 3 demonstrates the results. In the extreme conservative scenario, the ICER is £47,887. Therefore, atezolizumab would still represent a cost-effective treatment option in this extreme upper bound scenario.

Table 3 Cost-effectiveness results for BSC scenario

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Cost-effectiveness analysis 3: New company base-case								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,607	47,887
BSC	11,429	1.47	0.81	--	--	--	--	--

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Note: ICERs are provided including the amendment to model base case provided in clarification question B6

A7. The SACT document ('TA492 Atezolizumab_final SACT report'), page 9 and 12, refers to 2 atezolizumab doses "1200 mg every 3 weeks or 1680mg every 4

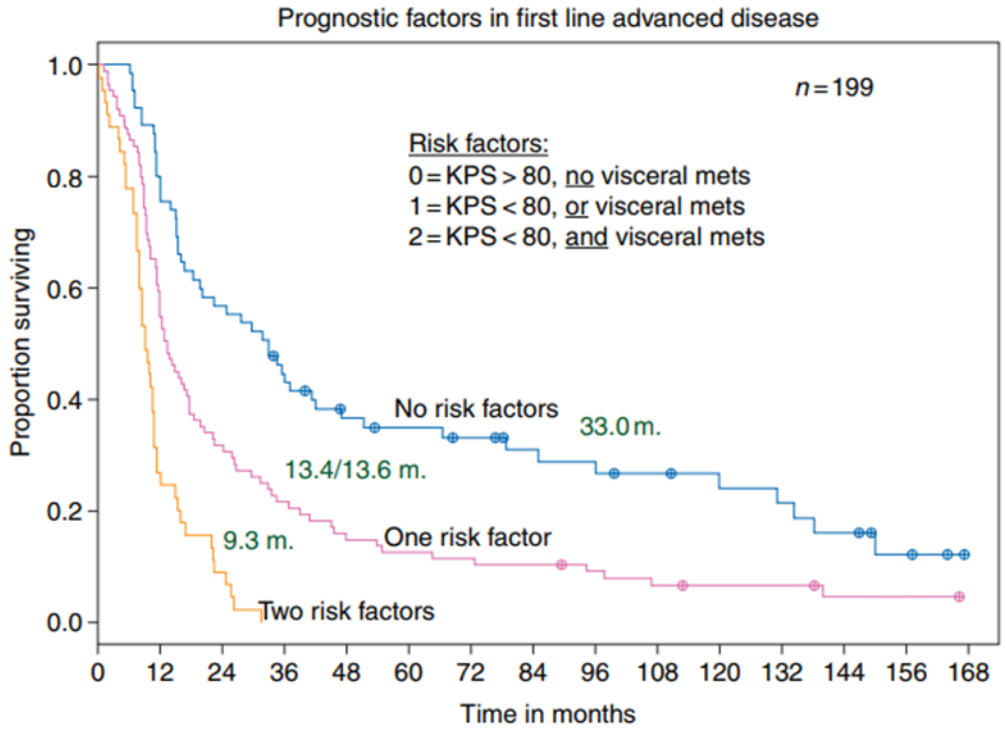
weeks". Can you please clarify, if known, whether the higher dose was administered and for what purpose?

The recommended dosing of Tecentriq is 1200mg every 3 weeks or 1680mg every 4 weeks.(14) Clinicians who treat mUC patients with atezolizumab monotherapy may choose which regimen they wish to use when treating their patients. Some clinicians or patients may prefer 4-weekly dosing as this results in less frequent infusions although the proportion of mUC patients currently receiving the 4-weekly dose is unknown.

A8. What are the known/likely prognostic factors in the patient population eligible to receive atezolizumab for urothelial carcinoma?

Key factors for poor prognosis for survival in patients receiving first-line treatment for mUC are poor performance status (Karnofsky PS < 80%) and the presence of visceral metastases (i.e., lung, liver, or bone), as described by Bajorin et al.(15) (Figure 1) and subsequently validated in independent research.(5, 16, 17) The presence of these Bajorin risk factors was associated with a median survival of 4 months compared with 18 months in patients without these features.(18) These characteristics have been augmented with factors such as white blood cell (WBC) count, number of metastatic sites and response to first-line treatment;(19, 20) as independent variables predicting survival after completion of first-line therapy. Performance status, presence of visceral metastases and WBC count were also shown to be prognostic factors, irrespective of type of platinum therapy (cisplatin or carboplatin based regimens), as determined in a retrospective analysis of real-world data in the first-line metastatic setting.(21) In bladder cancer, expression of PD-L1 has been associated with poor prognosis. In a study completed by Nakanishi et al.(22) PD-L1 (B7-H1) expression was significantly associated with a high frequency of disease recurrence and poor survival rate.

Figure 1 PS (Karnofsky PS of 80% or less) and the Presence of Visceral Metastases are Independent Poor Prognostic Factors for Survival (15)



PS, performance status

In summary, poor performance status and presence of lung, liver, or bone metastases have been substantiated in multiple settings as poor prognostic factors that may be associated with poorer clinical outcomes.

Section B: Clarification on cost-effectiveness data

Subsequent treatment

B1. The unit and list prices presented in the CS, Section A.8.7, Table 14, page 31, for carboplatin, gemcitabine and gemcitabine hydrochloride, and the unit of pembrolizumab, differ from the values shown in the subsequent treatment

sheet in the company model. Please confirm whether the values in Table 14 of the CS or in the model are correct.

The values in the economic model were correct and the values in the CS, Section A.8.7, Table 14, page 31 were typographical errors. Table 1 outlines the updated version of Table 14 (CS, Section A.8.7, page 31) for the identified treatments. The "List price cost (£)" column has been amended to reflect the correct costs, as per the economic model. There is no impact on any model results presented.

Table 4 Subsequent treatment acquisition and administration costs (Updated relevant rows of CS, Section A.8.7, Table 14, page 31)

Drug	Dose	List price cost (£)	Source	Unit (mg)	Admin. Cost (£)	Source
Carboplatin	400mg/m^2 Q3W	3.75	eMIT	200	199	NHS ref.
Gemcitabine	1,000mg/m^2 Q3W	3.28	eMIT	50	199	NHS ref.
Gemcitabine hydrochloride	1,000mg/m^2 Q3W	3.28	eMIT	50	199	NHS ref.
Pembrolizumab	200mg Q3W	2,630.00	BNF	200	199	NHS ref.

CS, company submission; BNF, British National Formulary; eMIT, electronic market information tool; NHS, National Health Service

B2. The proportion of patients receiving subsequent treatment after discontinuation from atezolizumab differs between Table 12 (55%) of the CS, Section A.8.7, page 30, and the company model (99%), cell AB72 on the subsequent treatments sheet. Please confirm whether the values in Table 12 of the CS or in the model are correct.

The figure of 55% presented in the CS is correct (Section A.8.7, Table 12, page 30). The model assumes 44% of patients receive carboplatin + gemcitabine and a further 11% receive paclitaxel (total 55%) as per clinical expert advice.

The figure of 99% presented in the company model (cell AB72 on the subsequent treatments sheet) is somewhat misleading as this takes a simple summation of subsequent treatments and ignores combination treatments. This ignores that 44% of patients are modelled to receive both carboplatin and gemcitabine simultaneously and therefore displays 99% (44% + 44% + 11%) instead of the correct 55%. The

updated economic model provided has amended this. This has no impact on model results.

B3. For scenario 5 with subsequent treatments from the IMvigor130 trial, 3 drugs (B-701, doxorubicin and vinblastine) are omitted from the cost calculation, cell AD91 on the subsequent treatments sheet, for the chemotherapy arm. Please clarify why these treatments have been omitted.

This is a calculation error in the model. This has been fixed and is provided in the updated version of the model. The impact of this error on the results of Scenario 5 is negligible. There is no impact on base case results.

Following clarification question B4, it was identified that the time on treatment for pembrolizumab was incorrectly assumed to be 10.46 (CS, Section A.8.7, Table 13, page 30) instead of 6.84 months (where 10.46 represents the number of administrations). This was amended in the latest version of the economic model. The updated Scenario 5 is presented in Table 5 and updated results section in the associated Clarification Questions Appendix.

Table 5 Key scenario analysis (Updated relevant rows of CS, Section A.12.2, Table 19, page 40 – including pembrolizumab time on treatment error identified in clarification question B4)

No	Parameter and cross reference	Base-case	Scenario	Brief rationale	Inc. costs	Inc. QALYs	ICER/ QALY
Base-case					[redacted]	[redacted]	32,071
Scenarios							
5.	Subsequent treatment distribution	UK standard practice based on clinical expert opinion	IMvigor130	For costs to reflect the IMvigor130 efficacy data	[redacted]	[redacted]	34,593

CS, company submission; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UK, United Kingdom
Note: ICERs are provided including the amendment to model base case provided in clarification question B6

B4. It is unclear how the treatment duration for subsequent treatment has been calculated from the NICE appraisals for atezolizumab (TA525) and pembrolizumab (ID1536), as stated in the CS, Section A.8.7, page 29. Please

provide more details on how the duration of subsequent treatments were estimated for atezolizumab and pembrolizumab.

Treatment duration was estimated from the mean time on treatment from previous NICE appraisals. Given the availability of previous NICE appraisals for atezolizumab and pembrolizumab, this was seen as a more robust estimate of subsequent treatment duration compared to subsequent treatment duration in IMvigor130 where patient numbers were small (atezolizumab n=4, pembrolizumab n=1).

The time on treatment for atezolizumab was taken from TA525 that represents atezolizumab in second-line mUC. A limitation is that this population is not specific to PD-L1-positive and cisplatin-ineligible patients. The estimate of 10.73 is the mean time on treatment (months) of atezolizumab in this indication as calculated from area under the TTD curve as modelled by a gamma distribution. The final cost-effectiveness model for this appraisal is provided in the updated reference pack (23).

In responding to this clarification question, it was identified that the time on treatment for pembrolizumab was incorrectly assumed to be 10.46 (CS, Section A.8.7, Table 13, page 30) instead of 6.84 months (where 10.46 represents the number of administrations). This was incorrectly identified from TA519 ID1538 Section A.6.3, Table 6, page 14 (24). This was amended in the updated version of the economic model. Base case results were not impacted. See response to clarification question B3 for the impact on Scenario 5 (Table 5).

Utility values

B5. Priority question. Please provide mean utility values [EuroQol 5 Dimensions (EQ-5D) 3L] for the atezolizumab and platinum-based chemotherapy arms in the IMvigor130 trial at all relevant time points, including at baseline. Also, if possible, please provide utility values for the chemotherapy arm for the progression free (PF) health state for on/off treatment.

Alongside the response to these clarification questions, Roche have uploaded an excel document (“B5_Mean_util_cycle_ITTBCFL_IC23_CISNELAB_14JUN2020. 2021”) to NICE Docs which displays the mean utility estimates across treatment

cycles for the atezolizumab and platinum-based chemotherapy arms in the IMvigor130 trial.(25) The utility estimates presented in the output are mean utilities for each treatment cycle across all patients who completed the EQ-5D instrument at those treatment cycles. These estimates are “naive” in the sense that they do not take into account the longitudinal nature of the data. The utility estimates presented in the economic model are obtained by means of an appropriate mixed-effects model, which accounts for changes in utility over time as well as correlation among observations within subjects. Therefore, these two sets of utility estimates cannot be compared with each other. This explains why utilities shared are generally higher than those used in the economic model.

Utility values for the platinum-based chemotherapy arm for the PF health state for on/off treatment are displayed in Table 6.

Table 6 Utility values for the chemotherapy arm for the PF health state for on/off treatment

Drug	Mean	95% CI
On treatment	0.531	0.389, 0.672
Off treatment	0.536	0.397, 0.675

CI, confidence intervals; PF, progression-free

B6. In the base case model submitted, the PFS utility value used for gemcitabine/carboplatin appears to be 0.567 (progressed disease utility value) for the [redacted], rather than 0.527 (PF utility value). Please can you confirm whether this is an error or if not, please explain why this value has been used.

It should be noted that this assumption was included in the economic model to estimate the ICERs at point of CDF entry (CS, Section A.1, page 6). After discussion with the ERG at the clarification questions call (28th May 2021), the base case was updated to remove this assumption. With the updated base case analysis, the PF in the health state utility is now 0.527 for all patients at all time points in that health state. The impact on base case results are negligible (<£1,000). The updated economic model has been amended to reflect this. The results after this amendment

are displayed in Table 7. Full results are displayed in the associated Clarification Questions Appendix.

Table 7 CS vs. updated cost-effectiveness results (before and after PF utility assumption removed)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
CS base case (before utility amendment identified in clarification question B6)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,838	32,708
Platinum-based chemotherapy	22,085	1.47	0.82	--	--	--	--	--
Updated base case (after utility amendment identified in clarification question B6)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,838	32,071
Platinum-based chemotherapy	22,085	1.47	0.81	--	--	--	--	--

CS, company submission; CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PF, progression-free; QALYs, quality-adjusted life years

PFS and OS extrapolation

B7. Please consider running an OS scenario analysis extrapolating from the SACT Kaplan-Meier data for atezolizumab, and using the platinum-based chemotherapy arm from the IMvigor130 trial.

Roche do not see this as a suitable scenario analysis to conduct in relation to the decision problem. As per the Terms of Engagement document, the committee requested evidence from the IMvigor130 clinical trial to inform this CDF review.

Relative efficacy and survival are key uncertainties as outlined by the Committee in the Terms of Engagement document. The Committee requested that IMvigor130 data is used to estimate relative efficacy and survival in this appraisal. Roche are in agreement with the Committee and the NICE reference case (26) that IMvigor130 data represents the most robust way to estimate survival and the relative treatment effect (and therefore cost-effectiveness results) for this appraisal.

The treatment effect in this scenario will not be representative of the true treatment effect as it will be obscured by the differences in the patient population as outlined in CS Appendix B (including an older patient population, worse Eastern Cooperative

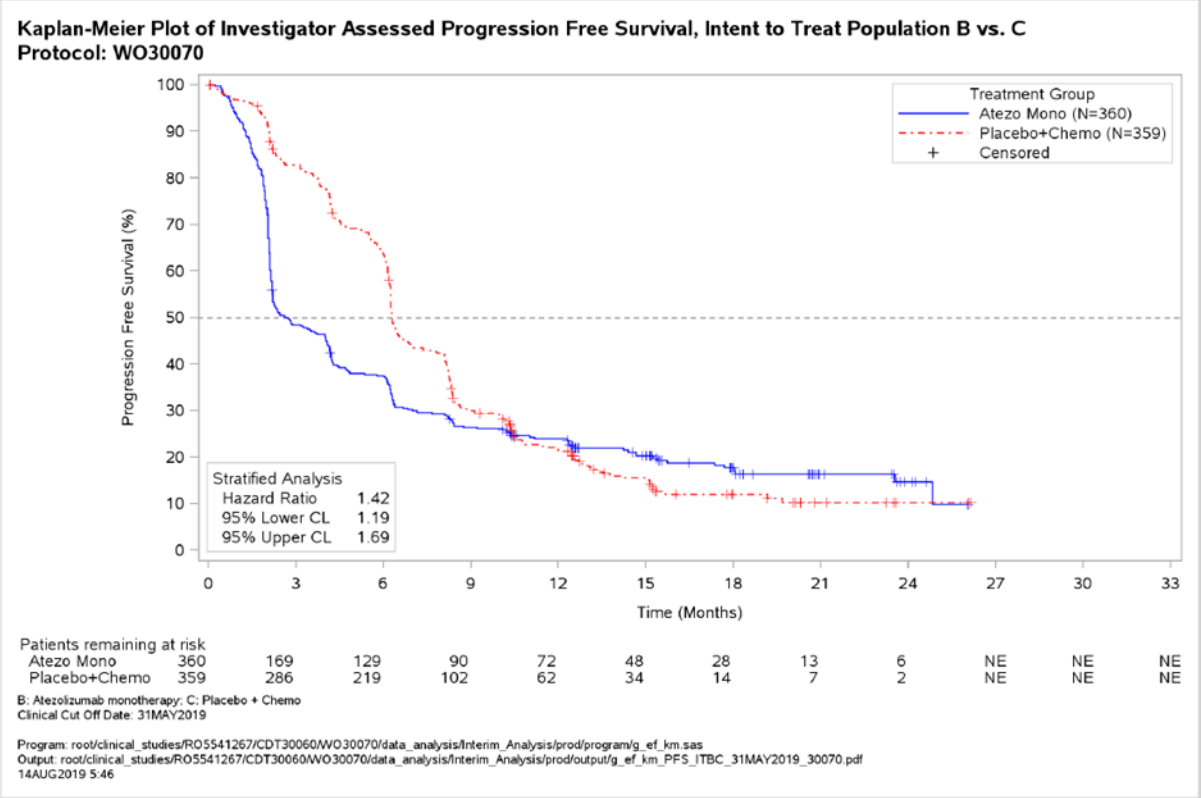
Oncology Group (ECOG) status, and the impact of real world evidence vs. a clinical trial).

B8. CS, Section A.6.1, Figure 2, page 16, shows a sharp drop in the atezolizumab PFS compared to platinum-based chemotherapy at around 2.5 months (at which point the curves diverge). Are you aware of any clinical or protocol explanation for this? This appears at odds with the total IMvigor130 population, where both arms experience a similar sharp drop at 2.5 months (Figure 24, Galsky et al, Lancet 2020).

Roche acknowledges that there is a drop in PFS compared to platinum-based chemotherapy at around 2.5 months compared to platinum-based chemotherapy. From a clinical viewpoint, this is a typical pattern with immunotherapies. Patients may initially respond to chemotherapy treatment; however, these responses may not be durable whereas patients on immunotherapy who do not progress quickly tend to have longer responses. It appears the study referenced in this question (Figure 24, Galsky et al, Lancet 2020 - where there is an approximate 10-15% drop observed at the 2.5-month mark) is in reference to an atezolizumab+platinum-based chemotherapy combination (Arm A of IMvigor130) instead of atezolizumab monotherapy (Arm B of the IMvigor130 trial, pertaining to this submission). Therefore, it is difficult to draw firm conclusions from comparing that published figure to the one in this submission.

A more relevant comparison may be the intention to treat (ITT) population of Arm B (atezolizumab monotherapy). The Kaplan-Meier plot for Investigator Assessed PFS in the ITT arm B vs C has been provided in Figure 2. A sharper drop in PFS is observed in the atezolizumab monotherapy arm (Arm B) in the ITT than in the cisplatin-ineligible, PD-L1-positive subgroup (pertaining to this submission) highlighting that patients within this subgroup may be less likely to progress quickly versus the ITT population. However, given the small patient numbers, it is difficult to draw firm conclusions.

Figure 2 IMvigor130 Kaplan-Meier plot of ITT PFS for atezolizumab monotherapy vs. platinum-based chemotherapy (Arm B vs. C)



B9. In the IMvigor130 PD-L1 subgroup, we note 11 patients in the atezolizumab monotherapy treatment arm and 5 patients in the platinum-based chemotherapy arm received cisplatin despite the target population being cisplatin ineligible (CS, Appendix C, Section C.2.7.3, Table 18, page 49). How does OS, PFS, and time to treatment discontinuation (TTD) in these patients compare to patients who did not receive cisplatin?

Table 8 and Table 9 display PFS, OS and TTD for subjects assigned cisplatin by investigator choice of chemotherapy compared to subjects who were assigned carboplatin. It should be noted that subjects were assigned a choice of chemotherapy before randomisation. Therefore, 11 subjects in the atezolizumab arm we assigned to cisplatin but did not receive either cisplatin. A further 39 subjects were assigned carboplatin but did not receive carboplatin.

Table 8 Imvigor130 PFS, OS and TTD in the atezolizumab arm by investigator choice of platinum-based chemotherapy

	Investigator choice of cisplatin (n=11)	Investigator choice of carboplatin (n=39)
Median PFS (95% CI)	7.2 (2.0, NE)	6.4 (4.2, 12.6)
Median OS (95% CI)	23.6 (13.1 NE)	18.6 (12.7, NE)
Median TTD (95% CI)	3.5 (1.4, NE)	6.2 (4.2, 12.6)

CI, confidence intervals; OS, overall survival; PFS, progression-free survival; NE, not evaluable; TTD, time to treatment discontinuation

Note: patients in the atezolizumab arm did not receive cisplatin or carboplatin but investigators still made a choice of cisplatin or carboplatin before randomisation

Table 9 Imvigor130 PFS, OS and TTD in the platinum-based chemotherapy arm by investigator choice of platinum-based chemotherapy

	Investigator choice of cisplatin (n=5)	Investigator choice of carboplatin (n=38)
Median PFS (95% CI)	6.3 (2.6, NE)	5.9 (4.2 8.2)
Median OS (95% CI)	14.6 (3.5, NE)	9.9 (7.4 22.9)
Median TTD (95% CI)	2.1 (1.8, NE)	3.4 (2.5, 3.7)

CI, confidence intervals; OS, overall survival; PFS, progression-free survival; NE, not evaluable; TTD, time to treatment discontinuation

B10. For OS, in the CS, Section A.8.2, page 23, it is stated that proportional hazards 'cannot be rejected' and independent curves were fitted to the IMvigor130 arms. For PFS, it is stated in the CS, Section A.8.3, page 24, that proportional hazards 'can be rejected' and independent curves were again fitted to the IMvigor130 arms. This is not consistent. Please clarify why you did not consider fitting a parametric model to the entire dataset for OS with treatment as a covariate?

In the case of OS, it should be noted that a failure to reject the proportional hazards assumption is not the same as the proportional hazards assumption holding. In this instance, the sample size in each treatment arm (n=50, 43) is small and the test is not sufficiently powered to actually reject the hypothesis of proportional hazards. Therefore, in this instance independent curves were used.

Further, for the first part of the OS curves (until 20% of patients are at risk); Kaplan-Meier curves have been used to model OS. Kaplan-Meier curves are not impacted by the choice of independent/dependent curves. This limits the sensitivity of model results to the choice of independent/dependent curves.

In the base case scenario, independent exponential curves are used to model atezolizumab and platinum-based chemotherapy. Due to the properties of exponential curves with a constant hazard function, two independent exponential curves and curves estimated from dependent model fitted to the exponential distribution will be identical. Therefore, base case results will be unaffected.

Section C: Textual clarification and additional points

C1. In the CS, Section A.9, Table 15, page 32, we think that column 3, updated parameter/assumption, PFS and TTD extrapolations should read "KM+exponential" not "Weibull".

This is was a typographical error. Column 3, updated parameter/assumption, PFS and TTD extrapolations should read "KM+exponential" instead of "Weibull".

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA492

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) ID3777

Clarification Questions Response: Appendix

June 2021

File name	Version	Contains confidential information	Date
ID3777_NICE_Atezolizumab_Clarification_Questions_Appendix_1LmUC_CIC	V3	Yes	4th June 2021

A.1 Introduction

As part of the evidence review group's (ERG's) clarification questions pertaining to this submission (atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable: Cancer Drugs Fund (CDF) Review of TA492 [ID3777]), the ERG identified that in the original submission an amendment was made to progression-free (PF) utilities used in the platinum-based chemotherapy arm for the first 10 cycles. In these 10 cycles, the PF utility used was 0.567 rather than 0.527. At the clarifications questions call, an agreement was made by the company and ERG that this should be removed from the base-case analysis. This has a minor impact on the economic model base-case results [impact on incremental cost-effectiveness ratio (ICER) less than £1,000]. The remainder of this Appendix displays the updated results in an identical format to the results sections in the company submission.

A.2 Cost-effectiveness results (deterministic)

Table 1 shows the deterministic results for the three CDF results criteria.

- Cost-effectiveness analysis 1 shows results from the original submission (Committee discussion TA492, 3.13 (1).
- Cost-effectiveness analysis 2 shows those results replicated but with IMvigor130 data replacing IMvigor210.
- Cost-effectiveness analysis 3a represents the base case in the company submission with assumptions amended to reflect best practice with the updated clinical trial data and to reflect the present day conditions (before utility amendment identified in clarification question B6).
- Cost-effectiveness analysis 3b represents the updated base case with identical assumptions to cost-effectiveness analysis 3a but after utility amendment identified in clarification question B6.

All analyses include a PAS for atezolizumab.

[redacted]

By comparing the analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cost-effectiveness analysis 1) with the identical analysis

but incorporating the updated clinical evidence (cost-effectiveness analysis 2), we observe that atezolizumab demonstrates a higher incremental outcome benefit in the updated analysis [inc. life years gained (LYG) [redacted] vs [redacted], inc. QALYs [redacted] vs. [redacted]. This demonstrates the improved survival in the IMvigor130 data and the updated patient population.

In the new company base case (cost-effectiveness analysis 3b), atezolizumab provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted] in comparison to platinum-based chemotherapy. This represents an ICER of £21,838 per LYG and an ICER of £32,071 per QALY gained. This represents a slightly more cost-effective result compared to cost-effectiveness analysis 3a. As per the original appraisal and Terms of Engagement document, atezolizumab meets the end-of-life criteria.

Table 1 Cost-effectiveness results (deterministic, Table 73, TA492, Section 5.7.1 p204 (2))

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,065	66,735
Platinum-based chemotherapy	12,397	1.10	0.65	--	--	--	--	--
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,658	84,967
Platinum-based chemotherapy	14,110	1.47	0.82	--	--	--	--	--
Cost-effectiveness analysis 3a: Company submission base case (before amendment identified in clarification question B6)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,838	32,708
Platinum-based chemotherapy	22,085	1.47	0.82	--	--	--	--	--
Cost-effectiveness analysis 3b: Updated base case (after amendment identified in clarification question B6)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,838	32,071
Platinum-based chemotherapy	22,085	1.47	0.81	--	--	--	--	--

CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A.3 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. A Monte-Carlo simulation was conducted, where 1,000 iterations were used to ensure convergence.

The results of the new company base case PSA are presented in Table 2. In the new company base case (cost-effectiveness analysis 3), atezolizumab provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted] in comparison to platinum-based chemotherapy. This represents an ICER of £22,330 per LYG and an ICER of £32,651 per QALY gained. In 93.5% of iterations, the ICER was lower than £50,000. The PSA demonstrates the reduction in uncertainty in the model associated with the updated data and that results are robust to probabilistically varying assumptions.

Table 2 PSA results (new company base case, Table 90, TA492, Section 5.8.1 p216 (2))

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,330	32,651
Platinum-based chemotherapy	22,589	1.48	0.81	--	--	--	--	--

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 1 displays the cost-effectiveness plane for the new company base case based on 1,000 iterations.

Figure 1 Cost-effectiveness plane results of atezolizumab and platinum-based chemotherapy (new company base case, Figure 42, TA492, Section 5.8.1 p217 (2))

QALYs, quality-adjusted life years

A.4 Key sensitivity and scenario analyses

A.4.1 *Deterministic sensitivity analysis*

A deterministic sensitivity analysis (DSA) was performed to investigate key drivers of the base-case results. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. The base-case parameter values were varied across their 95% CI where possible. The parameter values used in the DSA are displayed in Table 3. The tornado diagram for atezolizumab versus platinum-based chemotherapy is presented in Figure 2 with the six most influential parameters shown. The DSA highlighted that the PD supportive care costs for atezolizumab and the PF health state utility value for atezolizumab had the greatest impact on the cost-effectiveness results. The ICER remained below £50,000/QALY in all analyses. Results with the atezolizumab list price are included in Appendix J.

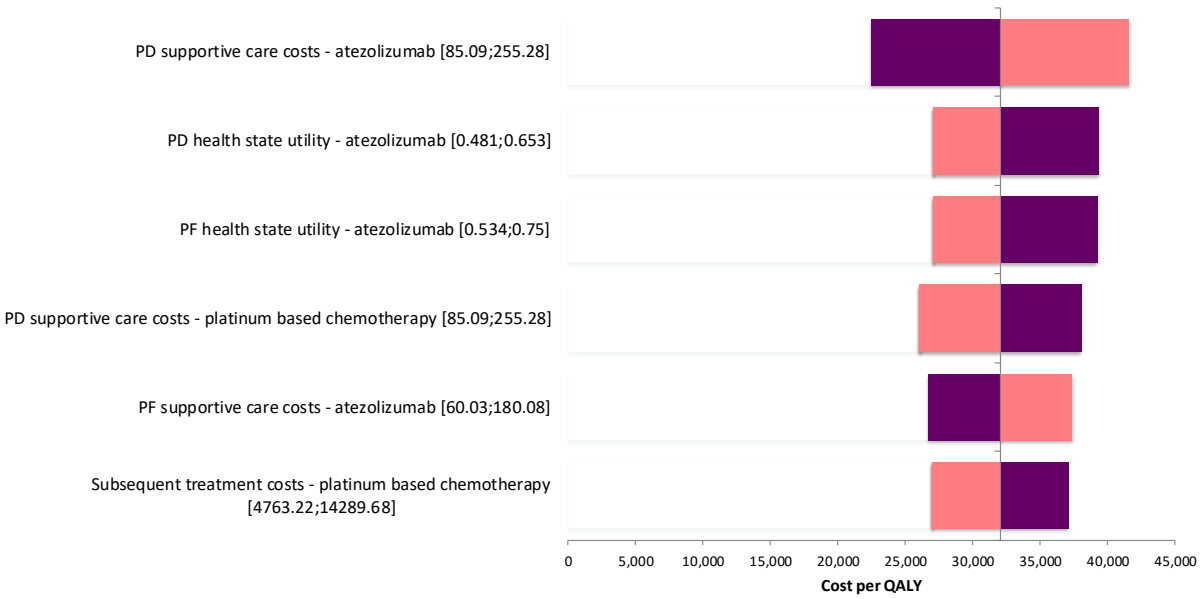
Table 3 Parameter values used for DSA and results (new company base case, Table 92, TA492, Section 5.8.2 p219 (2))

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	1.77	1.42	32,013	2.13	32,059	+/-20%
First admin cost - atezolizumab	183.54	146.83	32,013	220.25	32,059	+/-20%
First admin cost – platinum-based chemotherapy	259.08	207.27	32,306	310.90	32,118	+/-20%
Subsequent admin cost - atezolizumab	183.54	146.83	31,052	220.25	31,867	+/-20%
Subsequent admin cost – platinum-based chemotherapy	259.08	207.27	32,907	310.90	32,238	+/-20%
PF supportive care costs - atezolizumab	120.06	60.03	26,781	180.08	37,360	+/-50%
PF supportive care costs – platinum-based chemotherapy	120.06	60.03	35,253	180.08	28,888	+/-50%
PD supportive care costs - atezolizumab	170.19	85.09	22,537	255.28	41,605	+/-50%
PD supportive care costs – platinum-based chemotherapy	170.19	85.09	38,071	255.28	26,071	+/-50%
Subsequent treatment costs - atezolizumab	1,360.18	680.09	31,418	2,040.28	32,724	+/-50%
Subsequent treatment costs –	[redacted]	[redacted]	37,114	[redacted]	27,027	+/-50%

platinum-based chemotherapy						
PF health state utility - atezolizumab	0.642	0.534	39,225	0.75	27,124	95% CI
PF health state utility - platinum-based chemotherapy	0.527	0.404	28,508	0.649	36,609	95% CI
PD health state utility - atezolizumab	0.567	0.481	39,334	0.653	27,072	95% CI
PD health state utility – platinum-based chemotherapy	0.567	0.481	28,732	0.653	36,288	95% CI

BSA, body surface area; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PD, progressed disease; PF, progression-free

Figure 2 Tornado plot (new company base case, Figure 46, TA492, Section 5.8.2 p220 (2))



PD, progressed disease; PF, progression-free

A.4.2 *Scenario analyses*

Scenario analyses were conducted to assess uncertainty around structural assumptions of the new company base case. Results for five key scenario analyses are presented in Table 4. Full scenario results are presented in Section A.6 . In every

scenario in the analysis, the ICER remains under £50,000, demonstrating robustness of results.

Table 4 Key scenario analysis (new company base case, Table 93, TA492, Section 5.8.3 p222 (2))

No.	Parameter and cross reference	Base-case	Scenario	Brief rationale	Inc. costs	Inc. QALYs	ICER/ QALY
Base-case					[redacted]	[redacted]	32,071
Scenarios							
1.	OS curve selection for atezolizumab and platinum-based chemotherapy	KM curve with exponential tail	KM curve with log-logistic tail	Deemed alternative plausible curve choice	[redacted]	[redacted]	27,726
2.	PFS curve selection for atezolizumab and platinum-based chemotherapy	KM curve with exponential tail	KM curve with log-logistic tail	Deemed alternative plausible curve choice	[redacted]	[redacted]	29,811
3.	TTD curve selection for atezolizumab and platinum-based chemotherapy	KM curve with exponential tail	Weibull	Deemed alternative plausible curve choice	[redacted]	[redacted]	44,499
4.	PD health state utility values	Atezolizumab and platinum-based chemotherapy PD: 0.567	Atezolizumab and platinum-based chemotherapy PD: 0.500	To align with the most conservative scenario demonstrated in Committee discussion (TA492, 3.12 (2))	[redacted]	[redacted]	33,877
5.	Subsequent treatment distribution	UK standard practice based on clinical expert opinion	IMvigor130	For costs to reflect the IMvigor130 efficacy data	[redacted]	[redacted]	34,593

KM, Kaplan-Meier; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation; UK, United Kingdom
Note: Scenario 5 has been updated with amendment from clarification question B3.

A.5 Disaggregated base case results: cost-effectiveness analysis 3

Table 5 shows the disaggregated base case results for the new company base case (cost-effectiveness analysis 3).

The incremental difference in outcomes is driven by both PF and PD health states with [redacted] of the LY benefit and [redacted] of the QALY benefit coming in PF (vs. [redacted] and [redacted] in PD respectively). The incremental difference in costs is mainly driven by drug costs with the atezolizumab costs being [redacted] greater than platinum based chemotherapy costs. However, this cost is offset by savings [redacted]) in the subsequent treatments of the atezolizumab arm.

Table 5 Disaggregated results for cost-effectiveness analysis 3: New company base-case (Table 78,82,86, TA492, Section 5.7.3 p212 (3))

	Atezolizumab	Platinum- based chemotherapy	Incremental
PF LYs	[redacted]	0.63	[redacted]
PD LYs	[redacted]	0.84	[redacted]
Total LYs	[redacted]	**1.47**	[redacted]
PF QALYs	[redacted]	0.33	[redacted]
PD QALYs	[redacted]	0.48	[redacted]
Total QALYs	[redacted]	**0.81**	[redacted]
Atezolizumab drug costs (£)	[redacted]	[redacted]	[redacted]
Platinum based chemotherapy drug costs (£)	[redacted]	[redacted]	[redacted]
Administration costs (£)	[redacted]	[redacted]	[redacted]
Adverse events (£)	[redacted]	[redacted]	[redacted]
PF supportive care costs (£)	[redacted]	[redacted]	[redacted]
Total PF costs (£)	[redacted]	[redacted]	[redacted]
PD supportive care costs (£)	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (£)	[redacted]	[redacted]	[redacted]
Total PD costs (£)	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/ LYG) (£)	--	--	**21,838**
ICER (£/ QALY) (£)	--	--	**32,071**

ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life years gained; PAS, patient access scheme; PD, progressed disease; PF, progression-free; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

A.6 Scenario analysis results

Table 6 Key scenario analysis (new company base case, Table 93, TA492, Section 5.8.3 p222 (3))

No.	Parameter and cross reference	Base-case	Scenario	Brief rationale	Inc. costs	Inc. QALYs	ICER/ QALY
Base-case					[redacted]	[redacted]	32,071
Scenarios							
1.	OS curve selection for atezolizumab and platinum based chemotherapy	KM curve with exponential tail	KM curve with log-logistic tail	Deemed alternative plausible curve choice	[redacted]	[redacted]	27,726
2.	PFS curve selection for atezolizumab and platinum based chemotherapy	KM curve with exponential tail	KM curve with log-logistic tail	Deemed alternative plausible curve choice	[redacted]	[redacted]	29,811
3.	TTD curve selection for atezolizumab and platinum based chemotherapy	KM curve with exponential tail	Weibull	Deemed alternative plausible curve choice	[redacted]	[redacted]	44,499
4.	PD health state utility values	Atezolizumab and platinum based chemotherapy PD: 0.567	Atezolizumab and platinum based chemotherapy PD: 0.500	To align with the most conservative scenario demonstrated in Committee discussion (TA492, 3.12 (3))	[redacted]	[redacted]	33,877
5.	Subsequent treatment distribution	UK standard practice based on clinical expert opinion	IMvigor130	For costs to reflect the IMvigor130 efficacy data	[redacted]	[redacted]	34,593
6.	Discount rate –	3.5%	0%	As per NICE recommendations	[redacted]	[redacted]	31,479

7.	costs and QALYs		5%		[redacted]	[redacted]	32,305
8.			1.5%	To align with exploratory analysis in NICE methods review	[redacted]	[redacted]	31,740
9.			Costs: 3.5% Outcomes: 1.5%		[redacted]	[redacted]	30,209
10.	Duration of OS treatment effect	Treatment effect waned from 5-7 years	Treatment effect maintained	Exploratory scenarios investigated	[redacted]	[redacted]	30,724
11.			7-year cap		[redacted]	[redacted]	31,556
12.			5-year cap		[redacted]	[redacted]	32,744
13.	Health state utility values to treatment or progression	Pre/post progression	On/off treatment	To align with scenario explored in original company submission (TA492 Section 5.4.6, page 179 (3))	[redacted]	[redacted]	32,151
14.	Health state utility values	Atezo PF: 0.642; platinum based chemotherapy PF: 0.527; PD: 0.567	Atezo PF: 0.75; platinum based chemotherapy PF: 0.75; PD: 0.5	To align with scenario explored in original company submission (TA492 Section 5.4.6, page 179 (3))	[redacted]	[redacted]	35,536
15.	PD health state utility values	Overall: Atezo PD: 0.567, platinum based chemotherapy PD: 0.567	Treatment-specific: Atezo PD: 0.625, platinum based chemotherapy PD: 0.510	To explore the impact of potential atezolizumab HRQoL benefit into PD	[redacted]	[redacted]	26,691
16.	Cost year used	2016	2020	Demonstrate impact of inflation from point of CDF entry to exit on results	[redacted]	[redacted]	31,061
17.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18.	Dose of carboplatin	400 mg/m^2	330.31mg	Using actual dose received in IMvigor130 clinical trial	[redacted]	[redacted]	32,139
19.	Platinum based chemotherapy	6 cycle treatment cap	No treatment cap	To explore the effect of no treatment cap on platinum based chemotherapy	[redacted]	[redacted]	30,821

				as per Imvigor130			
20.	Cost per dose of platinum based chemotherapy	£59.59	£53.62	Weighted so that costs account for proportion of patients who received cisplatin in order to demonstrate minimal impact on costs	[redacted]	[redacted]	32,112
21.	Subsequent treatment costs	Included	Excluded	To align with scenario explored in original company submission (TA492 Section 5.2.2, page 149 (3))	[redacted]	[redacted]	40,852
22.	Distribution of subsequent treatments	As per clinical experts/UK practice	As per clinical experts/UK practice- adjusted to match IO use	To represent the expected costs in UK standard practice with subsequent IO use adjusted in the platinum based chemotherapy arm to match IO use in IMvigor130 (20.9% vs. 49.5%)	[redacted]	[redacted]	37,572
23.	Duration of subsequent IO treatment	Previous NICE appraisals	As per IMvigor130	Taking treatment duration for IOs from IMvigor130 trial. This is thought to underestimate IO treatment duration	[redacted]	[redacted]	40,167

IO, immunotherapy; OS, overall survival; PAS, patient access scheme; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation; UK, United Kingdom

References

1. Excellence NIfHaC. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492] - Committee discussion 2017 [Available from: https://www.nice.org.uk/guidance/ta492/chapter/3-Committee-discussion.
2. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492] 2017 [Available from: https://www.nice.org.uk/guidance/ta492.
3. National Institute for Health and Care Excellence (NICE). Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492] 2017 [Available from: https://www.nice.org.uk/guidance/ta492.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Action Bladder Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	UK bladder cancer charity. We have three main strands to our work: • Improving outcomes for bladder cancer patients • Improving research into bladder cancer • Improving patient support We are working to improve outcomes for bladder cancer patients by: • Raising awareness of the signs and symptoms among the public so they seek advice sooner • Improving awareness and investigation techniques among health professionals to improve early diagnosis • Improving the treatment and management of bladder cancer to increase patient survival rates in line with that achieved for other common cancers We are working to improve research into bladder cancer by: • Identifying the key research priorities • Encouraging, contributing to and funding research • Improving research data and statistics We are working to improve patient support through: • Our high quality information materials and resources library • Actively increasing the number of bladder cancer patient support groups across the UK • Providing advice and support to both new and existing groups and helping to bring groups together

	• Helping to give bladder cancer patients a voice The charity is funded by donations, legacies, fundraising events and by corporate donations. Our corporate donors are bound by our corporate statement as follows: *CORPORATE STATEMENT Action Bladder Cancer UK is a charity working to support those with bladder cancer and to improve outcomes for patients. We are committed to working in ethical collaboration with commercial and corporate partners in the interest of people affected by bladder cancer. We will accept funding from appropriate corporate and industry supporters. Neither our work, our campaigning nor our information materials will be influenced by accepting any corporate donations or sponsorship. We feel it is important to work with companies that manufacture drugs, treatments or devices which will treat or support bladder cancer patients. We will work in a transparent partnership with appropriate pharmaceutical companies and the medical device industry where these relationships will help promote and improve the interests of bladder cancer patients and fit within the objectives of our charity. We would not accept support from any pharmaceutical or medical industry company for work that we consider to that lie outside the agreed objectives of our charity. We are happy to accept funding, or support in kind, from appropriate corporate supporters outside the health or pharmaceutical sectors. Each corporate collaboration will be assessed and agreed on an individual basis by the charity executive. We are grateful for the support shown by our existing corporate supporters which help us in our work.*
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	A number of pharmaceutical companies have offered to provide our charity funding during the coronavirus epidemic. This is in recognition that many charities such as ours are experiencing a shortfall in income, as fundraising activities by supporters are curtailed. These donations are typically around £10,000. We have been in discussion with Roche about the possibility of a donation from them to support the general activities of the charity. We have received a donation from a consortium including Pfizer, a comparator company, also to support the general activities of the charity.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	All our Trustees and staff work closely with patients, both directly and via our network of support groups. In addition, four of our trustees and many of our volunteers and fundraisers are patients or carers. It is absolutely fundamental to our work that we have a deep and current understanding of our patients, their hopes and fears and their treatment options, current and future.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Initial diagnosis is invariably a shock, not just because this is cancer, but because bladder cancer is so poorly known or understood. It can be difficult to talk about, as the impact can be so personal, not just with family and friends but also with clinicians. Although treatment for non-muscle invasive bladder cancer is *relatively* straightforward and effective, that for muscle invasive bladder cancer can be drastic, less effective, and can often recur. The particular condition for this consultation is the advanced case where platinum chemotherapy cannot be given and where survival rates are especially poor, typically measured in months.

	This group of patients has already gone through the mill. Bladder cancers are not well known or understood, so the initial diagnosis will have come as a particular shock to most patients. From often quite mild symptoms they will have already experienced a battery of tests, some of which are intrusive such as cystoscopies and/or TURBT. They will have experienced a roller coaster of emotions as they learn of the seriousness of their condition. Many experience pain and discomfort, and struggle to maintain control of their bladder function. They will know that there is no cure available, so the issue is solely how long they can remain healthy enough to enjoy what life they have left. Most patients in this group are older, in their sixties or seventies, many have other health issues. Their partners, carers and family members are often feeling pretty desperate, and both patients and their families can feel hopeless. It is not just the patient, but carers, partners and the family can all feel physically, emotionally and mentally battered.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatment of this specific condition would normally be with platinum based chemotherapy. However, due to the relatively advanced age and other illnesses present in so many patients with advanced bladder cancer, a significant number are unable or unwilling to take cisplatin. Currently, the only option is best supportive care, usually palliative, and so there is an urgent need for alternatives or improvements for this group of patients. Carers are forced to watch their love ones approach the end of life with increasing weakness, great discomfort and chronic pain. There is a great deal of physical, emotional and mental stress for both patients and their carers. Without treatment, there is no hope.

8. Is there an unmet need for patients with this condition?	Yes. Patients with metastatic bladder cancer have an average life expectancy of only a few months. About 5,000 patients die each year from this condition, and this has not improved in over 30 years. So there is a huge unmet need and bladder cancer patients in general feel overlooked. Atezolizumab represents an innovative treatment and potential lifeline for patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Atezolizumab represents hope for many where other treatment options have been exhausted. The main benefits include: • complete response in some cases • prolonging life • improved quality of life for patient, carers and family, as the drug is reasonably well tolerated as well as beneficial. We think a major potential benefit to both patients and those who care for them is the creation of real hope for the future where none currently exist, and has not existed for decades
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	ABC UK is not aware of any disadvantages perceived by patients or carers. However, some may find regular attendance for treatment a challenge.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Currently about 5,000 patients die each year in the UK from metastatic bladder cancer. All of these could potentially benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None known**

Other issues	
13. Are there any other issues that you would like the committee to consider?	Bladder cancer is not a rare cancer. It is the 4th most prevalent cancer in men and the 7th most prevalent overall. The five year survival rate for all stages and grades of bladder cancer is only 50%. This figure has not improved at all in well over 30 years. This compares very badly with any of the other ten most prevalent cancers. For instance, the five year survival statistics for breast cancer, prostate cancer and bowel cancer show that patients are two or three times more likely to survive the disease today than 30 years ago. Bladder Cancer recurs more than any other common cancer requiring long term surveillance and repeat treatments. This makes bladder cancer one of the most expensive cancers for the NHS to treat, per patient. Bladder cancer patients are among the highest of all cancer patients who present at A&E with advanced disease. And those in this group have a mean life expectancy measured in months rather than years, typically around 15 months. Despite these bleak statistics, bladder cancer receives less than 1% of the cancer research spend. In many other cancer settings, the expected impact of immunotherapy drugs may not be particularly significant at this stage of disease, compared with available alternatives. However, in the case of cancer patients with advanced disease as here, the outlook is very poor, the patient experience often dire and there are no available treatments. There is a huge unmet need for advanced bladder cancer patients, and atezolizumab offers the prospect of a step change improvement for many of the patients in this group.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • There has been little or no improvements in care for these patients in over 30 years, and they are left with ‘best supportive care’. • Patients, on average, have only a few months to live, and the last months of life are particularly harrowing for both them and their carers • This treatment has been shown to have a positive effect, and in some cases a dramatic effect, on life expectancy, and is relatively well tolerated. • Atezolizumab gives hope to many for whom other treatment options have been exhausted, and for whom there is no alternative. • ABC UK strongly supports the licensing and use of the treatment within the NHS

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

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- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Fight Bladder Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight Bladder Cancer is a patient advocacy group and charity for bladder cancer, based in the UK. We run a 24/7 confidential online support group that has approx. 4,800 users, local support groups around the country and a national 1 to 1 bladder buddy service. As a patient-led charity, our knowledge of the patient experience with bladder cancer is second to none in the UK. The charity is funded by individual donations, grants, and financial support from industry.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	BMS £8,000 - continued provision of patient support services during the COVID-19 outbreak as a result of reduced income and an increased demand on services – 30 June 2020 Ferring £1,500 - continued provision of patient support services during the COVID-19 outbreak as a result of reduced income and an increased demand on services – 15 May 2020 Janssen £3,000 – core funding – 22 January 2021 £6,300 – core funding – 21 December 2020

If so, please state the name of manufacturer, amount, and purpose of funding.	£210 - Advisory Board - 30 November 2020 £840 - participation in Patient Advisory Council activity in quarter 1, 2020 – 5 August 2020 £10,000 - Strengthen information and support for people living with bladder cancer – 3 July 2020 £240 - participation in Patient Advisory Council activity in quarter 4, 2019 – 15 June 2020 £5,000 – Deliver key support services for bladder cancer patients during the COVID-19 Pandemic – 21 May 2020 Merck £10,000 – Patient information booklets - 23 September 2020 £1,000 – Participation in Global Patient Advisory Board – 31 August 2020 Pfizer £1,000 – participation in advisory board – 21 November 2020 £10,000 – patient information booklets – 23 September 2020 £10,000 - Donation to support existing activities, any increased demands on its services and its continued work to support Patients and the wider community during the COVID19 pandemic – 22 June 2020 MSD £15,000 – Exemplar pathway policy project – 16 April 2021 £10,000 – Cancer community grant programme – 29 September 2020

	Roche £1,826 - Clinical trial patient advisory – 2 April 2021 £14,538 – website development – 31 December 2020 £20,000 - Donation to support existing activities, any increased demands on its services and its continued work to support Patients and the wider community during the COVID19 pandemic – 10 August 2020 Fight Bladder Cancer offers support to patients with advanced cancer, including information about treatments including the technology and comparator products. Fight Bladder Cancer lists all clinical trials currently recruiting patients within the UK, including clinical trials for this technology and comparator products
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We reached out to people on our private online forum of 5,000 patients and carers to ask them about advanced bladder cancer, and their experience with atezolizumab. We also spoke to our Support Services Manager, nurses, medical oncologists, and collaborated with our sister charity in Canada to better understand the patient experience.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	What is it like to live with the condition? Advanced urothelial cancer has a very poor prognosis. At this point in the pathway there is currently limited choice on treatments. Most current treatments are also very invasive, have significant side effects and often have quite serious side effects that significantly reduce the quality of life for the final months. It is a constant battle to delay the further growth and spread of the cancer. The condition is physically and emotionally tough with a regime of chemotherapy, a known low survival rate, and the understanding that the battle is to "prolong life" rather than resulting in a cure. Patients report that this condition has a substantial impact on their ability to work, ability to travel, and ability to exercise. “It’s like a gun to my head every single minute of the day and night” “Everything I do is tinged with a sadness and a sorrow of "will this be the last time I do this?".” “It’s totally all consuming” What do carers experience when caring for someone with the condition? For carers, the pressure is on them, from day one, to help support and care for their loved ones. Carers report that it has a substantial impact on their ability to work, ability to travel ,and ability to spend time with family and friends. “Caring for her means constant worry and constant vigilance. I wish we could go back to the time before 2020 when we were free of all this and could enjoy life. I have nothing to look forward to but the eventual end of her life, and then having to go on after she has left me behind.”

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	For advanced/metastatic urothelial cancer, prognosis is very poor with very limited treatments being available. In addition to the chemotherapy treatments, the patients are likely to need other treatments such as radiotherapy to the part of the body where the cancer has spread, surgery to remove the cancer, surgery to unblock the ureters or urethra, and drugs to strengthen the bones. "There's a lack of understanding of bladder cancer by medical staff. Our dad's bladder cancer has taken over our whole life - even when we pretend things are normal, the next scan, the next treatment, fear of the future never go away. The physiological impact on patients and their families is truly underestimated. Supporting my dad leaves me little time or energy for much else!" "Nearly 7 years with advanced bladder cancer, 40+ operations, 3 rounds of chemotherapy, radiotherapy minus a kidney and the one remaining will have to go too. Life is different, I'm different, but I'm still here. I would not be if it wasn't for the NHS, good or bad, and I've had both experiences. They have saved my life many many times and I will be forever grateful"
8. Is there an unmet need for patients with this condition?	The existing treatments for urothelial cancer have limited effectiveness which results in the poor prognosis for those with advanced/metastatic cancer. There is a substantial unmet need for treatment options that can meaningfully improve survival and quality of life in patients with advanced bladder cancer following chemotherapy. "I would love a wonder pill, even if it could just get rid of the fatigue that comes with the procedures and stress" "Every ache or twinge makes me feel uneasy. It really does suck, especially with Covid-19 all over the place. My life consists of the internet, writing, and TV."

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We spoke with patients who had experienced atezolizumab. "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." "My cancer started in the bladder and then spread to the prostate and then 4 months later had spread to the base of my spine and in the bones, so therefore inoperable and incurable. Speaking personally, in my opinion it's given me extended life. I call the drug my life saver, as I honestly believe that's what it is. I can't praise this drug enough. I know immunotherapy doesn't work for everyone and I had to wait 3 months to see if my body accepted it, or not. In my case I've been extremely lucky, as back in 2017 I was given about 10 months to live." "I've been on it now for 20 months. I've another 4 months. It's been great for me."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients report minimal side effects, but note that while the treatment is life-extending for many, it is not a cure. Out of the patients we spoke with, 3/4 stated that they responded well to the treatment, while 1/4 stated that the drug did not work for them. "I had Tecentriq infusions for metastatic bladder cancer and it did not work. A good surgeon and a sharp knife was my cure." "The only side effect I experienced was profuse perspiration." "Some fatigue and tinnitus and that's it."

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	NICE should examine the evidence to see if it still supports the assertion that PD-L1 should be used as a biomarker to identify a population that is more likely to respond to atezolizumab, or whether it is merely a prognostic marker that is associated with higher survival rates overall
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Women with bladder cancer have worse outcomes compared to men. Women tend to present with advanced stage, experience differences in quality of life following treatment, and suffer worse cancer-specific mortality (Hart ST, Woods ME, Quek ML. Gender disparities in bladder cancer management. Urology Times, February 20, 2019, Volume: 47, Issue: 2)

Other issues	
13. Are there any other issues that you would like the committee to consider?	Urothelial cancer has come near the bottom of the annual NHS cancer patient experience survey since its launch. The technology offers a ray of hope for a step change in treatment for this much ignored cancer. The high risk of recurrence and progression has led to this cancer seeing one of the highest associated suicide rates for cancer patients due to the emotional strains of the treatment and quality of life issues.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Advanced bladder cancer is physically and emotionally tough with a known low survival rate, and the understanding that the battle is to prolong life rather than resulting in a cure
- Advanced cancer has an impact on the ability to enjoy daily life, work, ability to travel, and ability to exercise of both the patient and their family
- In cisplatin-ineligible patients, atezolizumab has demonstrated durable response rates, survival, and tolerability
- There are very few treatment options for cisplatin-ineligible patients with advanced bladder cancer
- Patients who have experienced this drug overwhelmingly call for it to be available for others on the NHS

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Professional organisation submission

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Professional membership organisation for pathologists.**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop further progression of metastatic disease
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Unable to comment.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	NA for my role
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Unable to comment as I do not treat patients.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care. The use is limited to patients with metastatic disease thus the numbers are few. We have on an average only 1 case per month, sometimes 2.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The test incurs an added cost which includes setting up the service in the pathology laboratory, training of laboratory staff and pathologists who need to validate and interprete the test accurately. The antibody used for testing has a shelf life which if not used would lead to waste. Thus testing in centralised labs would be the way forward. However, this would mean extra work for the lab offering the test. This needs to be recognised and funded.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Outside my expertise.
• Do you expect the technology to increase length of life more than current care?	outside my expertise
• Do you expect the technology to increase health-related quality of life more than current care?	Outside my expertise
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Unable to comment
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The test is done on available diagnostic tissue so the patient does not have to be subjected to more biopsies. However, when a metastatic tumour appears years after the primary urothelial carcinoma, the test should ideally be done in the tissue from the most recent metastatic site and not the original tumour because tumour expression of PDL1 can change over time. Other that the technical know how, cost of test and evaluation of the test (which involved counting lymphoid cell expressing PDL1), there are no additional factors directly affecting the patient. The test itself is added work to the laboratory and the pathologist only. The test involves counting PDL-1 expressing inflammatory cells and NOT tumour cells. Sometimes the biopsies are small and may contain the tumour itself but very few inflammatory cells making interpretation difficult and less reliable. It is a subjective assessment esp when the percentage of staining cells are low (3-5%). Also, there will be times when the test may not work due to technical reasons so a positive control has to be used before rendering the tissue negative for PDL1 expression.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not for patients considered for Atezolizumab. Sometimes, when the percentage of PDL1 expressing inflammatory (immune) cells are <5%, I have got requests from the oncologist to test for Pembrolizumab.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unable to comment.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Unable to comment
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any	

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	outside my expertise.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	

21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- The pathologist's perspectives: centralised labs should perform tests to reduce waste as the Antibody has a shelf life.
- Pathologist at all treating hospitals should train to report so work is equally divided.
- The interpretation of the test involves counting positive immune (inflammatory) cells and not tumour cells which can be subjective and associated with inter and intra observer variations.
- The cost of the test and the time involved for interpretation should be recognised and funded

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Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

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

Post factual accuracy check version with corrections

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Declared competing interests of the authors and advisors

The authors and their advisors report none.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Keith Cooper critically appraised the economic evaluation and drafted the report; Karen Pickett critically appraised the clinical effectiveness evidence, drafted the report and co-project managed the review; Inês Souto Ribeiro critically appraised the economic evaluation and drafted the report; David Alexander Scott critically appraised the economic evaluation and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness evidence, drafted the report, co-project managed the review and is the project guarantor.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CDF	Cancer Drugs Fund
DSU	Decision Support Unit
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITT	Intent to treat
mITT	Modified intent to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life

RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Critique of the adherence to the committee's preferred assumptions from the Terms of Engagement

The company has adequately adhered to the committee's preferred assumptions, with the exception that best supportive care is not included as a comparator in the company's base case cost effectiveness analysis due to a lack of available evidence. However, both the company and the ERG provide exploratory scenario analyses in which best supportive care is a comparator to atezolizumab, based on assumptions.

1.2 Summary of the key issues in the clinical effectiveness evidence

In their submission, the company provide new clinical effectiveness data from two sources:

1. **IMVigor 130** a phase III randomised controlled trial comparing atezolizumab monotherapy against placebo and gemcitabine plus carboplatin in people with untreated locally advanced or metastatic urothelial cancer, who were eligible for platinum-based chemotherapy (cisplatin or carboplatin with gemcitabine). The data presented in the CS is from a subgroup of people with cisplatin-ineligible PD-L1-positive urothelial carcinoma, to correspond to the EMA marketing authorisation for this indication.
2. **The Systemic Anti-Cancer Therapy (SACT)** dataset on the real-world effectiveness of atezolizumab among people with PD-L1 positive, untreated metastatic urothelial cancer during treated via managed access through the Cancer Drugs Fund (CDF).

The ERG has assessed this new evidence and note the following key issues of uncertainty:

- The IMvigor 130 trial treatment effect estimates, including overall survival (OS) and progression-free survival (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).

- Within this subgroup there were baseline differences between trial arms in terms of sex and racial characteristics, and it is unclear if these differences could have biased the treatment effects.
- The median OS estimates for atezolizumab monotherapy obtained from the SACT dataset and the IMVigor 130 trial differ substantially (SACT dataset: 12.4 months (95% CI: 8.3, 20.1); IMvigor 130 trial: 18.6 months (95% CI: 14.0, NE). This may be due to people included in the SACT dataset being older and having a poorer performance status than the participants included in the IMvigor 130 trial. We consider the SACT dataset estimates of OS are more likely to be representative of people seen in clinical practice.
- As mentioned above, no comparison was made between atezolizumab and best supportive care in the company's base case. The ERG concurs that evidence on best supportive care is sparse, inconsistently defined and difficult to identify. Expert clinical advice on typical best supportive care practice for this patient group may help inform further, more targeted, searches to identify potentially relevant best supportive care data.

1.3 Summary of the key issues in the cost-effectiveness evidence

- The company's economic model included parametric survival curves based on the IMVIgor 130 trial (section 4.1.1). To assess the long-term outcomes of OS, PFS and time to treatment discontinuation (TTD), the company used the trial's Kaplan Meier survival data, at the end of which they fitted an exponential distribution to model the tail of the survival curves. Because of the small number of participants in the cisplatin-ineligible PD-L1-positive subgroup, there is large uncertainty in survival estimates. Therefore, the ERG considers it preferable to fit a parametric distribution to the whole survival curve, rather than the company's approach extrapolating from the Kaplan Meier data. Based on visual fitting and an analysis of the hazards of the survival curves, our preferred extrapolation is the exponential for OS and the Weibull for PFS and TTD.
- The utility values used are based on EQ-5D data collected in the IMVIgor 130 trial (section 4.1.2). However, the ERG is unable to verify the utility values from the description and data submitted by the company. It is unclear to the ERG how the values used in the model have been obtained from the naïve patient-level values submitted in response to ERG clarification questions. We have concerns about the progression-free utility value for platinum-based chemotherapy being lower than the pooled estimate for progressed disease which appears implausible.

- As per the Terms of Engagement agreement, the company included the costs of subsequent treatments received by patients whose disease has progresses after first line treatment (section 4.1.3). The ERG and the company differ in the approach taken to estimate the duration of subsequent treatments, with differing results. The estimated TTD was 7.9 months in the atezolizumab arm (ERG), and 10.7 months (the company).

1.4 Summary of ERG's preferred assumptions and resulting ICER

Based on the ERG's critique of the company's economic evaluation, we identify six key aspects of the company base case with which have concerns. Our preferred model assumptions are the following:

- Extrapolation of PFS: Weibull curve.
- Extrapolation of OS: Exponential curve.
- Extrapolation of TTD: Weibull curve.
- Subsequent treatment: duration of in the atezolizumab arm of 7.9 months.
- Utilities: 0.567 for the progression free health state with platinum-based chemotherapy.

Table 1 reports the cost effectiveness estimates based on the ERG's preferred assumptions and with the confidential Patient Access Scheme (PAS) discount price for atezolizumab. The ICER increases from £32,708 (company base case) to £49,301 per QALY.

Table 1 Cost effectiveness results of atezolizumab compared to platinum-based chemotherapy using the ERG's preferred assumptions

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£49,301
Platinum-based chemotherapy	£17,657	0.85			

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG performed the following scenario analyses in addition to the ERG preferred assumptions above:

- We applied the company's scenario analyses that led to a change in the ICER of ≥ £5,000 per QALY.

- We used alternative curves to extrapolate PFS (exponential, KM + Weibull, KM + exponential), OS (Weibull, KM + exponential) and TTD (exponential, KM + Weibull, KM + exponential)
- We used the OS for atezolizumab and applied a hazard ratio to model OS for the platinum-based chemotherapy arm and varied the hazard ratio across its 95% confidence interval (CI).
- We used alternative utilities for the progression free health state for platinum-based chemotherapy from the IMVigor 130 dataset (0.527 and [redacted])
- We used alternative utilities from the a study of pembrolizumab for a similar indication (Keynote 052)[1] (0.842 and 0.8 for progression free for atezolizumab and platinum-based chemotherapy respectively, and 0.8 for progressive disease)

Table 2 reports the results of the ERG's scenario analyses. The use the OS upper bound 95% CI hazard ratio has the greatest impact on cost-effectiveness results (ICER varied from £37,428 to £95,076 per QALY). Using alternative curves to extrapolate TTD and applying alternative utility values also has a large impact on cost-effectiveness results: £37,657 per QALY (scenario: KM + exponential to extrapolate TTD), £38,681 per QALY (scenario: utilities from Keynote 052), £42,052 per QALY (scenario: exponential to extrapolate TTD), £52,504 per QALY (scenario: [redacted] as the utility for progression free for platinum-based chemotherapy). The remaining scenarios change the ICER to a lesser extent.

Table 2 Additional scenario analyses using the ERG's preferred model assumptions (discounted, PAS price for atezolizumab)

Scenario	ICER (£/QALY)
ERG preferred base case	£49,301
PFS extrapolation: exponential	£50,717
PFS extrapolation: KM + Weibull	£48,766
PFS extrapolation: KM + exponential	£50,310
OS extrapolation: Weibull	£47,843
OS extrapolation: KM + exponential	£45,422
OS hazard ratio: 0.29	£37,428
OS hazard ratio: 0.87	£95,076
OS hazard ratio: 0.5	£44,661
TTD extrapolation: exponential	£42,052
TTD extrapolation: KM + Weibull	£46,991
TTD extrapolation: KM + exponential	£37,657

Progression-free utility for platinum-based chemotherapy: 0.527	£47,277
Progression-free utility for platinum-based chemotherapy: [redacted]	£52,504
Utilities: from Keynote 052	£38,681
OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life years; TTD, time to treatment discontinuation.	

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to the NICE Cancer Drugs Fund (CDF) review of TA492 on the clinical effectiveness and cost effectiveness of atezolizumab for untreated PD-L1 positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable. Clarification on some aspects of the CS was requested on 25th May 2021. The company's response was received by the ERG on 7th June 2021.

Atezolizumab (Tecentriq) is a monoclonal antibody that binds to programmed death ligand 1 (PD-L1). It was granted marketing authorisation in September 2017, with an indication as monotherapy for adults with locally advanced or metastatic urothelial carcinoma after prior treatment with a platinum-containing chemotherapy or for people who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression of ≥ 5%. According to the SmPC on the EMA website, the recommended dose of atezolizumab monotherapy is 840 mg administered intravenously every two weeks or 1,680 mg intravenously every four weeks, until loss of clinical benefit or unmanageable toxicity.[2] We note the Electronic Medicines Compendium (EMC) states the dose is 1,200 mg administered intravenously every three weeks.[3]

In the original appraisal (TA492), NICE recommended atezolizumab for use within the Cancer Drugs Fund (CDF) as a treatment option for untreated locally advanced or metastatic urothelial carcinoma in adults for whom cisplatin-containing chemotherapy is unsuitable only if:

- they had tumours with PD-L1 expression of 5% or more;
- and, the conditions set out in the managed access agreement were followed.

TA492 states that the restriction to adults with high levels of PD-L1 was based on the European Medicines Agency (EMA) limiting use to this population in July 2018.[4] As set out in the NICE Terms of Engagement for this appraisal, the committee originally recommended atezolizumab irrespective of PD-L1 status, because the company had not provided cost-effectiveness analyses in this population. TA492[4] concluded that atezolizumab met NICE's criteria to be considered a life-extending end-of-life treatment, but that a key uncertainty in the evidence was how the effectiveness of atezolizumab compared with that of other treatments. The cost-effectiveness estimates were also uncertain, but NICE stated that atezolizumab had the potential to be cost-effective subject to further data collection and appraisal review. Since atezolizumab became available on NHS via the CDF, data have

been collected on patient use of atezolizumab as part of a managed access agreement. The intention was that these data, in addition to new data from an ongoing phase III trial of atezolizumab (IMvigor 130), could help address the identified uncertainties.

In the company's CDF review submission, clinical effectiveness data are provided from two sources:

1. **The phase III IMvigor 130 trial** for a subgroup of participants who had PD-L1 positive (tumours with a PD-L1 expression level of 5% or more), untreated locally advanced or metastatic urothelial cancer, who were ineligible to be treated with cisplatin.
2. **The Systemic Anti-Cancer Therapy (SACT)** cohort dataset on the real-world treatment effectiveness of atezolizumab among people with PD-L1 positive, untreated metastatic urothelial cancer, ineligible for cisplatin-based chemotherapy, treated within the CDF during the managed access period.

2.2 Background

The CS accurately reports the recommended use of atezolizumab within the CDF (CS Section A1) and the licenced indication (CS Section A4). CS Table 2 acknowledges that the indicated use of atezolizumab in people with PD-L1 positive tumours will require PD-L1 testing and states that the majority of people who are ineligible for treatment with cisplatin will receive PD-L1 testing in practice.

2.3 Critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement

Our critique of the company's adherence to the terms of engagement set by NICE is provided in Appendix 9.1. The company has adhered to the terms, except that:

- Subgroup data selected from the IMvigor 130 trial presented in the CS does not fully match NICE's preferred population of those who "cannot have cisplatin", as cisplatin was the investigators' preferred platinum-based chemotherapy for some of these participants despite their cisplatin-ineligible status. Relatedly, in the IMvigor 130 subgroup data presented in the CS, 11.6% of the participants in the comparator arm received placebo and gemcitabine plus cisplatin, rather than placebo and gemcitabine plus carboplatin. However, we do not consider this to be an issue as data provided by the company in their clarification response B9, Tables 8 and 9,

suggests that the inclusion of participants for whom the investigators' choice was cisplatin does not affect the OS and PFS treatment effect estimates.

- The company did not include best supportive care as a comparator in the base case due to a lack of evidence.

In addition to the committee's preferred assumptions below, the company notes in CS Section A.3 that after the consultation meeting with NICE on the terms of engagement, subsequent treatments were included in the economic model (which were not included in the original CS).

3 CLINICAL EFFECTIVENESS

3.1 Critique of new clinical evidence

3.1.1 The IMvigor 130 trial

3.1.1.1 Overview of the IMvigor 130 trial

The design and methodology of the IMvigor 130 trial (NCT02807636) is presented in CS Section A.5.1 and CS Appendix Section C1 and C.2.1 to C.2.6.2; summarised in Table 2 here. The company provided a journal article reporting the trial[5] and the Clinical Study Report (CSR)[6] with their submission. CS Appendix Section C.2 outlines that the trial was initially designed as a two-arm study comparing atezolizumab in combination with carboplatin and gemcitabine to placebo in combination with carboplatin plus gemcitabine in participants ineligible for cisplatin. The trial was subsequently altered to include an atezolizumab monotherapy arm and to include participants eligible for cisplatin treatment as well as those who were ineligible. Investigators could choose at baseline, prior to randomisation, their preferred platinum-based chemotherapy for each participant (cisplatin or carboplatin), but were encouraged to use the Galsky criteria[7] to guide their decision. The intervention and comparator arms relevant to this CDF review are shown in Table 2. Interim data from a cut-off of 14th June 2020 are presented in the CS. CS Appendix C Table 14 states that a total of 579 deaths were reported up to this cut-off. This is 86.8% of the 667 deaths required for the final analysis. The company have stated that the final analysis is estimated to be available in Q2-3 2022 (clarification response A5).

Table 2 Summary of IMvigor 130 trial design and methodology

Study aspect	IMvigor 130 trial design and methodology
Design	Phase III, multicentre, randomized, partially-blinded placebo-controlled study, conducted internationally at 229 sites, including the UK
Overall participant population	Adults with previously untreated locally advanced or metastatic urothelial cancer, who were in the investigators' judgement eligible to receive platinum-based chemotherapy
Randomisation stratification factors	PD-L1 expression (IC0 [<1%] vs. IC1 [≥1% and <5%] vs. IC2/3 [≥5%]), Bajorin risk factor/liver metastasis (0 vs.1 vs. 2 or patients with liver metastasis), chemotherapy

	regimen (gemcitabine/carboplatin vs. gemcitabine/cisplatin) as determined by the investigator
Overall number of participants randomised	1213
Intervention arm relevant to this CDF review and NICE's final scope	Atezolizumab monotherapy, administered intravenously at a dose of 1,200 mg on day 1 of each 21-day cycle until investigator-assessed disease progression
Comparator arm relevant to this CDF review and NICE's final scope	Placebo and gemcitabine plus cisplatin or carboplatin (referred to as 'platinum-based chemotherapy' in the CS and, hereafter, in this report). The comparator drug doses are described in CS Table 3 and CS Appendix Section C2.4.1.
Sponsor	F Hoffmann-La Roche and Genentech (a member of the Roche group)
Outcomes relevant to this CDF review and used in the company's economic model base case	OS, PFS, TTD, EQ-5D and subsequent treatments (the latter only in a scenario analysis)
Data cut-off	14th June 2020 (interim data)

Source: this table is based on CS Table 3, but we have substantially adapted it and included information from CS Section A.5.1, CS Appendix Sections C1 and C.2.1 to C.2.6.2 and the trial paper[5]
CS: company's submission; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; TTD: time to treatment discontinuation.

3.1.1.2 IMvigor 130 trial PD-L1 positive, cisplatin ineligible subgroup

The CS presents OS, PFS, TTD, ORR, duration of follow-up, EQ-5D and subsequent treatment data for the subgroup of participants (n = 93) who had untreated PD-L1 positive (tumour expression ≥5%) locally advanced or metastatic urothelial cancer, who were ineligible to be treated with cisplatin according to the Galsky criteria.[7] The company states that this subgroup and the Galsky criteria matches the EMA marketing authorisation criteria. OS, PFS, TTD, EQ-5D and subsequent treatment outcomes from this subgroup were used in the company's economic model base case.

Five of the 43 (11.6%) subgroup participants in the comparator arm were treated with cisplatin during the trial instead of carboplatin, reflecting investigator choice. The ERG also notes that Table 18, of CS Appendix C shows that the investigator choice of chemotherapy at baseline was cisplatin for 11 of the 50 (22.0%) participants in the cisplatin-ineligible

subgroup atezolizumab monotherapy arm. The company noted that none of these 11 participants were actually treated with cisplatin (clarification response B9). In Table 11, we summarise the number of participants in the subgroup who were assigned to each of the treatment arms and the numbers for whom the investigators' choice of platinum-based chemotherapy at baseline was either cisplatin or carboplatin. As discussed in Section 2.3, we conclude that inclusion of participants where the investigators' choice was cisplatin has not affected the OS, PFS or TTD results, so we do not consider this to be an issue.

Table 3 Number of participants in the IMvigor 130 PD-L1 positive, cisplatin-ineligible subgroup who were assigned to each trial treatment

	Atezolizumab monotherapy	**Platinum-based chemotherapy[a]**
Number of subgroup participants assigned	50	43
Investigator choice of chemotherapy: carboplatin	39/50 (78.0%) [b]	38/43 (88.4%)
Investigator choice of chemotherapy: cisplatin	11/50 (22.0%) [b]	5/43 (11.6%)

Source: CS Appendix Table 18.

[a] Placebo and gemcitabine plus cisplatin or carboplatin

[b] Company's clarification response B9 states that none of these participants were actually treated with cisplatin or carboplatin during the trial

3.1.1.3 IMvigor 130 PD-L1 positive, cisplatin-ineligible subgroup baseline characteristics

The company provides baseline characteristics for the cisplatin-ineligible, PD-L1 positive subgroup in CS Appendix Table 18 and clarification response A1, Table 1). Table 4 below summarises notable differences in baseline characteristics between the two relevant trial arms identified by the ERG. There were proportionally more males and people of an Asian race in the atezolizumab monotherapy arm than in the platinum-based chemotherapy arm. Proportionally fewer participants in the atezolizumab monotherapy arm than in the comparator arm had a baseline Bajorin risk factor score/liver metastases score of zero. We note that the analyses of PFS and OS were stratified and the statistical analysis plan provided by the company states

[redacted]. It is unclear, however, what impact the sex and race baseline differences may have on the treatment effect.

Table 4 IMvigor 130 trial PD-L1 positive, cisplatin-ineligible subgroup: differences in baseline characteristics between trial arms

Characteristic	Atezolizumab monotherapy (n=50)	Platinum-based chemotherapy [a] (n = 43)
Sex, n (%)		
Male	39 (78.0)	25 (58.1)
Female	11 (22.0)	18 (41.9)
Race, n (%)		
Asian	12 (24.0)	4 (9.3)
White	38 (76.0)	39 (90.7)
Bajorin risk factor score/liver metastases, n (%)		
0	18 (36.0)	23 (53.5)
1	17 (34.0)	14 (32.6)
2 or liver metastasis	15 (30.0)	6 (14.0)

Source: Reproduction of CS Table 18, adapted to show only three baseline characteristics here

[a] Placebo and gemcitabine plus cisplatin or carboplatin

3.1.1.4 Risk of bias assessment

The company did not provide a risk of bias assessment of the IMvigor 130 trial in the CS. In response to clarification questions, the company provided an assessment using criteria based on guidance from the Centre for Reviews and Dissemination (CRD) (clarifications response A3, Table 1). The use of these criteria is appropriate, but we note that the company did not include the CRD criterion of whether or not participants were similar at baseline in terms of prognostic characteristics. Table 5 shows the company and ERG critical appraisals of the IMvigor 130 trial. We based our assessment on the baseline characteristics and trial outcomes reported specifically for the cisplatin-ineligible, PD-L1 positive subgroup, rather than for the whole trial population. We identified that the trial results for this subgroup are at an unclear risk of selection bias due to some imbalances in baseline characteristics between the trial arms (see Section 3.1.1.3 for further discussion). We agree with the company that there is a high risk of bias on the criterion of blinding participants and personnel. This is because the participants received open-label atezolizumab monotherapy or blinded placebo plus open-label platinum-based chemotherapy.[5] Therefore, there is a risk of performance bias (i.e. knowledge of the treatment assigned could have affected the care provided or the participants' behaviour). Due to the open-label treatment, we also consider there is a high risk of detection bias for the HRQoL outcome, as this is a self-report measure and participants' responses could have been biased by their knowledge of the treatment assignment.

Table 5 Company's and ERG's critical appraisal of the IMvigor 130 trial

Quality assessment criteria	Company's response	ERG's response
Random sequence generation	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Low risk of bias
Groups similar at outset of study	No assessment made	Unclear risk of bias (see Section 3.1.1.3 for a discussion of baseline characteristic imbalances between the trial arms)
Blinding of participants and personnel	High risk of bias	High risk of bias
Blinding of outcome assessment	Low risk of bias	High risk of bias for HRQoL Low risk of bias
Incomplete outcome data	Low risk of bias	Low risk of bias
Selective reporting	Low risk of bias	Low risk of bias
Any other sources of bias	Low risk of bias	Low risk of bias

Source: company's clarification response Table 1

ERG: Evidence Review Group.

ERG conclusion

We consider that, overall, the IMvigor 130 trial was well conducted, but that the lack of blinding puts the trial at high risk of performance bias. It is unclear what impact baseline imbalances in race and sex may have had on the results for the PD-L1 positive, cisplatin ineligible subgroup.

3.1.1.5 Summary of the efficacy results of the IMVigor 130 trial in the PD-L1 positive, cisplatin-ineligible subgroup

OS, PFS and TTD

Table 6 summarises the OS, PFS and TTD results from the IMVigor 130 trial in the PD-L1 positive, cisplatin-ineligible subgroup. The associated Kaplan-Meier plots are provided in CS Figures 1, 2 and 3. Median OS and median PFS were longer in the atezolizumab monotherapy arm than the platinum-based chemotherapy arm. The associated HRs showed

statistically significant OS and PFS benefits in the atezolizumab arm compared with the platinum-based chemotherapy arm. Median TTD was longer in the atezolizumab monotherapy arm than the comparator arm, but the company did not report if this result was statistically significant.

We note that the 95% confidence intervals (CIs) around the OS HR are wide, suggesting some uncertainty in the relative treatment effect. There were also wide CIs around the median PFS stratified HRs and median TTD results in the atezolizumab arm, also suggesting uncertainty. This likely due to the small number of participants included in the subgroup analyses. We report a scenario analysis varying the hazard ratio of OS across its lower and upper CIs and using a mean hazard ratio of 0.5 to explore the impact of this uncertainty on the cost-effectiveness results (see Section 6.1).

Table 6 IMVigor 130 trial results for OS, PFS and TTD among the PD-L1 positive, cisplatin-ineligible subgroup

Outcome	Statistic	Trial arm		Difference
		Atezolizumab, n = 50	**Platinum-based chemotherapy, [a] n = 43**	
OS	Patients with event, n (%)	28 (56%)	30 (70%)	Stratified HR = 0.50, (95% CI 0.29 to 0.87), p=0.0125
	Median OS, months (95% CI)	18.6 (14.0, NE)	10.0 (7.4 ,18.1)	
PFS	Patients with event, n (%)	36 (72%)	37 (86%)	Stratified HR = 0.56, (95% CI 0.34 to 0.93), p=0.0235
	Median PFS, months (95% CI)	6.4 (4.2, 12.5)	6.0 (4.2, 7.4)	
TTD	Patients with event, n (%)	39 (78%)	43 (100%)	Not reported
	Median TTD, months (95% CI)	6.0 (3.5, 12.6)	3.7 (2.6, 3.9)	

CS Tables 5, 6 and 7

CI: confidence intervals; HR: hazard ratio; NE: not evaluable; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation

[a] Placebo and gemcitabine plus cisplatin or carboplatin

HRQoL

The company provides a summary of the HRQoL findings from the IMvigor 130 trial, as measured by the EQ-5D, in CS Section A.6.1 and CS Table 9. The company states atezolizumab had a statistically significantly greater HRQoL compared with platinum-based chemotherapy in terms of the progression-free (0.642 vs. 0.527 p<0.01) and progressed disease (0.625 vs. 0.510 p<0.01) health states.

Subsequent treatments

In the CS, subsequent treatment results are presented in Section A.6.1 and Table 10. Individual drugs are listed and each of these could be used alone or in combination with other treatments. The most commonly used subsequent treatments were: paclitaxel in the platinum-based chemotherapy arm (23% of participants), and carboplatin and gemcitabine in the atezolizumab monotherapy arm (24% and 32% of participants, respectively).

Inclusion of participants for whom investigators' choice of chemotherapy at baseline was cisplatin does not impact on PFS, OS and TTD results

In their clarification response B9, Tables 8 and 9, the company provided PFS, OS and TTD results for each subgroup of participants assigned to the intervention or comparator treatments according to whether the investigator choice was cisplatin or carboplatin. We have replicated the tables here. We note that median OS is longer for participants in both arms where the investigator chose cisplatin rather than carboplatin (although it should be noted that these results are uncertain because the number of participants on which these results are based is small). In both treatment arms, the median OS for participants for whom the investigator chose carboplatin is similar to the results for the total subgroup for the corresponding trial arm. Therefore, the inclusion of participants where the investigator's choice was cisplatin does not appear to have impacted the OS results for the overall PD-L1 positive, cisplatin-ineligible subgroup discussed above. The inclusion of participants where the investigator's choice was cisplatin also does not appear to have impacted the PFS or TTD results for the overall subgroup either.

Table 7 IMvigor 130 PFS, OS and TTD in the atezolizumab arm by investigator choice of platinum-based chemotherapy

	Investigator choice of cisplatin (n=11)	Investigator choice of carboplatin (n=39)
Median PFS (95% CI)	7.2 (2.0, NE)	6.4 (4.2, 12.6)
Median OS (95% CI)	23.6 (13.1 NE)	18.6 (12.7, NE)
Median TTD (95% CI)	3.5 (1.4, NE)	6.2 (4.2, 12.6)

Source: reproduction of the company's clarification response Table 8

CI: confidence intervals; OS: overall survival; PFS: progression-free survival; NE: not evaluable; TTD: time to treatment discontinuation

Table 8. IMvigor 130 PFS, OS and TTD in the platinum-based chemotherapy arm by investigator choice of platinum-based chemotherapy

	Investigator choice of cisplatin (n=5)	Investigator choice of carboplatin (n=38)
Median PFS (95% CI)	6.3 (2.6, NE)	5.9 (4.2 8.2)
Median OS (95% CI)	14.6 (3.5, NE)	9.9 (7.4 22.9)
Median TTD (95% CI)	2.1 (1.8, NE)	3.4 (2.5, 3.7)

Source: reproduction of the company's clarification response Table 9.

CI: confidence intervals; OS: overall survival; PFS: progression-free survival; NE: not evaluable; TTD: time to treatment discontinuation

3.1.1.6 Key issues identified by the ERG with the IMVigor 130 trial data reported in the CS

The ERG has identified the following concerns about the IMVigor 130 trial data reported in the CS:

- Results relevant to NICE's final scope and the terms of engagement are from an interim data analysis of a small subgroup of participants who had PD-L1 positive tumours and who were ineligible to receive cisplatin – this means that there is some uncertainty in the treatment effect estimates.

- Within the subgroup, there were some imbalances in baseline characteristics in sex and race between the atezolizumab monotherapy and the placebo and platinum-based chemotherapy arms. It is unclear how these may have impacted the treatment effect estimates.

3.1.2 SACT data cohort study

3.1.2.1 Overview of the SACT dataset

Public Health England (PHE) was commissioned to assess the real-world treatment effectiveness of atezolizumab in clinical practice in England among people treated under the CDF during the managed access period. This data was collected through the Systemic Anti-cancer Therapy (SACT) dataset. Data was originally intended to be collected between November 2017 and December 2020. The data collection period, however, was amended so that it started from 12 July 2018 to reflect the EMA's decision to limit the use of atezolizumab for those with PD-L1 positive tumours. The results provided in the CS and accompanying SACT dataset report are for applications made in the period 12 July 2018 to 11 August 2020. The minimum follow-up for OS was 5.5 months from the last application, with people being traced as alive or deceased on 26 January 2021.[8]

During the data collection period, 81 applications for atezolizumab among people with untreated metastatic urothelial cancer, for whom cisplatin was unsuitable, were identified. People with locally advanced disease were eligible for treatment, but presumably no applications were made for people with locally advanced disease. After 17 of the identified applications were excluded due to being duplicates or due to the person dying before treatment, or, in one case, not receiving the treatment, 64 people were included in the analyses. All 64 people had PD-L1 positive tumours.

Atezolizumab was administered as a monotherapy at a fixed dose of 1200 mg every three weeks or 1680 mg every 4 weeks. Treatment was given until loss of clinical benefit, excessive toxicity or until the patient chose to discontinue.[8] The SACT dataset does not compare the effectiveness of atezolizumab with other treatments for the disease.

The committee's main uncertainties that the SACT data collected was intended to address were clinical efficacy estimates of treatment duration and overall survival from the beginning of treatment.[8] As stated in CS Section A.5.2, the company did not use results from the SACT

dataset in their economic model: the results were used to validate the efficacy estimates from IMvigor 130.

3.1.2.2 Baseline characteristics

Minimal baseline characteristics for the SACT cohort are presented in the SACT report (just sex, age and performance status). We note that a similar proportion of males and females were included in the SACT dataset as in the IMvigor 130 trial. CS Appendix B, Section B.1.3 notes differences between the SACT dataset and IMvigor 130 for TTD and OS results, and it is suggested that this may be due to differences in age and performance status (Table 9). (We note, however, that while OS results differed, TTD results, in terms of median months, were qualitatively similar.) The ERG concurs with the company that these differences may plausibly impact on the efficacy estimates. We note that the SACT cohort comprises patients treated in the NHS and the results are more likely to reflect the outcomes of a typical 'real world' clinical practice than those outcomes observed under clinical trial conditions.

Table 9 Differences in baseline characteristics between the SACT dataset and the IMVigor 130 PD-L1 positive, cisplatin-ineligible subgroup

Characteristic	SACT dataset (Atezolizumab)	IMvigor 130 trial arm	
		Atezolizumab	Platinum-based chemotherapy
Age (years)[a]	<40 to 69: n = 16 (25.0%) 70 to 80+: n = 48 (75.0%) Median: 76	Mean (SD): 69.2 (9.2) Median: 71	Mean (SD): 68.5 (10.6) Median: 70
Performance status, n (%)			
0	6 (9)	18 (36.0)	20 (46.5)
1	28 (44)	24 (48.0)	16 (37.2)
2	20 (31)	8 (16.0)	7 (16.3)

Source: Systemic Anti-Cancer Therapy (SACT) dataset report [8] and CS Appendix Table 18

SACT: Systemic Anti-Cancer Therapy; SD: standard deviation

[a] SACT data number and percentages of participants calculated by the ERG using data in the SACT dataset report Table 4.

The company also states in Appendix B Section B.1.3 that the impact of the COVID-19 pandemic on the SACT dataset results is unknown, but notes that the data collection period

included 5 months of the pandemic (that is, up to August 2020; although we note that vital status was traced in the SACT on 26 January 2021). They state at the interim report which goes up to 11th July 2019 the median OS was 15 months (n = 35). We note that this contrasts to the median OS of 12.4 months based on the cohort of 64 people (see below for full OS results from the dataset). Given the July 2019 analysis was based on 35 people, we consider that this estimate would be highly uncertain and does not provide an indication of the impact of the pandemic on OS in this population. We also consider it unlikely that a substantial number of the 64 people included in the SACT dataset would have caught coronavirus and died due to it, or would have experienced an indirect impact from the pandemic on their health and care that might have reduced OS. Therefore, it is unlikely to be a plausible explanation for the differences observed in OS.

We did not identify any other differences between the two studies that may account for the differences in clinical efficacy estimates found.

3.1.2.3 Summary of the SACT dataset results

In Table 10, we present the OS and TTD results found in the SACT dataset alongside those found in the IMvigor 130 trial. We have already reported the IMvigor 130 trial results in Section 3.1.1.5, but they are reiterated here for ease of comparison. We also provide a comparison of the OS results to those found in the IMvigor 210 trial, which were used to inform the committee's decisions in TA492. (NB. as reported earlier in section 2.1, variations to the patient population were made in the decision problem for this update CDF review, which should be taken into account when making comparisons with IMvigor 210).
Median OS was found to be shorted in the SACT dataset than the IMvigor 130 trial by around 6 months. Median TTD months were similar.

Table 10 Comparison of the OS and TTD results found in the SACT dataset and the IMvigor trials

Outcome	Study	Atezolizumab	Platinum-based chemotherapy	Difference
Median OS, months (95% CI)	SACT dataset	12.4 (8.3, 20.1)	N/A	N/A
	IMvigor 130	18.6 (14.0, NE)	10.0 (7.4, 18.1)	Stratified HR = 0.50, (95% CI 0.29 to 0.87), p=0.0125

	IMvigor 210 [a]	15.9 (10.4, NE)	N/A	N/A
Median TTD, months (95% CI)	SACT dataset	5.9 (3.4, 8.5)	N/A	N/A
	IMvigor 130	6.0 (3.5, 12.6)	3.7 (2.6, 3.9)	Not reported
	IMvigor 210	Not reported, but modelled by extrapolation in the economic analysis	N/A	N/A

Source: Systemic Anti-Cancer Therapy (SACT) dataset report,[8] CS Tables 5 and 7, and TA492 ERG report

[a] Cohort 1 data presented in the TA492 ERG report (Table 14).

3.1.2.4 Key issues identified by the ERG relating to the SACT dataset

The ERG has identified the following key issues of uncertainty:

- The SACT dataset included 64 people. Therefore, like the IMvigor 130 trial, estimates of OS and TTD are based on a small number of people, which increases uncertainty in the efficacy estimates.
- As noted by the company, people included in the SACT dataset were, on average, older and proportionally more had a performance status of 2 than in the IMvigor 130 trial. These differences may account for the worse OS found for people treated with atezolizumab in the SACT data than those treated with it in IMvigor 130.
- We consider the SACT dataset estimates of OS, however, are more likely to be representative of the participants seen in clinical practice due to being based on real-world data.

3.1.3 Systematic review to identify best supportive care evidence

3.1.3.1 The company's overall approach

The company conducted a systematic literature review (SLR), current to September 2020, to identify relevant studies to facilitate an indirect comparison between atezolizumab and best supportive care. Brief details of the SLR are reported in the main submission document (Document B), with further detail given in CS Appendix A. The company report that the SLR did not identify any relevant evidence of best supportive care and they were therefore unable to include best supportive care as a comparator in their base case (though they subsequently provided a scenario analysis comparing atezolizumab with best supportive care in their response to clarification questions – discussed below). In this section we provide a brief critique of the company's SLR methods and describe exploratory ERG searches for best supportive care evidence.

Overall, the ERG considers the company's SLR to be of a good methodological standard and is generally well documented (see CS Appendix A). The CS states that the SLR "looked to identify studies of atezolizumab and comparator treatments in patients with untreated locally advanced or mUC" (Document B, page 9). From the description of the SLR given in CS Appendix A, it was not initially clear to the ERG if the purpose of the SLR was to find evidence for best supportive care. Notably, no definition of best supportive care for this patient group is provided in the CS, and none of the search terms appear to explicitly mention best supportive care and the specific interventions used (the search terms listed are for active treatments). The only mention of best supportive care given in the methods section of the SLR in is in relation to the 'study design' inclusion criterion which permitted "Prospective RCTs (phase 2-4) with active or placebo or Best supportive care controls with no restriction on blinding" (CS Section A.3, Table 7, page 19). The ERG therefore asked the company to clarify the methods used to identify and screen evidence for best supportive care (clarification question 6a). The company responded that (active) treatments included in the SLR had been cross-referenced against all previous meta-analyses of this topic, and all possible treatments in first-line metastatic urothelial carcinoma were included and searched for. The aim, it transpires, is to identify studies of active treatments for this condition and to select any studies in which best supportive care was a comparator.

The ERG considers this to be a reasonable strategy to find best supportive care evidence, but it is not comprehensive. We note that it may overlook other sources of evidence, for example non-comparative studies of best supportive care or routinely collected hospital data (e.g. patient registries). Hence, we asked the company if they searched for real world

evidence of best supportive care (clarification question 6a). The company confirmed that such evidence was not searched for, but "any relevant clinical studies (RCTs and non-RCTs) which had a best supportive care arm would have been identified and considered for inclusion". Whist the ERG agrees that the company's search has the potential to identify real world evidence, it was not designed with this intention and may, therefore, miss relevant data not published in the academic literature and identifiable through database searching.

3.1.3.2 Real world evidence of best supportive care

As part of their response to clarification question 6b, the company discusses the feasibility of obtaining real world evidence from the Flatiron dataset for a possible indirect comparison between atezolizumab and best supportive care. Flatiron is described as a United States based electronic health record that contains de-identified real-world data on cancer patient's treatments and outcomes. The company lists a number of limitations associated with the Flatiron dataset for their intended purpose (for brevity we do not mention these here, please see response to clarification question 6b). It is not stated why Flatiron was selected as a potential source of real-world evidence per se, or in preference to any alternative relevant datasets. (NB. The ERG is aware that Flatiron was acquired by the company in 2018, and also, that Flatiron commenced a partnership with NICE in 2020 to explore how real-world evidence can inform the clinical and cost effectiveness of health technologies. This may, therefore, explain the selection of Flatiron as a potential source of real-world data). The conclusion reached by the company is that "The BSC population from a real world evidence study would not lead to an accurate representation of the true treatment effect in relation to this decision problem" (clarification question response document, page 7). The ERG considers this a blunt over-generalisation of the apparent limitations of a single database to all real-world evidence of best supportive care. We comment on two specific issues raised by the company:

1. It is stated that the Flatiron dataset may contain incomplete information on best supportive care oral medications, due to difficulties in recording the use of certain drugs, including over-the-counter medications. We consider this a reasonable assertion, but we note that, in addition to drugs, best supportive care can include a range intervention types (e.g. nutritional support, blood transfusions, radiotherapy).[9] The company's apparent focus on use of oral medication data would, therefore, be an incomplete attempt to identify evidence across the spectrum of best supportive care.

2. The company argues that data from Flatiron would result in a small and incomplete patient population "which could lead to bias in the comparative analysis making it

unsuitable for decision-making". The ERG cannot verify this statement without examining the Flatiron database. The company does not acknowledge the potential for bias in its own evidence, namely the small cisplatin-ineligible PD-L1-positive subgroup from the IMVigor 130 trial. Similarly, there is a small number of patients treated with atezolizumab in SACT cohort.

Given the limitations of the company's literature search the ERG conducted a targeted search for best supportive care evidence, details of which are reported below in section 3.2.1.

3.1.3.3 Randomised trial evidence on best supportive care

The ERG is aware a couple of RCTs of active treatments for locally advanced or metastatic urothelial cancer which include a best supportive care comparator arm. Neither trial is cited in the CS and it is unclear whether the trials were identified by the company's database search.

- A randomized phase III study of vinflunine and best supportive care versus best supportive care alone for patients with advanced transitional cell carcinoma of the urothelial tract who had experienced progression after a first-line platinum-containing regimen.[10 11] Best supportive care in the trial was based on institutional standards and included palliative radiotherapy, antibiotics, analgesics, corticosteroids, and transfusion. We also note that data from this study was used to provide a best supportive care comparator in the 2018 NICE appraisal of nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (NICE TA530).

- The JAVELIN Bladder 100 trial.[12] This is a recent (published in 2020) randomised phase III trial of avelumab plus best supportive care maintenance treatment compared to best supportive care without maintenance treatment for people with unresectable locally advanced or metastatic urothelial cancer who did not have disease progression with first-line chemotherapy. Best supportive care was based on local practice and clinical judgement and the patient's condition and could include antibiotic agents, nutritional support, hydration, and pain management; and palliative

The ERG notes that the patient populations in these trials are not completely aligned with that of the current appraisal (i.e. cisplatin-ineligible PD-L1-positive patients). Nonetheless, they illustrate that evidence on best supportive care from randomised trials is available and could potentially be informative.

ERG conclusion

The ERG acknowledges that evidence on best supportive care is sparse, inconsistently defined and difficult to identify. Expert clinical advice on typical best supportive care practice for this patient group may help inform further, more targeted, searches to identify potentially relevant best supportive care data.

3.2 Additional work on clinical effectiveness undertaken by the ERG

3.2.1 ERG search for best supportive care evidence

As an alternative to the company's literature search, the ERG performed a targeted search of Embase looking for observational evidence (e.g. cohort studies) on best supportive care (search date: 14th June 2021). We used a combination of free text and subject heading search terms relating to best supportive care interventions, based on those mentioned in NICE guideline NG2 'Bladder cancer: diagnosis and management' (2015).

A set of 214 titles and abstracts identified by the search were scanned by a single reviewer for potential relevance to the appraisal. We did not identify any studies of apparent relevance. This was an exploratory exercise using pragmatic methods to inform this report, and we consider that some minor adjustments the search strategy would likely identify potentially relevant evidence. Further searching attempts should ideally include other medical databases (e.g. Medline, Cinahl), as well as wider, non-academic, evidence sources. Ideally, expert clinical opinion would help inform a working definition of best supportive care in this patient group to guide the selection of search terms and sources.

3.3 Conclusions on the clinical effectiveness evidence

In the CS, the company has adhered to NICE's preferred assumptions, as set out in the Terms of Engagement, and the evidence submitted reflects the NICE scope. The only exception to this is that the company did not include best supportive care as a comparator in their base case due to a lack of evidence.

In the original appraisal of atezolizumab (TA492),[4] the committee could not recommend atezolizumab for the PD-L1 subgroup specifically, as the company had not provided cost-effectiveness analyses in this group. The IMvigor 130 trial was expected to provide data on the effectiveness of atezolizumab in PD-L1 subgroups, including duration of treatment and quality of life. These data and cost-effectiveness analyses for the PD-L1 subgroup have been provided in the current CS.

The key clinical effectiveness uncertainty discussed by the committee in TA492 was the relative effectiveness of atezolizumab compared with other treatments, as the data provided at that time was from the IMvigor210 single arm trial and the committee did not consider the simulated treatment comparison and network meta-analysis provided by the company robust. In the current CS, the company has provided data on the comparative effectiveness of atezolizumab monotherapy compared to placebo and gemcitabine plus carboplatin in a subgroup of people with PD-L1 positive, untreated, locally advanced or metastatic urothelial cancer, who were ineligible to be treated with cisplatin. In the ERG's opinion, these data provide an indication of the relative efficacy of atezolizumab in this population, but uncertainty remains about its comparative efficacy for these reasons:

- For the comparison with platinum-based chemotherapy, the treatment effect estimates come from an interim data analysis of a small subgroup of participants from the IMvigor 130 trial.
- Within the subgroup, there were baseline characteristic differences in sex and race between the trial arms, and it is unclear if these differences could have biased the treatment effect.
- The median OS results for atezolizumab monotherapy obtained from the SACT dataset and the IMVigor 130 trial differ substantially from each other (SACT dataset: 12.4 months (95% CI: 8.3, 20.1); IMvigor 130 trial: 18.6 months (95% CI: 14.0, NE). This may be due to people included in the SACT dataset being older and having a poorer performance status than the participants included in the IMvigor 130 trial. We consider the SACT dataset estimates of OS are more likely to be representative of the participants seen in clinical practice due to being based on real-world data.
- No comparison was made to best supportive care in the company's base case.

4 COST EFFECTIVENESS

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

The following sections describe and critique the new evidence submitted for this CDF review:

- OS, PFS and TTD data from the IMVigor 130 trial
- Utility values from the IMVigor 130 trial
- Subsequent treatment

As other model parameters have not changed since the original appraisal of atezolizumab (NICE TA492) we have not discussed them further in this report.

The results from the SACT cohort study were not used by the company directly in the economic model. The ERG has conducted an exploratory using the SACT data in section 6.1.1.

4.1.1 Treatment effectiveness and extrapolation

4.1.1.1 Overall survival

The company fitted independent curves to the IMvigor 130 arms but a common distribution was used in accordance with NICE Decision Support Unit Technical Support Document 14 (CS Appendix E.1). The model fit to the observed data was determined using the Akaike information criteria / Bayesian information criteria (CS Appendix Table 31, 32) and a full range of parametric functions were considered for extrapolation (CS Appendix Figures 10 and 12).

As noted in section 3.1.2 above, the SACT patient cohort survival estimates were poorer than those from the IMVigor 130 trial. However, the SACT population can be considered more typical of the patient population treated by the NHS than the IMVigor 130 trial population. Hence, the ERG suggested that the company consider running an OS scenario analysis extrapolating from the SACT KM data for the atezolizumab arm and using the comparator arm from IMvigor 130 (clarification question B7). The company declined stating the terms of engagement with NICE requested that IMVigor 130 be used to inform this CDF review, and any comparisons between the SACT dataset and IMVigor 130 would be affected by differences in patient characteristics (clarification response B7). The ERG agrees that a this would introduce further bias in terms of a likely imbalance of baseline characteristics

between intervention and comparator. Nevertheless, for exploratory purposes we include a scenario using the SACT OS data and retaining the HR for the treatment effect relative to gemcitabine and carboplatin from IMVigor 130 (section 6.1.1).

The company favoured the KM curve with exponential extrapolation for their base case (CS Appendix Figures 11 & 13) because:

- It provided a good statistical fit to the data (CS Appendix E Tables 31, 32)
- It was considered the most conservative extrapolation for atezolizumab
- It has the closest alignment to the SACT data
- It was the preferred choice of the company's three experts

The KM curve with a log-logistic tail (also a good statistical fit) was used by the company in a scenario analysis.

The ERG favours the use of a parametric function over the whole survival period rather than extrapolation from the end of the KM data since there is considerable uncertainty in survival estimates associated with the small sample size in the cisplatin-ineligible PD-L1-positive subgroup (N=50 for atezolizumab, N=43 for platinum-based chemotherapy). Whilst the company followed the ERG's approach in the original appraisal (i.e. when KM curves were reduced to 20% of the population 'at risk', CS Appendix sections E.1, E.2) but this was based on the whole study population as opposed to the PD-L1-positive subgroup in the current appraisal.

We consider distributions with a long tail to be clinically implausible (i.e. lognormal, log-logistic, generalised gamma, Gompertz) and therefore the exponential and Weibull distributions are more appropriate.

Table 11 summarises observed survival estimates (IMvigor 130, SACT), and survival projections based on the company (expert opinion, KM + exponential, KM + log-logistic) and ERG (exponential, Weibull) base case and scenarios.

Table 11 Comparison of trial OS KM with parametric curve extrapolation (company and ERG base case and scenarios) and other sources at various time points

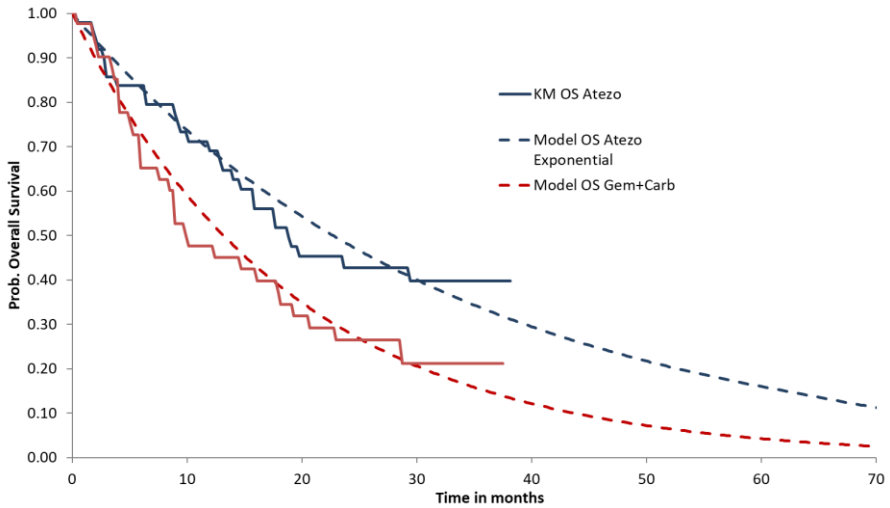
Treatment	Source	1 year	2 years	3 years	5 years	10 years	20 years
Atezolizumab	IMVigor 130	69%	43%	40%	--	--	--
	SACT cohort study	~54%	~36%	--	--	--	--
	Company expert opinion	--	--	--	5-30%	1-20%	1-6%
	KM + exponential	69%	43%	35%	17%	3%	0%

	KM + log-logistic	69%	43%	36%	24%	12%	6%
	Exponential	69%	48%	33%	16%	3%	0%
	Weibull	68%	48%	34%	18%	4%	0%
Platinum-based chemotherapy	IMvigor 130	48%	27%	21%	--	--	--
	De Santis 2012[13a]	34%	17%				
	Company expert opinion	--	--	--	1-5%	0-5%	0-5%
	KM + exponential	48%	27%	16%	5%	0%	0%
	KM + log-logistic	48%	26%	19%	10%	4%	2%
	Exponential	53%	28%	15%	4%	0%	0%
	Weibull	53%	28%	15%	4%	0%	0%

Adapted from company submission Appendix Table 33. [a] Not in a PD-L1-positive population.

The exponential and Weibull are very similar in terms of fit and survival predictions. We have selected the exponential as it is marginally more conservative (i.e., favours the comparator) and is favoured by the Akaike information criteria for atezolizumab and by the Bayesian information criteria for platinum-based chemotherapy (Tables 31, 32, CS appendices). Also, the hazard is approximately constant over time which is consistent with the exponential (Figure 1). The Weibull extrapolation is included as an ERG scenario analysis (Section 6).

Figure 1 Visual fit of atezolizumab and platinum-based chemotherapy OS KM curves compared to exponential fitted parametric curve (ERG base case)



4.1.1.2 Progression-free survival

The company concluded that proportional hazards "can be rejected" and fitted independent curves to the IMvigor 130 arms (Appendix E.2). A common distribution was used across both arms. The model fit to the observed data was determined using the Akaike information

criteria / Bayesian information criteria (CS Appendix Table 34, 35) and a full range of parametric functions were considered for extrapolation (CS Appendix Figures 17, 19).

The ERG notes an oddity in the early stages of the PFS KM curve. There was a sharp drop in the atezolizumab PFS compared to platinum-based chemotherapy at around 2.5 months (at which point the curves diverge) (CS Figure 2). The ERG queried with the company whether there was any clinical or protocol explanation. The company responded that this was a typical pattern seen with immunotherapy drugs, as they tend to have slower onset of efficacy with durable responses (clarification response B8). This pattern was also observed in the whole trial population (Figure 2, clarification responses).

The company chose the KM curve with exponential extrapolation for their base case (CS Appendix Figures 18,20) since two out of their three clinical experts advised that the exponential would be the best fit for atezolizumab whilst the other preferred the log-logistic which was included as a scenario analysis (CS Appendix E.2).

As with OS, the ERG 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. Excluding those distributions with an implausibly long tail, the ERG again favours the exponential and Weibull.

Table 12 summarises observed PFS (IMvigor 130), and survival projections from the company (expert opinion, KM + exponential, KM + log-logistic) and ERG (exponential, Weibull). The SACT dataset did not record PFS.

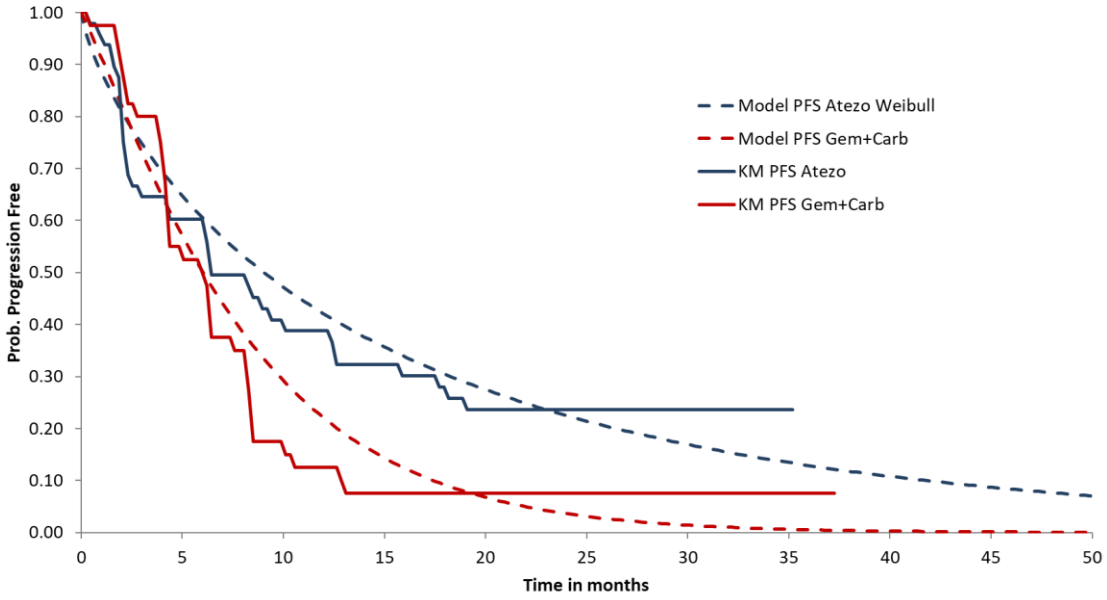
Table 12 Comparison of trial PFS KM with parametric curve extrapolation (Company and ERG base case and scenarios) and other sources at various time points

Treatment	Source	1 year	2 years	3 years	5 years	10 years	20 years
Atezolizumab	IMvigor 130	39%	24%	--	--	--	--
	Company expert opinion	--	--	--	0-20%	0-4%	--
	KM + exponential	39%	19%	8%	2%	0%	0%
	KM + log-logistic	39%	21%	14%	8%	4%	2%
	Exponential	44%	19%	9%	2%	0%	0%
	Weibull	42%	22%	13%	5%	1%	0%
Platinum based chemotherapy	IMvigor 130	13%	8%	8%	--	--	--
	Company expert opinion	--	--	--	0-20%	0%	--
	KM + exponential	17%	4%	1%	0%	0%	0%

	KM + log-logistic	15%	4%	2%	1%	0%	0%
	Exponential	23%	5%	1%	0%	0%	0%
	Weibull	22%	4%	1%	0%	0%	0%

The exponential and Weibull are relatively similar in terms of fit and survival predictions. Neither fits well to the KM data (Tables 34, 35, company submission appendices) but as stated previously there is considerable "lumpiness" in the observed data due to the small numbers of participants. As there is some evidence that the hazard is decreasing over time, our preference is for the Weibull extrapolation as our base case with the exponential included as a scenario analysis.

Figure 2 Visual fit of atezolizumab and platinum-based chemotherapy PFS KM curves compared to Weibull fitted parametric curve (ERG base case)



4.1.1.3 Time to treatment discontinuation

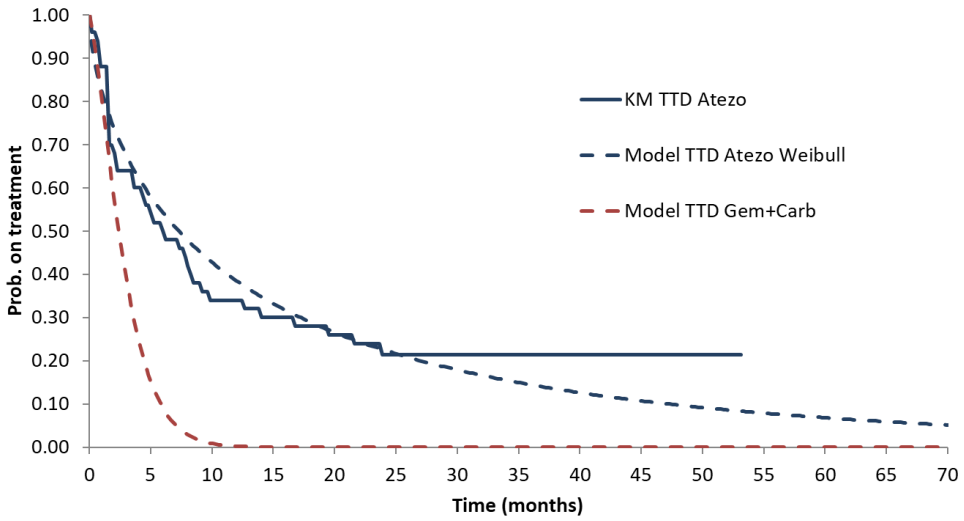
The company did not consider it relevant to assess proportional hazards for TTD, since the chemotherapy was based on an 18-week capped dosing schedule. Parametric curves were fitted to the observed TTD data from the IMVigor 130 trial and then assessed for goodness of fit using Akaike information criteria / Bayesian information criteria. Kaplan-Meier data with parametric tail models were also investigated with the parametric tails beginning when 20% of participants remained at risk in the Kaplan-Meier analysis.

The goodness of fit data for atezolizumab and platinum-based chemotherapy are shown CS Appendix Tables 38 and 39. Visual fits of the distributions compared to the KM data are shown in CS Appendix Figures 22-25. Based on the Akaike information criteria / Bayesian information criteria, the Gompertz model was the best fitting parametric model.

The company also asked clinical experts for their opinion on the curves most likely to represent UK clinical practice. The company noted that the TTD distribution is likely to follow a similar pattern to PFS and therefore selected the exponential distribution. The KM data was used for the early part of the curve as the exponential function provided a poor fit to the observed data. Therefore, the KM + exponential tail was used, and the Weibull was chosen as the next best fitting curve and used in a scenario analysis (CS Table 19).

As described above, the ERG favours the use of a parametric function over the time horizon, due to the low number of patients at risk towards the end of the KM data and the associated uncertainty. We note that the hazard for TTD is decreasing over time and this favours the Weibull distribution over the exponential distribution. We also note that the Weibull distribution provided a better fit to the KM data than the exponential distribution. We have therefore used the Weibull distribution for TTD in the ERG analyses in section 6. The visual fit for the Weibull distribution to the KM data is shown in Figure 3.

Figure 3 Visual fit of atezolizumab and platinum-based chemotherapy TTD KM curves compared to Weibull fitted parametric curve (ERG base case)



4.1.2 Health related quality of life

The company submitted new health state utility values for the atezolizumab and platinum-based chemotherapy arms, based on the IMVigor 130 trial. The trial collected EQ-5D-5L data and these were converted by the company to EQ-5D 3L using the van Hout crosswalk algorithm,[14] as recommended by NICE. The health state utility data from IMvigor 130 and the number of observations is shown in CS Table 9.

The company notes that the utility values collected in the trial for progression-free are lower than those used in the original submission (0.75, TA492[4]). The latter had been identified as an area of concern by the committee (Committee discussion TA492, 3.12[15]). In addition, the overall progressive disease health state utility (0.567) falls within and towards the lower end of the 0.71–0.5 range that the committee considered plausible (Committee discussion TA492, 3.12[15]).

For the progression free health state, the company uses treatment specific utility values as they claim that the utility value for atezolizumab for this health state has a statistically significant benefit over platinum-based chemotherapy. For the progressed disease health state, the company uses the pooled utility value for both treatment arms, due to the small number of observations (n=177). The utility values are shown in CS Table 11 and reproduced in Table 13 below.

Table 13 Summary of utility values from IMVigor 130 used in the company cost effectiveness analysis

Health state	Atezolizumab (95% CI)	Platinum-based chemotherapy (95% CI)
PF	0.642 (0.534, 0.750)	0.527 (0.404, 0.649)
PD	0.567 (0.481, 0.653)	

CI, confidence intervals; PD, progressed disease; PF, progression-free

The ERG notes that there is an error in the model for progression free in the platinum-based chemotherapy arm. For the [redacted], the progressive disease utility value has been used (0.567), instead of the progression free utility value (0.527). The ERG corrects this error in section 5.2.4. The company also corrected this error in their revised model submitted with their clarification response (Clarification question B6).

We requested more information about the utility analysis from the company (clarification question B5). In response to the clarification question, the company submitted mean utility

estimates across treatment cycles for the atezolizumab and platinum-based chemotherapy arms in the IMvigor 130 trial. The utility estimates presented are mean utilities for each treatment cycle across all patients who completed the EQ-5D instrument at those treatment cycles. The company notes that these estimates are “naive” in the sense that they do not take into account the longitudinal nature of the data. They state that the utility estimates presented in the economic model are obtained by means of an appropriate mixed-effects model, which accounts for changes in utility over time as well as correlation among observations within participants. Therefore, these two sets of utility estimates cannot be compared with each other. They state that this explains why the naive utilities are generally higher than those used in the economic model.

The ERG notes that the naïve utility values submitted by the company do not resemble those used in the company model. It is unclear how the utility values used in the model have been obtained from the naïve estimates, based on the description given in the CS and clarification response. Further, it is unclear to the ERG whether the company has adjusted for baseline utility. The ERG is therefore not able to verify the utility values used in the model.

With regard to the utility values, we note that there is an increased utility of 0.115 for the atezolizumab arm compared to the platinum-based chemotherapy arm, whilst the difference in the naïve values is [redacted]. We also note that the pooled utility value for progressive disease for platinum-based chemotherapy (0.567) is higher than the utility for progression free (0.527), which is unusual. In general, we consider that it is reasonable for the utility for progression free to be higher for the atezolizumab arm than the platinum-based chemotherapy arm due to the higher incidence of adverse events in the platinum-based chemotherapy arm, however the difference seen in this case seems much larger than seen in other studies. We also consider that it is reasonable to consider the two arms to have similar utility for progressed disease.

We note that the utilities are much lower than seen for patients in Keynote 052.[1] In this study, patients with advanced, unresectable or metastatic urothelial cancer ineligible for cisplatin-based therapy were treated with pembrolizumab. The utilities were estimated for patients with strongly PD-L1 positive tumours. The average utility was 0.842 for progression-free patients and 0.80 for patients after progression.

Based on our concerns raised above, we are unsure how representative the utility values used by the company are of this population. We do not consider it is plausible for the

progression-free utility value for the chemotherapy arm to be lower than the progressed-disease utility value. Therefore, for the ERG base case, we assume that the progression-free utility for platinum-based chemotherapy is the same as for the pooled utility estimate for progressed disease (0.567). We have conducted several scenario analyses using alternative estimates in section 6.

4.1.3 Subsequent treatment

In their analysis the company introduced the estimation of costs associated with subsequent treatments given when disease progresses following first line treatment. These costs were not previously included in the original CS, however since then atezolizumab has been recommended by NICE for patients with locally advanced or metastatic UC after platinum-based chemotherapy.[15] It was agreed during the Terms of Engagement meeting with NICE that the company should include subsequent costs. The ERG considers it reasonable to include subsequent treatment costs as these have a large impact on the total costs for the chemotherapy arm (for whom immunotherapy is a potential subsequent therapy).

The costs of subsequent treatments are shown in CS Table 14. We note that the unit and list prices presented in this table for carboplatin, gemcitabine and gemcitabine hydrochloride and the unit of pembrolizumab differ from the values shown in the company model. In response to clarification question B1, the company provided corrected costs and units for these medications, as per the economic model.

The distribution of subsequent treatments modelled were chosen to reflect UK practice and 55% of patients in each arm go on to receive second-line subsequent treatment (CS Table 12, and in this report
Table 14). Subsequent treatments used in the IMVigor 130 trial were largely unlicensed or not standard practice in the UK and therefore they were deemed inappropriate to use in the model, after consultation with clinical experts. The ERG agrees that the subsequent treatments used in the model are reflective of current UK practice.

Table 14 Subsequent therapies after discontinuation from atezolizumab and platinum-based chemotherapy as per expert opinion (base case)

Subsequent treatment	Atezolizumab		Platinum-based chemotherapy	
	Number of patients (%)	Mean treatment duration (months)	Number of patients (%)	Mean treatment duration (months)
Atezolizumab	0	--	50	10.7
Carboplatin + gemcitabine	44	4.0	0	--
Paclitaxel	11	4.0	6	2.8
Total	55		55	

Source: CS Table 12

However, we note that the proportion of patients receiving immunotherapies in the IMVigor 130 trial was 21% compared to 50% assumed to receive atezolizumab in the company analysis (CS Table 10). As treatment with atezolizumab is more effective than other non-immunotherapy treatments, potentially the company is underestimating OS in the platinum-based chemotherapy arm. The company acknowledge this and therefore run a scenario using the distributions of subsequent treatments from the IMVigor 130 trial (CS Table 19), in which the ICER was £32,676 per QALY (£34,593 in the company's updated corrected model).

For the scenario with subsequent treatments from the IMVigor 130 trial, the ERG notes that three drugs (B-701, doxorubicin and vinblastine) had been omitted from the cost calculation for the chemotherapy arm. In response to clarification question B3, the company acknowledged the calculation error and corrected the company model. This has a minor impact on the scenario results but no impact on the base case results.

The company based subsequent treatment durations for the immunotherapies on previous NICE appraisals; TA525 for atezolizumab and TA692 for pembrolizumab. The ERG requested further details on how the treatment duration for subsequent has been estimated (Clarification question B4). The company stated that the treatment duration for atezolizumab was taken from TA525 that represents atezolizumab in second-line metastatic urothelial cancer. However, the company noted that this population is not specific to PD-L1 positive and cisplatin-ineligible patients. In TA525, the treatment duration was the area under the TTD curve as modelled by the gamma distribution. The company clarified that the treatment duration for pembrolizumab had been incorrectly assumed to be 10.46 months, however the actual treatment duration from TA692 was 6.84 months. The company amended the economic model and provided an updated scenario with this treatment duration with their clarification response.

We digitised TTD curves from TA525 for patients who had previously been treated with chemotherapy and estimated the treatment duration by using the KM data with an extrapolated tail using the Weibull distribution. The estimated TTD duration was 7.9 months for atezolizumab, in contrast to the estimated duration of 10.7 months by the company. We used this treatment duration for subsequent treatment with atezolizumab in the ERG base case analyses.

5 COST-EFFECTIVENESS RESULTS

5.1 Company's cost-effectiveness results

CS section A.10 reports the company base case results for atezolizumab versus platinum-based chemotherapy (cost-effectiveness analysis 3). CS Appendix F describes the assumptions used in the company base case. The cost-effectiveness results are presented below in Table 15. They include a confidential PAS discount price for atezolizumab. The results show that atezolizumab offers a mean QALY gain of [redacted] for an additional mean cost of [redacted] versus platinum-based chemotherapy, giving an ICER of £32,708 per QALY gained.

Table 15 Company base case results, deterministic analysis (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,708
Platinum-based chemotherapy	£22,085	1.47	0.82				
Source: reproduced from CS Table 16. ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

CS section A.12.1 reports the deterministic sensitivity analyses results for the comparison of atezolizumab versus platinum-based chemotherapy. CS Table 18 presents the list of parameters alongside their base case values and the ranges used for deterministic

sensitivity analyses. The utility parameters were varied using the 95% confidence intervals, which we consider reasonable and standard practice for testing the sensitivity of individual parameters. The cost parameters as well as the body surface area were varied across a range of +/-20% and +/-50%. It is unclear however why some of the costs were varied +/-50%.

All relevant input parameters appear to be included, except for the parameters used to calculate survival curves and the proportion of patients receiving subsequent treatment. The impact of different survival curves and alternative distributions across subsequent treatments was tested as scenario analyses.

Results of the deterministic sensitivity analyses are presented in CS Table 18 and CS Figure 10 (in the form of a tornado diagram). These show that the costs incurred after disease progression by patients who received atezolizumab and the utility in the progression free state for atezolizumab have the greatest impact on the model results. The ERG notes that all the deterministic sensitivity analyses results remain lower than £50,000 per QALY. The company's updated corrected model, provided as a response to the ERG clarification questions, presents similar results for the deterministic sensitivity analyses. The same parameters have the greatest impact on model results.

5.2.2 Scenario analyses

CS section A.12.2, CS Table 19 and CS Appendix I report the results of the scenario analyses. The scenarios that have the most impact on the model results are the choice of TTD survival curve (company's original model: £45,383 per QALY; company's updated corrected model: £44,499 per QALY), the exclusion of subsequent treatment costs (company's original model: £41,663 per QALY; company's updated corrected model: £40,852 per QALY) and the duration of subsequent immunotherapy treatment (company's original model: £40,965 per QALY; company's updated corrected model: £40,167 per QALY). Similar to the deterministic sensitivity analyses results, the ICER remains under £50,000 in every scenario analysis.

We consider that the parameters explored by the company are reasonable, although we requested an additional analysis using the SACT survival data to extrapolate OS (clarification question B7). The company did not provide this scenario (see the rationale for this in section 4.1.1 above). The ERG ran a scenario using the SACT data to extrapolate OS

and TTD for atezolizumab but retaining the HR for the treatment effect relative to platinum-based chemotherapy from IMVigor 130 (section 6.1.1).
In response to clarification question A6, the company provided an additional scenario comparing atezolizumab to best supportive care. They note that this is an extreme conservative scenario analysis assuming that best supportive care is equal in clinical efficacy to platinum-based chemotherapy whilst assuming no acquisition costs, administration costs and adverse event costs in the comparator arm and no subsequent treatment costs in either arm. The scenario for atezolizumab versus best supportive care yields an ICER of £47,887 per QALY. The ERG acknowledge that this is an extreme conservative scenario, but we consider that other assumptions might also be taken into account in this analysis. For example, increasing the utility values for best supportive care given that the utility is expected to be better for best supportive care than for chemotherapy, and assuming that patients in the atezolizumab arm would still be eligible to receive subsequent treatment. The ERG provides an exploratory analysis comparing atezolizumab to best supportive care in section 6.1.2.

The ERG notes that the company's subsequent treatment distribution scenario analyses conducted by the company includes the PAS discount for atezolizumab but does not include PAS discounts applicable to subsequent therapies modelled (CS Table 19 scenario 5). Therefore, the ICER for this scenario does not reflect the actual prices that would be paid by the NHS. We present cost-effectiveness results including all agreed PAS discounts for subsequent therapies, as well as the company's proposed price discount for atezolizumab, in a separate confidential addendum to this ERG report.

5.2.3 Probabilistic sensitivity analyses

The company's probabilistic sensitivity analyses (PSA) were estimated for 1000 simulations. All the variables and corresponding distributions used in the PSA were summarised in CS Appendix G Table 40. A beta distribution was assigned for utilities and the distribution of subsequent treatments, a lognormal distribution was assigned for costs and a multivariate normal distribution was assigned for survival curves.

CS section A.11 and CS Table 17 summarise the probabilistic results. CS Figure 9 presents the cost-effectiveness plane. The probabilistic results are stable and consistent with the deterministic results. The CS reports an ICER of £33,602 per QALY for atezolizumab versus

platinum-based chemotherapy and the results of the company's updated corrected model show an ICER of £32,651 per QALY.

5.2.4 Model validation and face validity check

The economic model has been previously checked for transparency and validity. Therefore, the ERG checked only the parts of the model that were changed from last time. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all new parameter inputs against values reported in the CS and cited sources;
- Checking all model outputs against results cited in the CS, including base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses;
- Checking the individual equations underlying the new inputs within the model;
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.

The model has some minor errors in parameter inputs and coding, which affect the model results to a low extent. We also spotted a few inconsistencies in parameter values between the CS and the company's model. In response to the clarification questions sent by the ERG, the company has provided an updated model with some of the errors amended. Table 16 presents the company and ERG corrections to the original company model. We present the results from the company and ERG corrections in Table 17.

The corrected results lead to a slight decrease of the ICER from £32,708 to £32,071 per QALY gained versus platinum-based chemotherapy. This reduction was driven by the correction made in the utility of the progression-free health state for platinum-based chemotherapy for the [redacted]. The remaining corrections did not change the base case results. The amendment of time on treatment for pembrolizumab has an impact on the results of scenario 5 only (see CS Table 19). The ICER increased from £32,676 per QALY to £34,593 per QALY in this scenario. As stated above, the ICER including the PAS discounts for subsequent treatments included in scenario 5 is presented in a separate confidential addendum.

Table 16 Company and ERG corrections to the company model

Parameter	Company base case	Correction	Comments

Survival	PFS options used in the formula of cells AQ13:AQ1578 in 'Atezo' sheet	Use OS options	Corrected by the ERG
	No cap was applied to TTD so that TTD < OS (cells BR13:BR1578 in 'Atezo' sheet and BK13:BK1578 in 'Gem+Carb' sheet)	Use cap to TTD < OS	Corrected by the ERG
Utility	Progressive disease utility used for platinum-based chemotherapy progression-free health state for [redacted] (i.e., cell BC7 of 'analyses overview' sheet = "Yes")	Use progression-free utility, i.e., cell BC7 = "No"	Corrected by the company and provided as part of the updated model
	0.71 used in the formula of cells I42 and I43 in 'model inputs' sheet	Use 0.5	Corrected by the ERG
Subsequent treatments	Cell AA72 of 'subsequent treatments sheet' reports 99% as the proportion of patients receiving subsequent treatment after discontinuation from atezolizumab	Use 55%	Corrected by the company and provided as part of the updated model
	Cell L90 used in the formula of cell T32 in 'subsequent treatments' sheet	Use I90	Corrected by the ERG
	B-701, doxorubicin and vinblastine are omitted from the cost calculation for platinum-based chemotherapy arm (cell AD91 in 'subsequent treatments' sheet)	Include in cost calculation	Corrected by the company and provided as part of the updated model
	10.46 used as the time on treatment for pembrolizumab (cell S76 in 'subsequent treatments' sheet)	Use 6.84	Corrected by the company and provided as part of the updated model
OS, overall survival; PFS, progression free survival			

Table 17 ERG corrected company base case results (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,071
Platinum-based chemotherapy	£22,085	1.47	0.81				

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has identified six key aspects of the company base case with which we propose alternative assumptions / parameters. Our preferred model assumptions are listed below in Table 18.

Table 18 ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	5.1	£32,708
+ Company/ERG corrected base case	5.3	£32,071
+ Extrapolation of PFS: Weibull	4.2.2	£29,822
+ Extrapolation of OS: exponential	4.2.2	£34,892
+ Extrapolation of TTD: Weibull	4.2.2	£46,058
+ Subsequent treatment: duration of atezolizumab treatment of 7.9 months	4.2.4	£47,277
+ PF utility for platinum-based chemotherapy: 0.567	4.2.3	£49,301
ERG preferred base case		£49,301
ERG, Evidence Review Group; OS, overall survival; PF, progression free; PFS, progression free survival; TTD, time to treatment discontinuation		

Table 18 shows the cumulative cost-effectiveness results of applying the ERG preferred model assumptions to the corrected company's base case. Incorporating the ERG assumptions leads to an increase of the ICER from £32,708 to £49,301 per QALY versus platinum-based chemotherapy.

The change that has the biggest impact on the cost-effectiveness results is the use of Weibull distribution to extrapolate TTD (ICER increases by £11,166 per QALY). The use of the exponential distribution to extrapolate OS also changes the ICER significantly (ICER increases by £5,070 per QALY).

6.1.1 Scenario analyses conducted with the ERG's preferred assumptions

We performed a range of scenario analyses to analyse the impact of changing some of the ERG's preferred assumptions. We reproduced those company's scenario analyses, as previously described in section 5.2.2, in which the ICER changed by at least £5,000 per QALY. Table 19 summarises the results of the company's scenario analyses on the ERG base case. The following scenarios were also conducted to assess the impact of changing the ERG preferred assumptions (Table 20 below):

- PFS extrapolation
    - Use exponential
    - Use KM + Weibull
    - Use KM + exponential (company base case)
- OS extrapolation
    - Use Weibull
    - Use KM + exponential (company base case)
- OS hazard ratio of atezolizumab versus platinum-based chemotherapy: we have varied the hazard ratio of OS across its confidence interval due to the small sample size in IMvigor 130.
    - Low bound of hazard ratio confidence interval: 0.29
    - High bound of hazard ratio confidence interval: 0.87
    - Mean hazard ratio of 0.5
- TTD extrapolation
    - Use exponential
    - Use KM + Weibull
    - Use KM + exponential (company base case)
- Utilities
    - Utility for progression free health state for platinum-based chemotherapy: 0.527 (company base case)
    - Using a decrement for platinum-based chemotherapy as in naïve utilities for progression free health state: utility value [redacted]
    - Estimates from Keynote 052[1]
        - Progression free health state: 0.842 for atezolizumab and 0.8 for platinum-based chemotherapy
        - Progressive disease health state: 0.8.

The ICERs for the scenarios range from £37,428 per QALY (scenario: OS hazard ratio of 0.29) to £95,076 per QALY (scenario: OS hazard ratio of 0.87) for atezolizumab compared to

platinum-based chemotherapy. However, we suggest this result should be treated with caution as the platinum-based chemotherapy OS curve was varied, rather than the atezolizumab curve. Using alternative curves to extrapolate TTD and applying alternative utility values also have a significant impact on the cost-effectiveness results: £37,657 per QALY (for the scenario using KM + exponential to extrapolate TTD), £38,681 per QALY (for the scenario applying utilities from Keynote 052) £42,052 per QALY (for the scenario using the exponential to extrapolate TTD), and £52,504 per QALY (for the scenario with [redacted] as the utility for progression free for platinum-based chemotherapy). Excluding subsequent treatment costs increases the ICER to £52,265. The remaining scenarios change the ICER to a lesser extent.

For the scenario comparing atezolizumab against best supportive care, the company assumed that best supportive care was equivalent to platinum-based chemotherapy in terms of effectiveness while no costs were incurred for drug acquisition and administration and for treating adverse events. In addition, it was assumed that no subsequent treatment costs were incurred for either arms. This scenario yields an ICER of £58,600 per QALY.

Table 19 Company's scenario analyses using the ERG's preferred model assumptions (discounted, PAS price for atezolizumab)

Scenario	ICER (£/QALY)
ERG preferred base case	£49,301
Progressive disease utility values: 0.625 for atezolizumab and 0.510 for platinum-based chemotherapy	£41,610
[redacted])	[redacted]
Subsequent treatment costs: excluded	£52,265
Distribution of subsequent treatments: adjusted to match IO use	£51,210
Duration of subsequent IO treatment: as per IMvigor 130	£51,920
BSC scenario	£58,600
BSC, best supportive care; IO, immunotherapy; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; QALY, quality-adjusted life years; TTD, time to treatment discontinuation.	

Table 20 Additional scenario analyses using the ERG's preferred model assumptions (discounted, PAS price for atezolizumab)

Scenario	ICER (£/QALY)
ERG preferred base case	£49,301

PFS extrapolation: exponential	£50,717
PFS extrapolation: KM + Weibull	£48,766
PFS extrapolation: KM + exponential	£50,310
OS extrapolation: Weibull	£47,843
OS extrapolation: KM + exponential	£45,422
OS hazard ratio: 0.29	£37,428
OS hazard ratio: 0.87	£95,076
OS hazard ratio: 0.5	£44,661
TTD extrapolation: exponential	£42,052
TTD extrapolation: KM + Weibull	£46,991
TTD extrapolation: KM + exponential	£37,657
Progression-free utility for platinum-based chemotherapy: 0.527	£47,277
Progression-free utility for platinum-based chemotherapy: [redacted]	£52,504
Utilities: from Keynote 052	£38,681
OS, overall survival; PAS, patient access scheme; PFS, progression free survival; QALY, quality-adjusted life years; TTD, time to treatment discontinuation.	

6.1.1 Exploratory analysis using the SACT data

The ERG requested that the company run a cost effectiveness analysis using survival estimates from the SACT cohort (Clarification question B7). However, the company declined to as they consider the IMVigor 130 trial is a more appropriate source of survival data. They contend that treatment effect from the SACT cohort would not be representative of the true treatment effect as it will be obscured by differences in the patient populations between the two studies.

The ERG notes that the atezolizumab OS estimates from the SACT cohort are considerably lower than those seen in the IMVigor 130 trial (CS Figure 5 and section 3.1.2 of this report). We therefore consider it appropriate to present cost effectiveness results based on the SACT data as an alternative exploratory analysis for the NICE appraisal committee's deliberation.

We digitised the SACT OS and TTD curves (CS Figure 5 and 6) and fitted exponential parametric curves to the KM data. For the platinum-based chemotherapy arm, we assumed the same treatment effect as seen in the IMVigor 130 trial (hazard ratio 0.5). The results are

shown in Table 21. These show that using the SACT data with the ERG preferred assumptions produces an ICER of £30,883.

Table 21 ERG exploratory analysis using the SACT dataset and the ERG base case assumptions (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,883
Platinum-based chemotherapy	£9,634	0.81	0.46				
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							

6.1.2 Exploratory analysis comparing atezolizumab to best supportive care

The company provided an extreme conservative scenario comparing atezolizumab to best supportive care in response to clarification question A6. The company assumed that best supportive care was equivalent to platinum-based chemotherapy in terms of effectiveness while no costs were incurred for drug acquisition and administration and for treating adverse events. In addition, it was assumed that no subsequent treatment costs were incurred for either arms.

The ERG notes that this is an extreme conservative scenario with presumably poor clinical validity. Therefore, we think it is appropriate to explore the likely change in ICER if alternative assumptions were considered:

1. Company's assumption + utility of BSC equal to the utility of atezolizumab + subsequent treatment costs for atezolizumab.
2. Company's assumption + utility of BSC equal to the utility of atezolizumab + subsequent treatment costs for atezolizumab and BSC. We assumed that subsequent treatment for BSC would be the same as for platinum-based chemotherapy.

Table 22 and Table 23 show the results of these alternative analyses. Assuming the same utility as for atezolizumab and including subsequent treatment costs for atezolizumab increase the ICER to £64,379 per QALY while including subsequent treatment costs for both arms increases the ICER to £60,492 per QALY.

Table 22 ERG exploratory analysis versus best supportive care: analysis 1 (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,379
BSC	£11,630	1.50	0.90				
BSC, best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							

Table 23 ERG exploratory analysis versus best supportive care: analysis 2 (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,492
BSC	£13,804	1.50	0.90				
BSC, best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							

6.2 Conclusions on the cost effectiveness evidence

The company has included additional data from the IMVigor 130 trial for OS, PFS and TTD and utility values, as required by the Terms of Engagement of the CDF review. The company has used the original model submitted for the TA492 NICE appraisal, updated with the data from IMVigor 130. The ERG suggests alternative parametric curves for the OS, PFS and TTD extrapolations, a reduced treatment duration for second-line atezolizumab treatment and an alternative utility estimate for the progression-free health state for patients treated with platinum-based chemotherapy. The ERG's preferred assumptions increase the ICER for atezolizumab versus platinum-base chemotherapy to £49,301 per QALY.

7 END OF LIFE

In TA492, the committee considered that atezolizumab met the criteria for end-of-life treatments as the life expectancy for people with urothelial carcinoma is less than 24 months and atezolizumab is likely to extend life by at least 3 months.

The ERG considers that atezolizumab would still meet the criteria for end-of-of life treatments on the basis of the new evidence submitted. In the company analysis, the expected life expectancy for patients with urothelial carcinoma receiving platinum-based chemotherapy is 1.5 years and the expected increase in life expectancy with atezolizumab is [redacted] years (Table 15).

8 References

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9 Appendices

9.1 Preferred assumptions from Terms of Engagement

Assumption	Terms of engagement	Addressed by the company submission	Rationale if different	ERG comment
Population	Adults with untreated locally advanced or metastatic urothelial carcinoma whose tumours express PD-L1 at a level of 5% or more and cannot have cisplatin are the relevant population for the CDF review	Mostly – the company presents subgroup data for the cisplatin-ineligible (IMvigor 130 trial) and cisplatin-unsuitable (SACT study; people with metastatic urothelial cancer only) population. However, as acknowledged in CS Section A.5.1, 11.6% (n = 5) of the participants in the IMvigor 130 trial subgroup in the comparator arm received cisplatin during the trial. We also note that cisplatin was the investigators' choice of platinum-based chemotherapy at baseline for 22.0% (n = 11) of the subgroup participants atezolizumab monotherapy arm.	In the IMvigor 130 trial cisplatin ineligibility was defined by the Galsky criteria,[7] which the company states matches the EMA marketing authorisation criteria. The CS (Section A.5.1) states that clinicians in the IMvigor 130 trial could decide outside of the Galsky criteria whether participants received cisplatin or carboplatin platinum-based chemotherapy, "to reflect real-world practice". The CS states that although five participants in the comparator arm received cisplatin, they could still be considered part of the cisplatin-ineligible population in line with the Galsky criteria and licenced population.	The company clarified in response to the clarification questions that none of the 11 participants in the atezolizumab arm received cisplatin (clarification response B9). We do not believe that inclusion of participants where the investigators chose cisplatin in either trial arm has affected the treatment effect estimates – see Section 3.1.1.5. We therefore do not consider this to be an issue.

Comparators	Carboplatin plus gemcitabine and best supportive care are the relevant comparators within the CDF review	Partially – in the IMvigor 130 subgroup used in the company's base case, the majority of the 43 participants in the comparator arm received placebo and gemcitabine plus carboplatin (n = 38; 88.4%). As stated above and as acknowledged in CS Section A.5.1, five of the 43 (11.6%) participants in this comparator arm received placebo and gemcitabine plus cisplatin. The company has not included best supportive care in the submission.	As stated above, investigators could choose which platinum-based chemotherapy a participant could receive, although their choice was encouraged to be guided by the Galsky criteria. This means that some participants ineligible for cisplatin according to the Galsky criteria, received it. The company did not include best supportive care as a comparator due to a lack of available evidence (see CS Section A.3): no relevant evidence was found in a systematic literature review.	As above - we do not believe that inclusion of participants where the investigators chose cisplatin has affected the treatment effect estimates – see Section 3.1.1.5. We therefore do not consider this to be an issue. Evidence on best supportive care is sparse, inconsistently defined and difficult to identify. Expert clinical advice on typical best supportive care practice for this patient group may help inform further, more targeted, searches.
Comparative effectiveness	The company should use data from IMvigor 130 to inform the relative effectiveness of atezolizumab	Yes – IMvigor 130 trial data has been used to assess the relative effectiveness of atezolizumab on OS, PFS, treatment duration, ORR and quality of life.	N/A	The company has adhered to this assumption

Survival data	The company should use survival data from the IMvigor 130 trial and fully explore the most appropriate modelling	Yes – the company's economic model base case uses OS and PFS data from the IMvigor 130 trial (CS Table 15, Section A9). The CS states "curve selections were made following NICE guidance" (CS Table 15, Section A9). The company assessed the fit of six parametric distributions to the OS and PFS data (see CS Appendix E, Sections E1 and E2).	N/A	The company has adhered to this assumption. As discussed in Section 4.1.1 of this report, a full range of parametric functions were considered for extrapolation. The ERG has suggested alternative parametric curves for OS and PFS to those used by the company in the model.
Treatment duration	The company should use updated time-on-treatment data from the IMvigor 130 trial and validate the generalisability of this assumption using the data collected within the SACT dataset	Yes – time to treatment discontinuation data from the IMvigor 130 trial is used. The company validates this using time to treatment discontinuation data collected within the SACT dataset (CS Appendix C, Table 39, Section C.2.7.3).	N/A	The company has adhered to this assumption. We discussed how the company has used time to treatment discontinuation data in the economic model in Section 4.1.1. The ERG conducted a scenario including TTD from the SACT dataset (section 6.1.1).

Utilities	The company should use EQ-5D data from the IMvigor 130 trial to inform the economic model	Yes – the company uses utility values measured in the IMvigor 130 trial, using the EQ-5D-5L, for the progression-free (PF) and progressed disease (PD) health states in the economic model. EQ-5D-5L results were mapped to the EQ-5D-3L, using the van Hout algorithm.[14]	N/A	The company has adhered to this assumption. However, as we discuss in Section 4.1.2, it is unclear how the utility values used in the model have been obtained from the naïve estimates, and therefore we have not able to verify the utility values used in the model. We are unsure how representative the utility values used by the company are of this population.
Most plausible ICER	No cost-effectiveness analyses were provided by the company for those with high PD-L1 status, the relevant population of the CDF review	Cost-effectiveness analyses in this population were provided in the company's CDF review submission.	N/A	N/A
End of life	Atezolizumab meets the end-of-life criteria	N/A	N/A	N/A
CDF: Cancer Drugs Fund; CS: company's submission; EMA: European Medicines Agency; ERG: Evidence Review Group; ORR: objective response rate; OS, overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; SACT: Systemic Anti-Cancer Therapy				

National Institute for Health and Care Excellence

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ERG report – factual accuracy check and confidential information check

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 21 June 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect labelling of SACT population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1, page 14: "*The Systemic Anti-Cancer Therapy (SACT) cohort dataset on the real-world treatment effectiveness of atezolizumab among people with PD-L1 positive, untreated metastatic urothelial cancer treated within the CDF during the managed access period*" This incorrectly describes the eligible population for the SACT study as it fails to mention that patients must be considered unsuitable for cisplatin to be eligible.	It is recommended this sentence be amended to: "*The Systemic Anti-Cancer Therapy (SACT) cohort dataset on the real-world treatment effectiveness of atezolizumab among people with PD-L1 positive, untreated metastatic urothelial cancer where treatment with cisplatin is unsuitable treated within the CDF during the managed access period*"	Misrepresentation of SACT eligibility criteria	Corrected

Issue 2 Suggests subsequent treatments used in economic base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1.1.1, Table 2, page 17 "*Outcomes relevant to this CDF review and used in the company's economic model base case* [..] *OS, PFS, TTD, EQ-5D and subsequent treatments*"	It is recommended that this table is amended to denote that subsequent treatments are not used in the base case analysis (but are used in the scenario analysis).	Misrepresentation of company approach	Corrected

This row suggests that subsequent treatments from IMvigor130 are used in the base case analysis which is not the case.			

Issue 3 Identification of difference in patient populations between original appraisal and this CDF review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1.2.3, page 26 "*We also provide a comparison of the OS results to those found in the IMvigor 120 trial, which were used to inform the committee's decisions in TA492*." It could be confusing to suggest that results from IMvigor210 used in the original submission are comparable to the results pertaining to the current submission given the different patient populations between the original appraisal and the current CDF review.	It is recommended this sentence be amended to: "*We also provide a comparison of the OS results to those found in the IMvigor210 trial, which were used to inform the committee's decisions in TA492. However, it should be noted that due to the updated patient populations between the original appraisal and the current CDF review, direct comparisons are of limited relevance and are provided here for reference only*."	Clearer description here provided to avoid potential reader confusion	As worded this is not a factual inaccuracy. However, for clarity we have amended the wording as follows: *"(NB. as reported earlier in section 2.1, variations to the patient population were made in the decision problem for this update CDF review, which should be taken into account when making comparisons with IMvigor 210)."*

Issue 4 Incorrect trial name used

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1.2.3, page 26; Section 3.1.2.3, Table 10, page 27 Trial incorrectly titled "*IMvigor 120*" instead of "*IMvigor210*"	Change trial name to "*IMvigor210*"	Typographical error	We have amended the text as suggested.

Issue 5 Comparator incorrectly labelled

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.3, page 32: the comparator is labelled "*gemcitabine in combination with cisplatin*". Section 4.1.1.1, page 35: the comparator is labelled "*gemcitabine+carboplatin*" Suggest comparator is labelled "*platinum-based chemotherapy*" to avoid confusion and maintain consistency with the rest of the document	Suggest comparator is labelled "*platinum-based chemotherapy*"	Clearer description here provided to avoid potential reader confusion	Not a factual inaccuracy as worded, but for consistency we have amended the text as suggested.

Issue 6 Incorrect landmark OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.1.1, Table 11, page 35 "*Exponential 10-year OS* [..] *0.9%;* *Weibull 10-year OS* [..] *1%"* As per cells 'Atezo!:AB533:AC533' in the company economic model, these values are incorrectly reported.	It is recommended these values in Table 11 are updated to: "*Exponential 10-year OS: 3%;* *Weibull 10-year OS: 4%"*	Typographical error	The text has been amended as suggested.

Issue 7 Incomplete description of company approach to TTD curve selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.1.3, page 38 "*The company also asked clinical experts for their opinion on the curves most likely to represent UK clinical practice. The company noted that the TTD distribution is likely to follow a similar pattern to PFS and therefore selected the exponential distribution. The KM data was used for the early part of the curve as the exponential function provided a poor fit to the observed data.*" This provides an incomplete description of the company's	It is recommended this paragraph be amended to: "*The company also asked clinical experts for their opinion on the curves most likely to represent UK clinical practice. The company noted that the TTD distribution is likely to follow a similar pattern to PFS. The company made curve choices based on all aspects of curve selection recommended in NICE Decision Support Unit Technical Support Document 14. The company and the clinical experts agreed that a conservative curve choice should be made in order to reflect the SACT data set as closely as possible. Therefore, the exponential curve was used. The KM data was used for the*	Misrepresentation of company approach	Not a factual inaccuracy. The description of the company's extrapolation of TTD was based on a summary of the information given in CS section A8.4.and CS Appendix, Section E2, page 86-8. When writing our reports we are requested by NICE and the NIHR to be concise in our description of the company submission and to avoid reproducing large amounts of detail and data from company submissions. We therefore aim to provide a concise, balanced

approach to TTD curve selection. The description outlined here implies that the primary reason the company chose the exponential curves to model TTD was to maintain consistency with PFS and OS. In actual fact, this was a secondary consideration. The most important considerations in TTD curve selection were for the TTD curves to reflect the SACT study as closely as possible (as per the Terms of Engagement outlined in Section 9.1, page 57) and to maintain long-term clinical plausibility which was determined based on consultation with clinical experts. A more complete description is outlined in the Company Submission Appendix, Section E2, page 86-8: "*The patients in the SACT cohort demonstrated less TTD vs. subjects in IMvigor130. The potential reasons for this are outlined in Appendix B. A conservative curve choice was made in order for the model to reflect the real world evidence as closely as possible."* and "*Based on all aspects of the curve selection, KM curves with the exponential extrapolation were*	*early part of the curve as the exponential function provided a poor fit to the observed data."*		and comprehensive summary of the company's approach, but cannot describe every facet of the submission. Cross references to relevant parts of the company submission are given throughout our report, to enable the reader to obtain further detail if necessary.

selected as the most clinically plausible curves to represent both atezolizumab and platinum based chemotherapy TTD in UK clinical practice"			

Issue 8 Incorrect table label

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.3, page 41 "*CS Table 125*"	It is recommended this is amended to: "*CS Table 12*"	Typographical error	The text has been amended as suggested.

Issue 9 Incorrect description and results of subsequent treatment scenario

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.3, page 42 "*The company acknowledge this and therefore run a scenario using the treatment costs from the IMVigor 130 trial (CS Table 19), in which the ICER increases to £45,383 per QALY*" This description implies that "*treatment costs*" are taken from the IMvigor130 trial and does not mention that the key data taken from IMvigor130 are the distributions of subsequent	It is recommended this is amended to: "*The company acknowledge this and therefore run a scenario using the distributions of subsequent treatments from the IMVigor130 trial (CS Table 19), in which the ICER was £32,676 per QALY (£34,593 in the company's updated corrected model).*"	Misrepresentation of company approach and typographical error	We have amended the text as suggested.

treatments. Further, the result of £45,383 is not accurate for this scenario. In the original company submission the result is £32,676 (Section A.12.2, Table 19, page 40). After the amendment from clarification question B6, the result of this scenario is £34,593 (Clarification Questions Appendix Section A.4.2, Table 4, page 9).			

Issue 10 Incorrect labelling of BSC extreme upper bound scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, page 8; Section 5.2.2, page 45; Section 6.1.1, Table 19, page 50; Section 6.1.1, Table 19, page 50; Section 6.1.2, page 52; Section 6.1.2, Tables 22-3, page 53 There are consistent references to a "*scenario analysis*" against best supportive care. In some instances this is referenced as an "extreme conservative" scenario analysis. The company wish to make clear that the response provided in clarification question A6 in no way represents an estimate of the true	All references outlined in this report should clearly label that this is an "*extreme upper bound scenario analysis*" so as not to confuse the reader that this is an estimate of the cost-effectiveness of atezolizumab against best supportive care. Instead, this represents the upper bound and that we can only say that the true estimate of cost-effectiveness lies somewhere below this ICER. The updated label of "*extreme upper bound scenario analysis*" more accurately reflects this.	Clearer description here provided to avoid potential reader confusion	Not a factual inaccuracy. In their response to our clarification question (A6) the company refer to this analysis as both "extreme upper bound scenario analysis" and "extreme conservative scenario analysis". In the sections of our report where we discuss and critique this analysis we chose to describe it as "extreme conservative scenario analysis" as this is more likely to convey the purpose of the analysis to the appraisal committee than more abstract label of "extreme upper bound scenario

cost-effectiveness of atezolizumab against best supportive care. Instead, this represents the upper bound and that we can only say that the true estimate of cost-effectiveness lies somewhere below this ICER. With the current labelling it may not be completely clear to the reader that this is the case. An updated label of "*extreme upper bound scenario analysis*" more accurately reflects this. The company appreciates that the difference in wording is small, nuanced and that at one point in the company response to clarification questions, the company also referenced this as an "extreme conservative scenario analysis".			analysis". In these sections we have echoed the caveats that the company describes. Cross references made to this analysis in other parts of our report as being "scenario analysis" are not incorrect and out of context it may not be meaningful to the reader to use the term "extreme conservative scenario". Ultimately, the appraisal committee will make their judgement on what evidence represents the true cost effectiveness of atezolizumab, and both the ERG report and the company submission clearly state the limitations of this analysis.

Location of incorrect marking	Description of incorrect marking	Amended marking
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(Please add further lines to the table as necessary)

Public Health England

Protecting and improving the nation's health

Atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable – data review

Commissioned by NHS England and NHS Improvement

Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended commissioning of atezolizumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of atezolizumab in the CDF population, during the managed access period. This report presents the results of the use of atezolizumab in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 100% of patients and 69% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world-first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 12 July 2018 and 11 August 2020, 81 applications for atezolizumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figure 1 and Figure 2), 64 unique patients, who received treatment, were included in these

analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)(1).

Results

Sixty-four (100%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 5.9 months [95% CI: 3.4, 8.5] (179 days). 48% [95% CI: 35%,60%] of patients were receiving treatment at 6 months and 26% [95% CI: 15%, 38%] of patients were receiving treatment at 12 months.

At data cut off, 77% (N=49) of patients were identified as no longer being on treatment. Of these 49 patients, 33% (N=16) of patients stopped treatment due to disease progression, 14% (N=7) of patients stopped treatment due to acute toxicity, 4% (N=2) of patients chose to end their treatment, 33% (N=16) of patients died not on treatment, 6% (N=3) of patients died on treatment and 10% (N=5) of patients did not have a treatment record in SACT in at least 3 months and are assumed to have completed treatment.

The median OS was 12.4 months [95% CI: 8.3, 20.1] (377 days). OS at 6 months was 70% [95% CI: 57%, 80%], OS at 12 months was 54% [95% CI: 41%, 66%].

A sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results for treatment duration and OS were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real world data for patients treated with atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable in the CDF. It evaluates treatment duration, OS, treatment outcomes for all patients treated with atezolizumab for this indication.

Introduction

Urothelial cancer (ICD-10: C66) is a rare cancer type and accounts for <1% of all cancer diagnoses in England. In 2017, 596 patients were diagnosed with cancer of the ureter (males 385, females 211) (2).

Atezolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable, only if:

- their tumours express PD-L1 at a level of 5% or more, and
- the conditions of the managed access agreement for atezolizumab are followed (3)

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England (4). From the 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period (5).

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable [TA492]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of atezolizumab (Roche) in treating untreated metastatic urothelial cancer [TA492] and published guidance for this indication in November 20176.

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of atezolizumab through the CDF for a period of 37 months, from November 2017 to December 2020.

In July 2018 the European Medicines Agency restricted the use of atezolizumab for untreated urothelial carcinoma to use in adults with high levels of PD-L1. As a result, the data collection period was amended to 29 months, from July 2018 to December 2020. Only CDF (Blueteq) applications made for atezolizumab for the treatment of untreated metastatic urothelial cancer submitted on or after 12 July 2018 are included in this report.

During the CDF funding period, results from an ongoing phase III clinical study (IMvigor 130) evaluating atezolizumab in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee (7). Data collected from the phase III clinical study (IMvigor 130) are the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for atezolizumab for urothelial cancer in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the phase III clinical study (IMvigor 130) (7).

The committee identified the main areas of uncertainty below for re-appraisal at the end of the CDF data collection:

- treatment duration for the use of atezolizumab
- overall survival from the start of a patient's first treatment with atezolizumab

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Roche) formed a working group to agree the Data Collection Agreement (DCA) (6). The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of atezolizumab. It also detailed the eligibility criteria for patient access to atezolizumab through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for atezolizumab, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine).

As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Atezolizumab clinical treatment criteria

- patient has histologically or cytologically documented transitional cell carcinoma of the urothelial tract
- atient has disease that is either locally advanced (that is, TNM staging: T4b + any N, any T + N2-3) or metastatic (any T + any N + M1)
- patient has not received previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer
- patient has either:
    - not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy

or

    - if previously treated with platinum-based chemotherapy (as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy), has relapsed >12 months since completing the platinum-based chemotherapy
- patients meeting this criterion are eligible to be considered as treatment naïve for locally advanced or metastatic disease but must satisfy all other criteria
- patient has an ECOG performance status of 0 to 2
    - Note: treatment of patients with performance status 2 with atezolizumab should only proceed with caution as there is limited safety data on treatment of these patients with atezolizumab
- patient is ineligible for cisplatin based chemotherapy due to one or more of the following:
    - impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60mls/min)
    - hearing loss of 25dB as assessed by formal audiometry
    - NCI CTCAE peripheral neuropathy – grade 2 or worse

    - ECOG performance status of 2
- tumour expresses PD-L1 at a level of ≥5%, as defined by the presence of discernible PD-L1 staining of any intensity in tumour infiltrating immune cells covering ≥5% of tumour area occupied by tumour cells, associated intra-tumoural and contiguous peri-tumoural desmoplastic stroma
- patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody
- patient has no symptomatically active brain metastases or leptomeningeal metastases
- Atezolizumab is being given as monotherapy and will commence at a fixed dose of 1200 mg every 3 weeks or 1680mg every 4 weeks
- a formal medical review as to whether treatment with atezolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
- patient to be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner
- treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If 2 trusts apply for atezolizumab for the treatment of untreated metastatic urothelial cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If 2 trusts apply for atezolizumab for the treatment of untreated metastatic urothelial cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If 2 applications are submitted for atezolizumab for the treatment of untreated metastatic urothelial cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

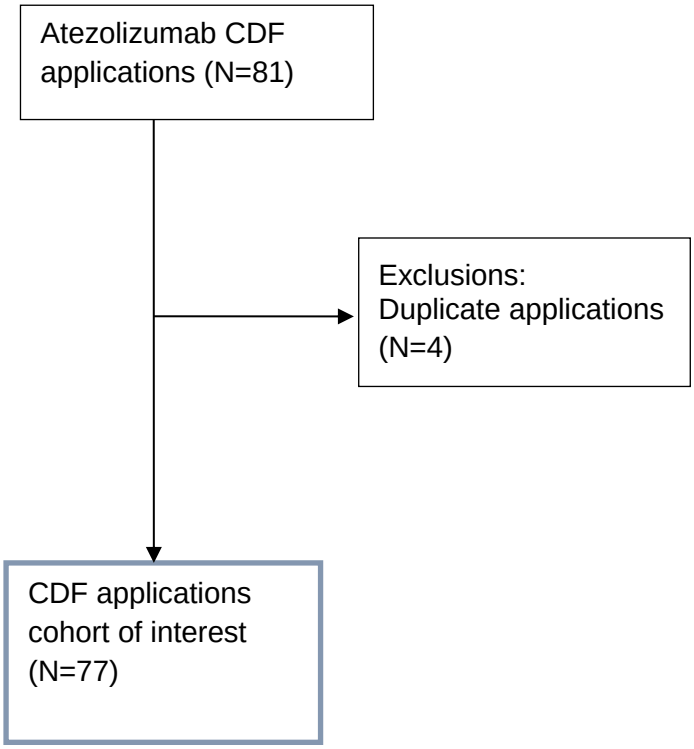
The analysis cohort is limited to the date atezolizumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different

eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 12 July 2018 and 11 August 2020. A snapshot of SACT data was taken on 5 December 2020 and made available for analysis on 11 December 2020 and includes SACT activity up to the 31 August 2020. Tracing the patients' vital status was carried out on 26 January 2021 using the personal demographics service (PDS) (1).

There were 81 applications for CDF funding for atezolizumab for the treatment of untreated metastatic urothelial cancer between 12 July 2018 and 11 August 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 77 unique patients.

Figure 1. Derivation of the cohort of interest from all CDF (Blueteq) applications made for atezolizumab for the treatment of untreated metastatic urothelial cancer between 12 July 2018 and 11 August 2020



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for atezolizumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items (8) used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)8 are used to identify a patient's final treatment date. The latest of these 3 dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example, a patient may be on a 3-weekly cycle with treatment being administered on the first and eighth day, but nothing on days 2 to 7 and days 9 to 20. The first day would be recorded as the 'start day of cycle'. The patient's next cycle would start on the twenty-first day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the twenty-first day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a ‘prescription length’, which is a set number of days added to the final treatment date to allow for the fact that they are effectively still ‘on treatment’ between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Atezolizumab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals are able to confirm that treatment administration has taken place on a specified date. A duration of 20-days or 27-days has been added to final treatment date for all patients; this represents the duration from a patient’s last cycle to their next (9) and will depend whether a patient receives a fixed dose of 1,200mg every 3 weeks or 1,680mg every 4 weeks.

Data item (8) used to determine the dose administered is:

- actual dose per administration – SACT data item #32

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days)

This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient’s treatment duration has been calculated, the patient’s treatment status is identified as one of the following:

No longer receiving treatment (event) if:

- the patient has died
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61
- there is no further SACT records for the patient following a 3-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

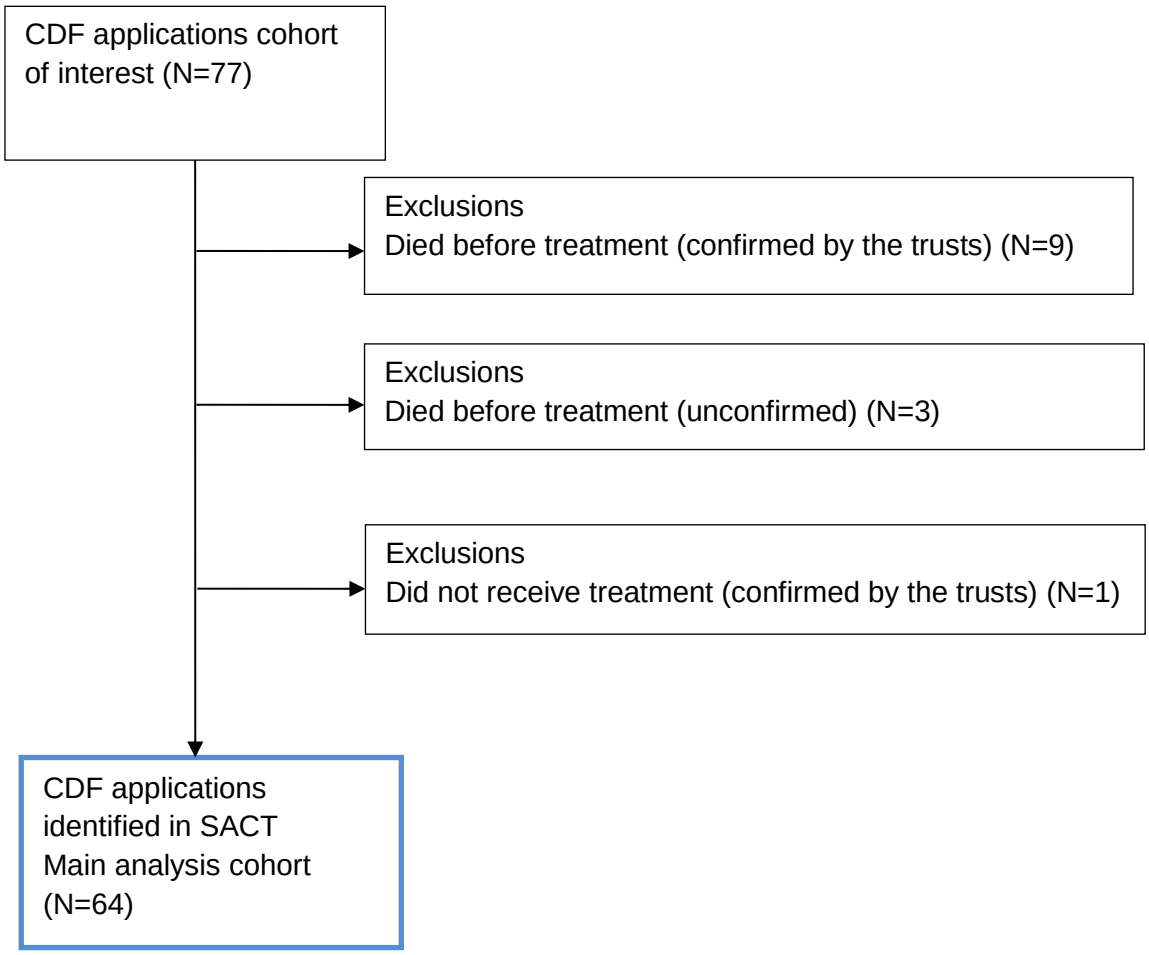
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 77 new applications for CDF funding for atezolizumab for the treatment of untreated metastatic urothelial cancer, one patient did not receive treatment and 12 patients died before treatment[1] (see Figure 2).

Figure 2. Matched cohort - SACT data to CDF (Blueteq®) applications for atezolizumab for the treatment of untreated metastatic urothelial cancer between 12 July 2018 and 11 August 2020



A maximum of 64 atezolizumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 100% (64/64) of these applicants for CDF funding have a treatment record in SACT.

[1] The one patient that did not receive treatment was confirmed by the relevant trust by the PHE data liaison team. Of the 12 that died before treatment, 9 have been confirmed by the relevant trusts by the PHE data liaison team, 3 patients were followed up by the data liaison team, but the relevant trust did not confirm if the patient died before treatment.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 84% complete.

Table 1. Completeness of key SACT data items for the atezolizumab cohort (N=64)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	84%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with atezolizumab in at least 3 months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 49. Of these, 34 (69%) have an outcome summary recorded in the SACT dataset.

Table 2. Completeness of outcome summary for patients that have ended treatment (N=49)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	69%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Reporting of tumour infiltrating immune cell PD-L1 expression is 100% complete (N=64).

Table 3. Tumour infiltrating immune cell PD-L1 expression (N=64)

Variable	Completeness (%)
PD-L1 expression	100%

Patient characteristics

The median age of the 64 patients receiving atezolizumab for urothelial cancer was 76 years. The median age in males and females was 76 and 78.5 years respectively.

Table 4. Patient characteristics (N=64)

Patient characteristics[2]			
		N	**%**
Sex	Male	50	78%
	Female	14	22%
Age	<40	0	0%
	40 to 49	0	0%
	50 to 59	1	2%
	60 to 69	15	23%
	70 to 79	27	42%
	80+	21	33%
Performance status	0	6	9%
	1	28	44%
	2	20	31%
	3	0	0%
	4	0	0%
	Missing	10	16%

[2] Figures may not sum to 100% due to rounding.

Blueteq data items

Tumour infiltrating immune cell PD-L1 expression distribution

The distribution of PD-L1 expression score in table 5 shows that 100% (N=64) of patients have a score ≥5%.

Table 5. Distribution of PD-L1 expression in Blueteq (N=64)

PD-L1 score	N	%
≥5	64	100%
Total	**64**	**100%**

Treatment duration

Of the 64 patients with CDF applications, 49 (77%) were identified as having completed treatment by 31 August 2020 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with atezolizumab in at least 3 months (see Table 9). The median follow-up time in SACT was 4.4 months (133 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal 2 months after the month's treatment activity has ended; this provides a maximum follow-up period of 25 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 26 months. SACT follow-up ends 31 August 2020.

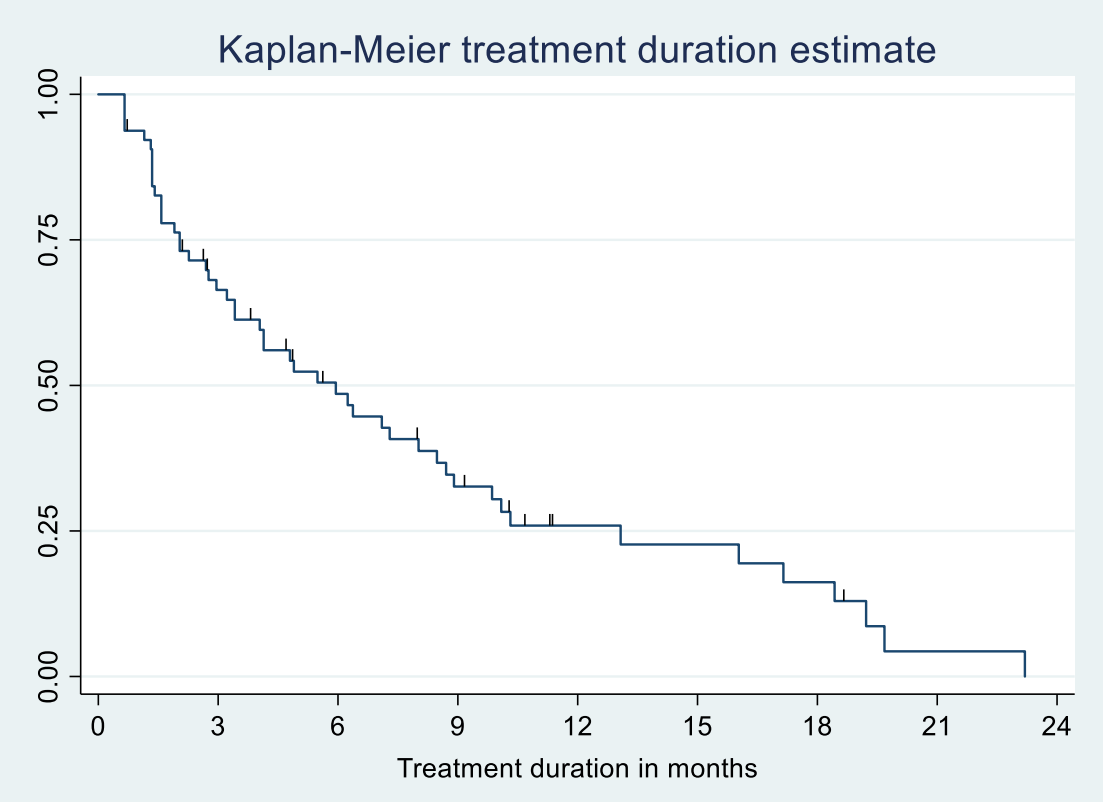
Table 6. Breakdown by patients' treatment status[3,4,5]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	33	52%
Patient died – on treatment	3	5%
Treatment stopped	13	20%
Treatment ongoing	15	23%
Total	**64**	**100%**

[3] Figures may not sum to 100% due to rounding.
[4] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[5] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 5.9 months [95% CI: 3.4, 8.5] (179 days) (N=64).
48% of patients were still receiving treatment at 6 months [95% CI: 35%,60%], 26% of patients were still receiving treatment at 12 months [95% CI: 15%, 38%].

Figure 3. Kaplan-Meier treatment duration (N=64)



Tables 7 and 8 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 25 months (760 days). SACT contains more follow-up for some patients.

Table 7. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Number at risk	64	39	25	16	8	7	5	1

Table 8 shows that for all patients who received treatment, 15 were still on treatment (censored) at the date of follow-up and 49 had ended treatment (events).

Table 8. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Censored	15	11	7	6	1	1	1	0
Events	49	28	18	10	7	6	4	1

Table 9 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 77% (N=49) of patients had ended treatment at 31 August 2020.

Table 9: Treatment outcomes for patients that have ended treatment (N=49)[6],[7]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	16	33%
Stopped treatment – acute toxicity	7	14%
Stopped treatment – patient choice	2	4%
Stopped treatment – died not on treatment[8]	16	33%
Stopped treatment – died on treatment	3	6%
Stopped treatment – no treatment in at least 3 months	5	10%
Total	**49**	**100%**

[6] Figures may not sum to 100% due to rounding.
[7] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[8] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 10: Treatment outcomes and treatment status for patients that have ended treatment (N=49)

Outcome[9]	Patient died [10] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	12	4	
Stopped treatment – acute toxicity	4	3	
Stopped treatment – patient choice	1	1	
Stopped treatment – died not on treatment	16		
Stopped treatment – died on treatment			3
Stopped treatment – no treatment in at least 3 months		5	
Total	**33**	**13**	**3**

Overall survival (OS)

Of the 64 patients with a treatment record in SACT, the minimum follow-up was 5.5 months (167 days) from the last CDF application. Patients were traced for their vital status on 26 January 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 9.6 months (292 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 26 January 2021. The median survival was 12.4 months [95% CI: 8.3, 20.1] (377 days) (N=64). Survival at 6 months was 70% [95% CI: 57%, 80%], 12 months survival was 54% [95% CI: 41%, 66%].

[9] Relates to outcomes submitted by the trust in table 9.
[10] Relates to treatment status in table 6 for those that have ended treatment.

Figure 4. Kaplan-Meier survival plot (N=64)

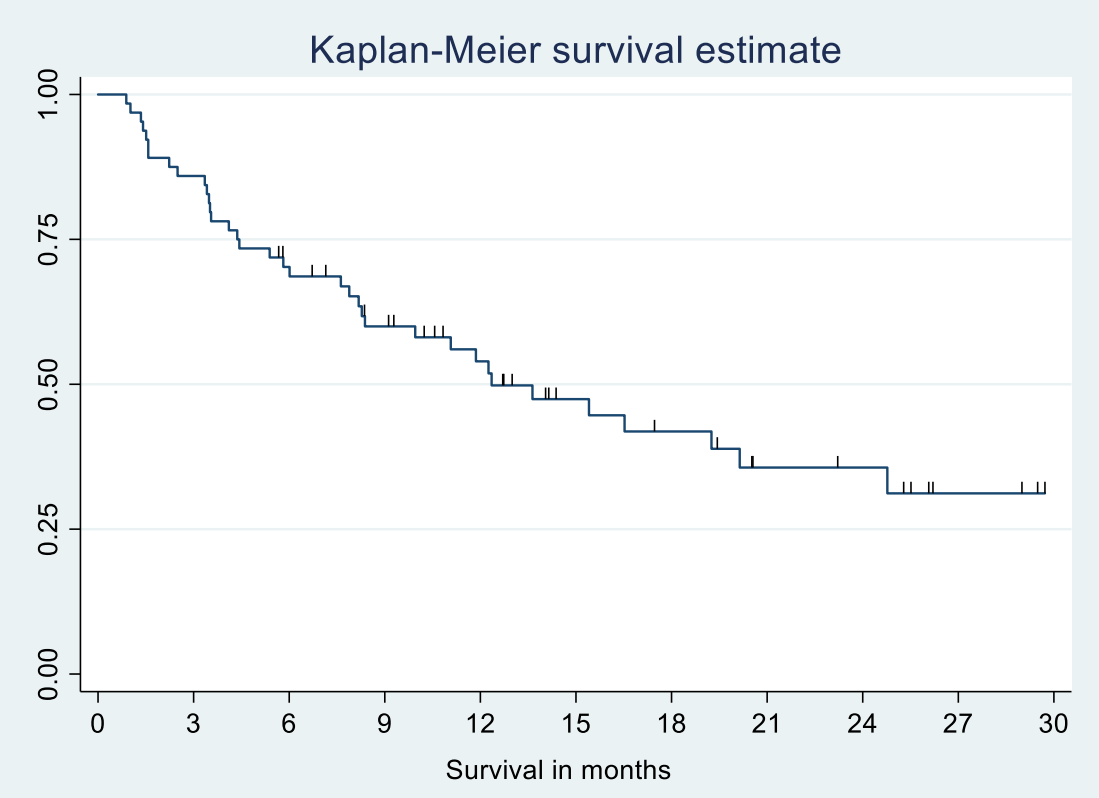


Table 11 and 12 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 30.5 months (928 days), all patients were traced on 26 January 2021.

Table 11. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Number at risk	64	55	43	34	26	17	14	9	8	3

Table 12 shows that for all patients who received treatment, 28 were still alive (censored) at the date of follow-up and 36 had died (events).

Table 12. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Censored	28	28	26	23	18	12	11	8	7	3
Events	36	27	17	11	8	5	3	1	1	0

Sensitivity analyses

Cohort 1: 6-month SACT follow up

Treatment duration

Sensitivity analyses was carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 12 July 2018 to 29 February 2020 and SACT activity was followed up to the 31 August 2020.

Following the exclusions above, 51 patients (80%) were included in these analyses. The median follow-up time in SACT was 5.5 months (167 days).

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 5.5 months [95% CI: 2.7, 8.5] (167 days) (N=51).

Figure 5. Kaplan-Meier treatment duration plot (N=51)

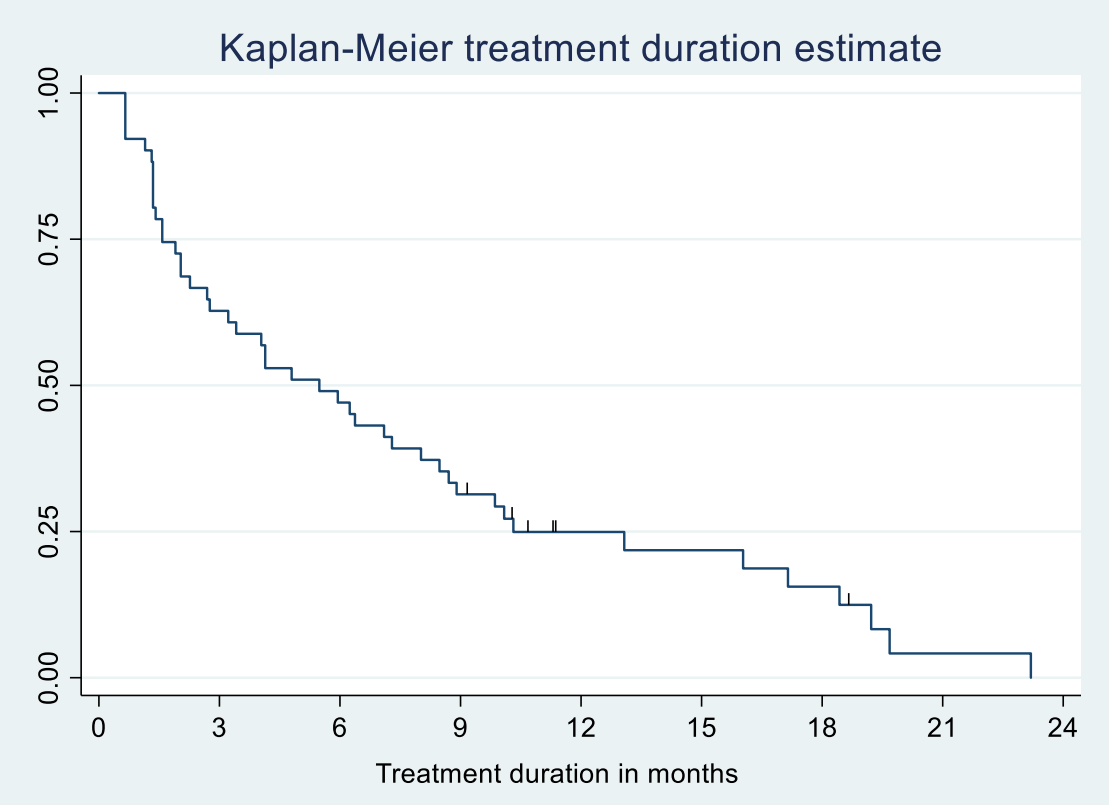


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 25 months (760 days).

Table 13. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Number at risk	51	32	24	16	8	7	5	1

Table 14 shows that for all patients who received treatment, 6 were still on treatment (censored) at the date of follow-up and 45 had ended treatment (events).

Table 14. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24
Censored	6	6	6	6	1	1	1	0
Events	45	26	18	10	7	6	4	1

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least 6 months follow-up in SACT. To identify the cohort, CDF applications were limited from 12 July 2018 to 26 July 2020.

Following the exclusions above, 62 patients (99%) were included in these analyses. The median follow-up time in SACT was 10 months (304 days).

Figure 6 provides the Kaplan-Meier curve for OS, censored at 26 January 2021. The median survival was 12.4 months [95% CI: 8.2, 20.1) (377 days) (N=62).

Figure 6. Kaplan-Meier survival plot (N=62)

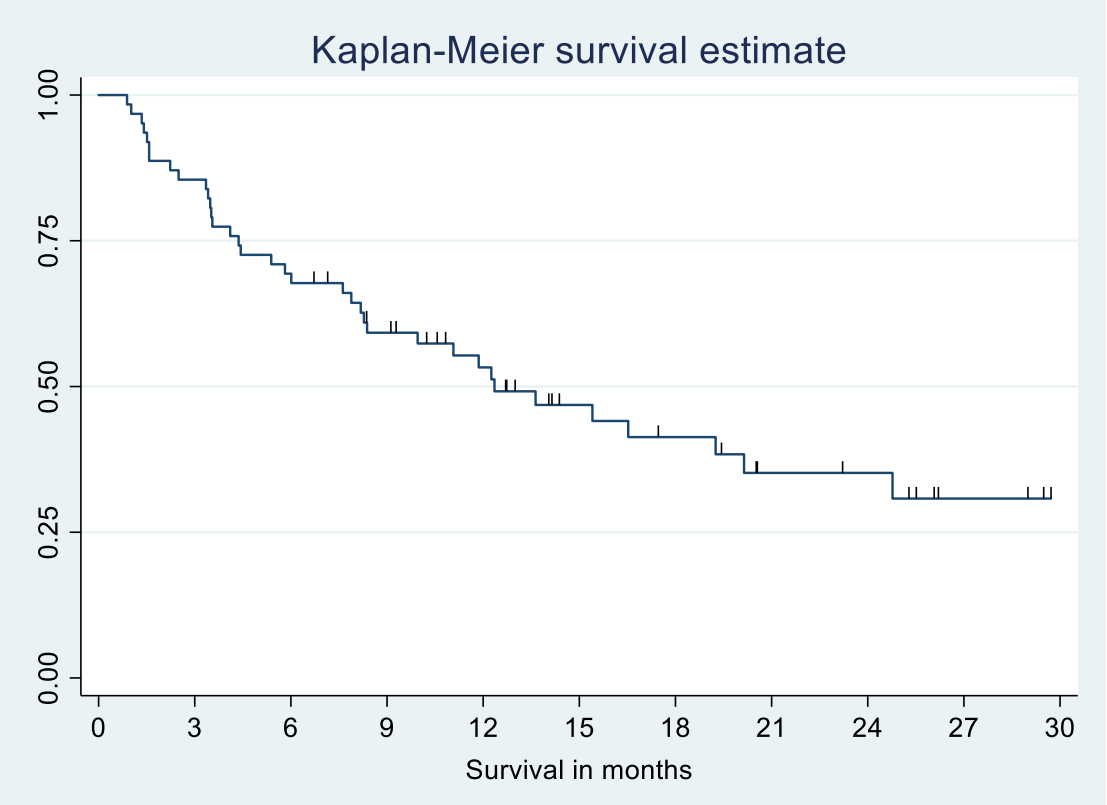


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 30.5 months (928 days), all patients were traced on 26 January 2021.

Table 15. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Number at risk	62	53	43	34	26	17	14	9	8	3

Table 16 shows that for all patients who received treatment, 26 were still alive (censored) at the date of follow-up and 36 had died (events).

Table 16. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30
Censored	26	26	26	23	18	12	11	8	7	3
Events	36	27	17	11	8	5	3	1	1	0

Table 17. Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	64	51	62
Median treatment duration	5.9 months [95% CI: 3.4, 8.5] (179 days)	5.5 months [95% CI: 2.7, 8.5] (167 days)	
OS[11]	12.4 months [95% CI: 8.3, 20.1] (377 days)		12.4 months [95% CI: 8.2, 20.1] (377 days)

[11] Confidence intervals could not be produced for OS as there was an insufficient number of events at the time this report was produced

Conclusions

Sixty-four patients received atezolizumab for the treatment of untreated metastatic urothelial cancer [TA492] through the CDF in the reporting period (12 July 2018 and 11 August 2020). All 64 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 100%. An additional one patient with a CDF application did not receive treatment and 12 patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 78% (N=50) of patients that received atezolizumab for the treatment of untreated metastatic urothelial cancer were male, 22% (N=14) of patients were female. Most of the cohort was aged 60 years and over (98%, N=63), and 84% (N=54) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 77% (N=49) of patients were identified as no longer being on treatment. Of these 49 patients, 33% (N=16) of patients stopped treatment due to disease progression, 14% (N=7) of patients stopped treatment due to acute toxicity, 4% (N=2) of patients chose to end their treatment, 33% (N=16) of patients died not on treatment, 6% (N=3) of patients died on treatment and 10% (N=5) of patients did not have a treatment record in SACT in at least 3 months and are assumed to have completed treatment.

Median treatment duration was 5.9 months [95% CI: 3.4, 8.5] (179 days). 48% [95% CI: 35%,60%] of patients were receiving treatment at 6 months and 26% [95% CI: 15%, 38%] of patients were receiving treatment at 12 months.

The median OS was 12.4 months [95% CI: 8.3, 20.1] (377 days). OS at 6 months was 70% [95% CI: 57%, 80%], OS at 12 months was 54% [95% CI: 41%, 66%].

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for treatment duration showed a difference of 0.4 months but this was not statistically significant (full cohort = 5.9 months; sensitivity analysis cohort = 5.5 months). The median OS was the same in both the full and sensitivity analysis, 12.4 months.

References

1. The Personal Demographics Service (PDS). NHS Digital: 2021 (cited 2021 Jan)
2. Office for National Statistics. Cancer Registration Statistics, England: 2017. 2020 (cited 2021 Jan)
3. National Institute for Health and Care Excellence: 2018 (cited 2021 Jan)
4. Cancer Drugs Fund. NHS England and NHS Improvement: 2017 (cited 2021 Jan)
5. Appraisal and funding of Cancer Drugs. NHS England and NHS Improvement: 2016 (cited 2021 Jan)
6. National Institute for Health and Care Excellence: 2018 (cited 2021 Jan)
7. Phase III clinical study (IMvigor 130) clinical trial: 2016 (cited 2021 Jan)
8. Systemic Anti-Cancer Therapy. SACT: 2019 (cited 2021 Jan)
9. CDF analytical methods. PHE: 2019 (cited 2021 Jan)

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SUSTAINABLE DEVELOPMENT GOALS

NICE National Institute for Health and Care Excellence

Technical engagement response form v2

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **14 July 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**--**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Clinical effectiveness issues		
Key issue 1 The IMvigor130 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.	**NO**	Roche acknowledges the uncertainty surrounding the small subgroup of the trial's total population. The small sample size is a by-product of the restricted European Medicines Agency (EMA) marketing authorisation after Cancer Drugs Fund (CDF) entry. It should also be noted that despite the small sample size, the confidence intervals on the hazard ratio (HR) do not cross 1. Roche believe the IMvigor130 trial, alongside the systemic anti-cancer therapy (SACT) data stet, provides robust enough evidence package to inform decision making for this appraisal.
Key issue 2: There were baseline differences between trial arms in terms of sex and racial characteristics, and it is unclear if these differences could have biased the treatment effects.	**NO**	Roche acknowledges some differences in the baseline characteristics between treatment arms in this subgroup of IMvigor130. Sex and racial characteristics may have bias in favour of atezolizumab. However, patients in the atezolizumab arm had a higher Bajorin risk factor (Bajorin risk factor of 2: 30% vs 14%). Further, a higher percentage of patients in the platinum-based chemotherapy arm had an Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 0 compared to atezolizumab (36% vs 47%). Therefore, there may also exist some bias in favour of platinum-based chemotherapy. Given the small sample sizes and opposing influences, it is not possible to determine the direction or magnitude of any potential bias on treatment effect.

Key issue 3: The overall survival estimates from the SACT dataset and the IMvigor130 trial differ substantially.	**NO**	Roche acknowledges the difference in survival between the SACT dataset and IMvigor130. As per the Terms of Engagement (Key Committee Assumptions, page 4) Roche were advised by the committee that the primary source of evidence to inform overall survival (OS) for this submission should be the IMvigor130 trial. Roche have used the SACT dataset for validation in the curve selection in the company submission, as per the committee's instructions in the Terms of Engagement (Key Committee Assumptions, page 4), in order to minimise any differences between the economic model and the SACT dataset. With regards to cost-effectiveness, Roche wish to highlight the evidence review group's (ERG's) exploratory analysis using the SACT dataset (ERG report, Section 6.1.1, page 50-51) which suggests the cost-effectiveness of atezolizumab is not sensitive to this issue. In the scenario using SACT data, atezolizumab is considered more cost-effective against platinum-based chemotherapy compared to the company and ERG base cases where IMvigor130 data is used.
Key issue 4: No comparison was made between atezolizumab and best supportive care in the company's base case.	**NO**	The ERG acknowledge the sparse available evidence for best supportive care (ERG Report, Section 3.1.3, page 30). In clarification question A6, an extreme upper bound scenario analysis was conducted in order to address this issue. During the Technical Engagement clarification call (6th July 2021) it was suggested by National Institute for Health and Care Excellence (NICE) that, given the absence of available suitable data, a lack of comparison to best supportive care was unlikely to be a considerable factor in decision making for the appraisal committee. Therefore, in order to prioritise other key issue statements and to be efficient with NICE, ERG, clinical expert and company resources, Roche will not include further analyses on best supportive care.

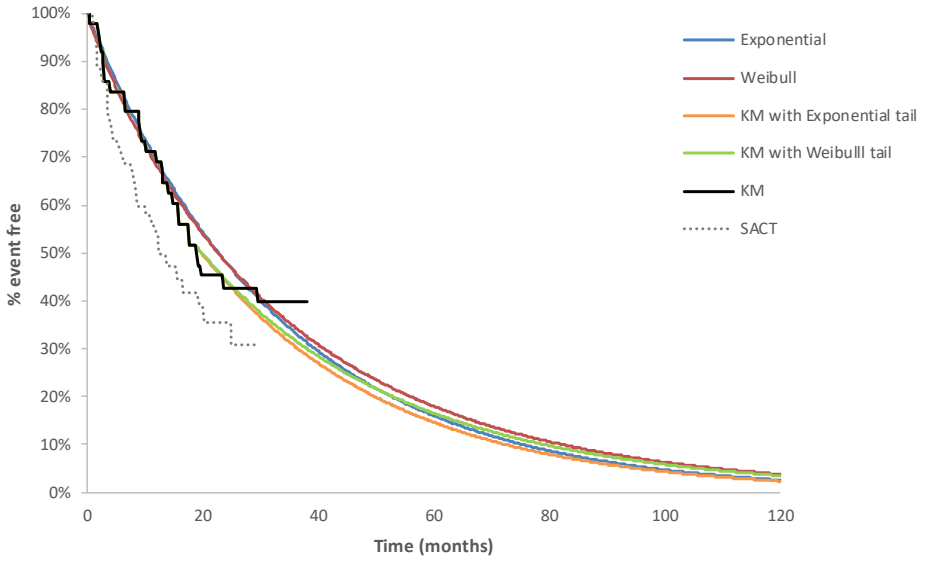
Cost effectiveness issues		
Key issue 5: The approach to modelling the long-term outcomes of overall survival, progression-free survival and time to treatment discontinuation.	**YES**	**OS** *Kaplan-Meier extrapolation* The ERG favours the use of a parametric function over the whole survival period rather than extrapolation from the end of the Kaplan-Meier data since there is uncertainty associated with the small sample size in the IMvigor130 subgroup used (ERG report, Section 4.1.1, page 33). Roche note that this uncertainty increases with time in the trial where there are a lower number of subjects at risk. In the original appraisal, the ERG suggested (and the Committee agreed - Committee Meeting, Section 3.9) that their preferred method for modelling OS was to use the Kaplan-Meier curve from the IMvigor210 clinical trial (n=119) until 20% (n=24) of patients were at risk. Roche suggest that in order to maintain consistency with the methodology used in the original appraisal and by going off the precedent set, using a Kaplan-Meier curve to model the early part of the curve until 24 (48%) patients are at risk in the atezolizumab arm is an acceptable approach. Roche has provided scenarios in Appendix A1-A6 with this updated methodology. *Exponential vs Weibull* The ERG note that the exponential and Weibull curves are both clinically plausible and very similar in terms of fit to observed data and long-term survival predictions (ERG report, Section 4.1.1, page 33). Roche does not consider the difference in Akaike information criterion (AIC) between the two curves to be meaningful for decision making. The shape parameter for the Weibull function is [redacted] for the atezolizumab arm and [redacted] for the platinum-based chemotherapy arm. This decreasing risk of mortality over time for immunotherapy could be considered clinically plausible and has been observed in other NICE appraisals. To use an exponential function and restrict both shape parameters to 1 may bias against

survival in the atezolizumab arm. Roche does not agree with the ERG's approach to select the exponential function on the basis of it being more conservative.

Updated company approach

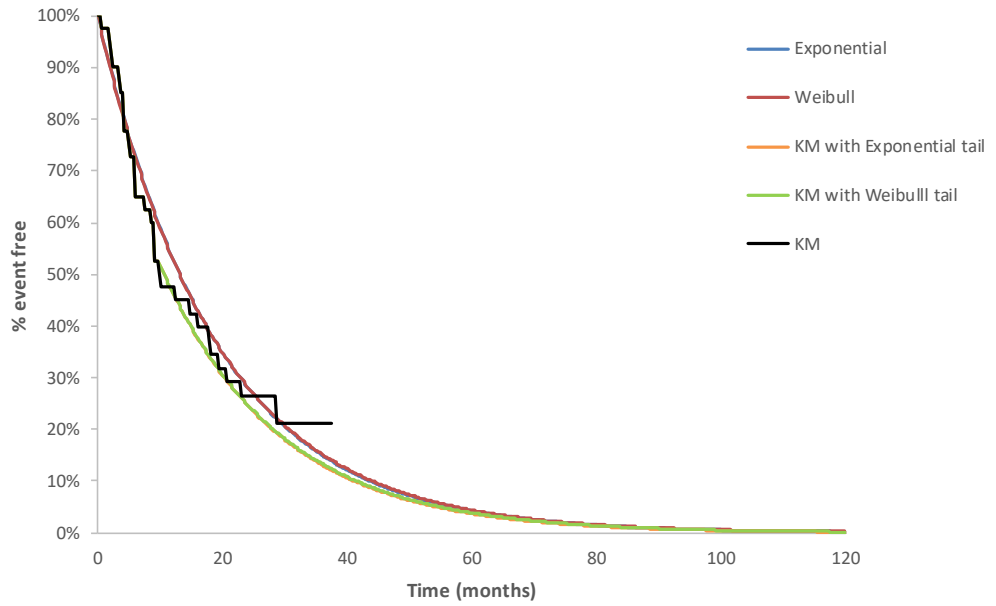
Roche believe that, as per the precedent set in the original appraisal, using a Kaplan-Meier + curve extrapolation is suitable. Further, Roche believe that using both the exponential and Weibull extrapolations are suitable. Roche have explored each of these four approaches to modelling OS in Appendix A1. Figure 1 and Figure 2 shows these approaches graphically. The results of the four approaches have been provided in Table 1 below for reference.

Figure 1 Approaches for modelling OS for atezolizumab



KM, Kaplan-Meier; OS, overall survival; SACT, Systemic-Anti-Cancer Therapy

Figure 2 Approaches for modelling OS for platinum-based chemotherapy



KM, Kaplan-Meier; OS, overall survival

Results are given with the updated application of utilities as per response to clarification question B6; Weibull curve to model progression-free survival (PFS) (as per key issue 5); subsequent treatment duration of atezolizumab of 7.9 months (as per key issue 7); Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model TTD (as per key issue 5); and updated company approach to estimating health state utilities (as per key issue 6).

Table 1 Scenarios for approaches to modelling OS

Approach	ICER (£/ QALY)
Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation	32,200

Kaplan-Meier curves (until 48% of patients are at risk) + Weibull extrapolation	30,970
Exponential extrapolation (ERG's preferred approach)	33,640
Weibull extrapolation	32,617

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life years

Roche believe that all four approaches are suitable for decision making to inform this appraisal. All four approaches:

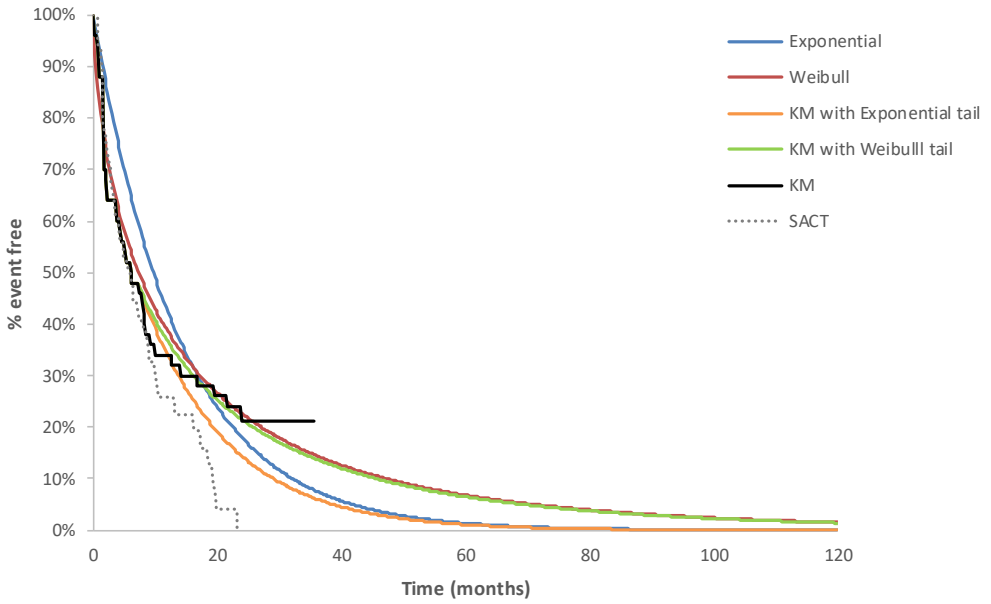
- Provide clinically plausible long-term OS in both treatment arms
- Are the most conservative choices to align closely with the SACT dataset in order to validate curve choice
- Provide a good fit to the observed data
- Do not use an unreasonably low number of patients at risk in the Kaplan-Meier curve to model an endpoint as per the precedent set in the original appraisal.

Roche feel that given all four approaches should be deemed acceptable, the full range of approaches should be considered to assess the cost-effectiveness of atezolizumab. The Weibull extrapolation has the advantage it doesn't force a constant hazard where there is some evidence of decreasing hazards in the atezolizumab arm. However, validation with SACT dataset should be seen as the most important priority in curve selection. Therefore, for the updated company base case analysis, Roche have selected the Kaplan-Meier curves + exponential extrapolation as this is the approach that most closely resembles the SACT dataset and is an approach with results falling towards the middle of the range of accepted approaches.

		PFS Roche have accepted the ERG's approach to modelling PFS and have updated the company base case to reflect this. **Time to treatment discontinuation (TTD)** The ERG suggested a Weibull curve as the recommended curve choice to model atezolizumab TTD. Roche disagree with this recommendation for two reasons: 1. Weibull curve to model atezolizumab TTD is above the range deemed clinically plausible by clinical experts Clinical experts suggested that after 5 years it was likely that 0-2% of patients were likely to still be on treatment with atezolizumab (vs. 7% predicted by the Weibull model). Clinical experts suggested that after 10 years no patients were likely to still be on treatment with atezolizumab (vs. 2% predicted by the Weibull model). Roche note that for OS, long-term clinical plausibility seemed to play a key role in decision making, being sure to use a curve selection in the range deemed clinically plausible by experts. This should also apply for curve selection for TTD. 2. Weibull curve to model atezolizumab TTD does not accurately reflect results from the SACT dataset. Roche note the lack of use of the SACT real world evidence dataset here to validate curve selection. In the SACT dataset, 0% of atezolizumab patients were still on treatment at 2 years (vs. 7% at 5 years and 2% at 10 years predicted by the Weibull model). Roche refer back to the Terms of Engagement "*The company should use updated time-on-treatment data from the IMvigor 130 trial and validate the generalisability of this assumption using the data collected within the SACT dataset*" (Terms of Engagement, Key Committee Assumptions, page 4).

		Roche believe that in recommending the Weibull curve, the ERG have failed to use the SACT dataset to validate curve selection and have therefore not taken the advice of the committee. For OS, Roche used the SACT dataset to validate curve choice in order to select the most conservative curve choice. Roche feel this approach was taken by the company and the ERG's recommendation to take a different approach does not align with the Terms of Engagement recommendations and does not follow NICE guidance on curve selection. *Alternative scenarios* Roche believe that the Weibull curve does not offer an acceptable generalisability to UK practice. Roche have explored the four most plausible curve choices for modelling TTD in Appendix A2: • Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation • Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation • Exponential extrapolation • Weibull extrapolation (ERG's preferred approach). Figure 3 shows these approaches graphically for atezolizumab. The results of the four approaches have been provided in Table 2 below for reference.

Figure 3 Approaches for modelling TTD for atezolizumab



KM, Kaplan-Meier; SACT, Systemic-Anti-Cancer Therapy; TTD, time to treatment discontinuation

Results are given with the updated application of utilities as per response to clarification question B6; Weibull curve to model PFS (as per key issue 5); subsequent treatment duration of atezolizumab of 7.9 months (as per key issue 7); Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model OS (as per key issue 5); and updated company approach to estimating health state utilities (as per key issue 6).

Table 2 Scenarios for approaches to modelling TTD

Approach	ICER (£/ QALY)
Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation	32,200

		<table><tr><td>Kaplan-Meier curves (until 48% of patients are at risk) + Weibull extrapolation</td><td>45,743</td></tr><tr><td>Exponential extrapolation</td><td>41,549</td></tr><tr><td>Weibull extrapolation (ERG's preferred approach)</td><td>48,942</td></tr></table> ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation *Updated company approach* The Weibull and the Kaplan-Meier curves with Weibull extrapolation both predict clinically implausible long-term TTD as per clinical expert opinion and over-predict TTD observed in the SACT dataset. The exponential curve displays a poor fit to the observed data and over-predicts survival in the first 18 months. Therefore the updated company base case will be the Kaplan-Meier curve + exponential extrapolation. This curve selection: • Provides clinically plausible long-term TTD for atezolizumab • Is the most conservative choice to align closely with the SACT dataset in order to validate curve choice • Provides a good fit to the observed data • Does not use an unreasonably low number of patients at risk in the Kaplan-Meier curve to model an endpoint as per the precedent set in the original appraisal.
Key issue 6: The utility values.	**YES**	The ERG Report (Section 1.3, page 9) summarises key issue 6: *"The ERG is unable to verify the utility values from the description and data submitted by the company. It is unclear to the ERG how the values used in the model have been obtained from the naïve patient-level values submitted in response to ERG clarification questions. We have concerns*

		about the progression-free utility value for platinum-based chemotherapy being lower than the pooled estimate for progressed disease which appears implausible." Roche sought to address the ERG's key issue regarding the lack of clarity over the company's approach estimating health state utilities by providing a more detailed response to the methodology used (Appendix A6). In order to estimate health state utility values for the current appraisal, Roche ran linear mixed-effects models on the patient level data in order to account for variables that may impact utility. Roche considered a variety of mixed-effects models. The current appraisal uses data from the treatment arm B vs. C comparison (atezolizumab monotherapy vs. platinum-based chemotherapy) cisplatin-ineligible, PD-L1-positive subgroup of IMvigor130. IMvigor130 also contained a treatment arm A vs. C comparison (atezolizumab + platinum-based chemotherapy vs. platinum-based chemotherapy) which was due to inform the evidence base of the now suspended NICE appraisal ID1206. Following the latest data cut for IMvigor130, evidence generation and the development of mixed-effects models to estimate health state utilities for the current appraisal and ID1206 were done in parallel. The mixed-effects model used in the original company submission includes time, treatment arm, progression status, gender and liver metastases as variables. At the outset of evidence generation for this appraisal, this model was selected as the approach to inform utilities in order to maintain consistency in methodology between the current appraisal and ID1206. Upon review of the methodology for estimation of these utilities as part of the technical engagement stage of this

current appraisal, this was decided to not be an appropriate justification for the selection of the model for utility estimation for this patient population.

An updated model is proposed by Roche which is seen as a more robust way to estimate health state utility values for the current appraisal. Health state utility values estimated by the updated mixed-effects model are presented in Table 3. The updated mixed-effects model includes only time, treatment arm and progression status as variables. These variables are critical variables to include. Off all mixed-effects models explored, the updated model has the lowest AIC of models that include time, treatment arm and progression status as variables. Roche have included the utilities estimated by the updated mixed-effects model in the updated company base case.

Table 3 Comparison of health state utility values from the original company submission with the updated company base case

Utilities provided in original company submission		
	Atezolizumab (95% CI)	**Platinum-based chemotherapy (95% CI)**
PF	0.642 (0.534, 0.750)	0.527 (0.404, 0.649)
PD	0.567 (0.481, 0.653)	
Utilities provided in updated company base case		
	Atezolizumab (95% CI)	**Platinum-based chemotherapy (95% CI)**
PF	0.648 (0.565, 0.732)	0.615 (0.532, 0.697)
PD	0.611 (0.537, 0.686)	

Adapted from Company Submission, Section 4.8.6, Table 11, page 28

CI, confidence intervals; PD, progressed disease; PF, progression-free

In the updated company base case, the PF health state utility value in the platinum-based chemotherapy arm (0.615) is higher than the pooled utilities in the PD health state (0.611). This was not the case for the utilities for the original company base case (0.527 vs. 0.567) which was identified as a key issue by the ERG. By providing additional information (Appendix A6) to detail the company's approach to estimating health state utility values and the updated values Roche believe they have addressed the ERG's concerns outlined in key issue 6.

Table 4 displays the impact on results of the updated company approach to estimating health state utilities compared to the health state utilities used in the original submission. Results are given with the updated application of utilities as per response to clarification question B6; Weibull curve to model PFS (as per key issue 5); subsequent treatment duration of atezolizumab of 7.9 months (as per key issue 7); Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model OS (as per key issue 5); and Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model TTD (as per key issue 5).

Table 4 Scenarios for approaches to estimating health state utility values

Approach	ICER (£/ QALY)
Company submission health state utility values (atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.527; pooled PD: 0.567)	30,236
Updated company approach to health state utility values (atezolizumab PF: 0.648; platinum-based chemotherapy PF: 0.615; pooled PD: 0.611; updated company base case)	32,200

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

		Updated company approach Roche believe the health state utilities put forward in Table 3 provide a suitable, robust and clinically plausible approach to estimating health state utility values for the current appraisal. Therefore, these health state utility values are used in the updated company base case.
Key issue 7: The approach to estimate the duration of subsequent treatments.	**NO**	Roche accepts the updated approach to estimation of subsequent treatment duration provided by the ERG. Roche have included this amendment in the updated company base case.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
--	--	--	--

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Company base case before technical engagement	Company base case in original submission after amendment made in clarification question B6.	--	£32,071
5: Extrapolation of PFS (as per ERG preferred assumption)	Kaplan-Meier curves + exponential extrapolation to model PFS	Weibull to model PFS	£29,822
7: Subsequent treatment duration of atezolizumab (as per ERG preferred assumption)	Subsequent treatment duration of atezolizumab in platinum-based chemotherapy arm: 10.7 months	Subsequent treatment duration of atezolizumab in platinum-based chemotherapy arm: 7.9 months	£32,500
5: Extrapolation of OS	Kaplan-Meier curves (until 20% of patients are at risk) + exponential extrapolation to model OS	Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation to model OS Roche feel that all four approaches to modelling OS outlined in Key Issue 5 of this response form are appropriate and the full range should be considered for decision making.	£34,757
5: Extrapolation of TTD	Kaplan-Meier curves (until 20% of patients are at risk) + exponential extrapolation to model TTD	Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation to model TTD	£30,236

6: Utilities	Company submission health state utility values (atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.527; pooled PD: 0.567)	Updated company approach to health state utility values (atezolizumab PF: 0.648; platinum-based chemotherapy PF: 0.615; pooled PD: 0.611; updated company base case)	£32,200
Company's preferred base case following technical engagement	Incremental quality-adjusted life years (QALYs): [redacted]	Incremental costs: [redacted]	£32,200

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA492

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) ID3777

Technicical Engagement Response: Appendix

July 2021

File name	Version	Contains confidential information	Date
ID3777_NICE_Atezolizumab_Technical_Engagement_Appendix_1LmUC_CIC	V2	Yes	15th July 2021

A.1 Key issue 5: Further OS scenarios

As per the technical engagement response form, Roche have suggest three further approaches to modelling OS to add to the ERG's preferred approach:

- Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation
- Kaplan-Meier curves (until 48% of patients are at risk) + Weibull extrapolation
- Exponential extrapolation (ERG's preferred approach)
- Weibull extrapolation

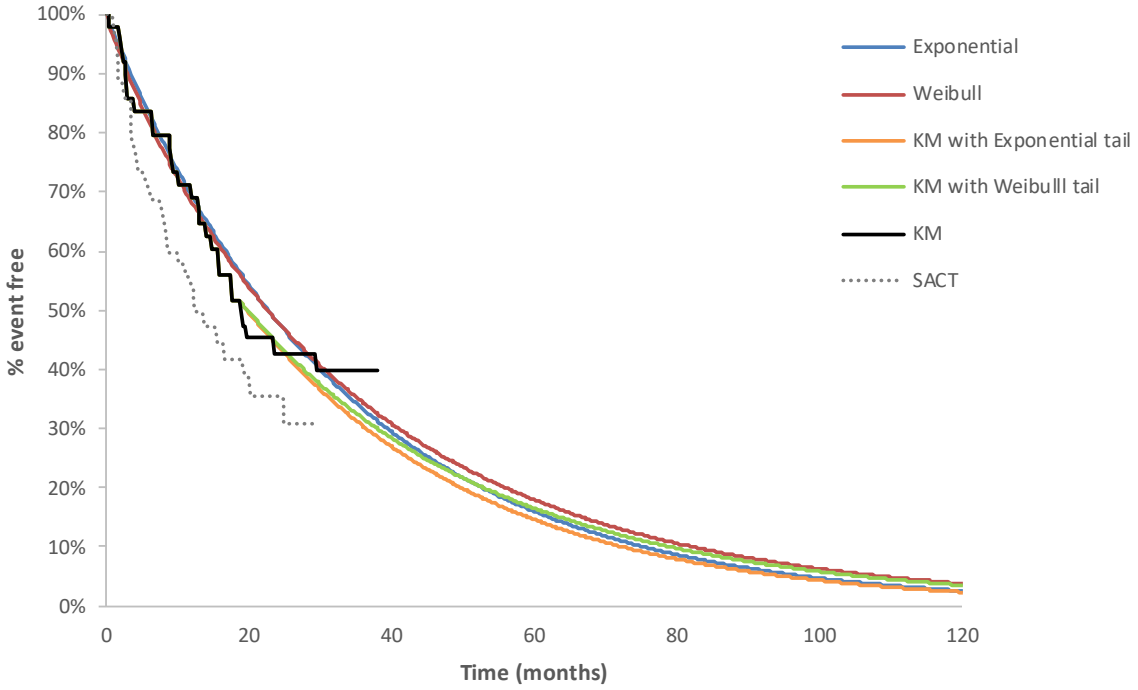
Table 1 compares trial, SACT and company expert opinion OS against the four different approaches to model OS. Figure 1 and Figure 2 show the modelling of the approaches graphically. Digitized versions of the SACT dataset have been added for reference.

Table 1 Comparison of trial OS KM with parametric curve extrapolation (company proposed approaches) and other sources at various time points

Treatment	Source	1 year	2 years	3 years	5 years	10 years	20 years
Atezolizumab	IMVigor130	69%	43%	40%	--	--	--
	SACT cohort study	~54%	~36%	--	--	--	--
	Company expert opinion	--	--	--	5-30%	1-20%	1-6%
	KM + exponential	69%	44%	31%	15%	2%	0%
	KM + Weibull	69%	44%	32%	17%	4%	0%
	Exponential	69%	48%	33%	16%	3%	0%
	Weibull	68%	48%	34%	18%	4%	0%
Platinum-based chemotherapy	IMVigor130	48%	27%	21%	--	--	--
	De Santis 2012(1)[a]	34%	17%	--	--	--	--
	Company expert opinion	--	--	--	1-5%	0-5%	0-5%
	KM + exponential	47%	25%	13%	4%	0%	0%
	KM + log-logistic	47%	25%	13%	4%	0%	0%
	Exponential	53%	28%	15%	4%	0%	0%
	Weibull	53%	28%	15%	4%	0%	0%

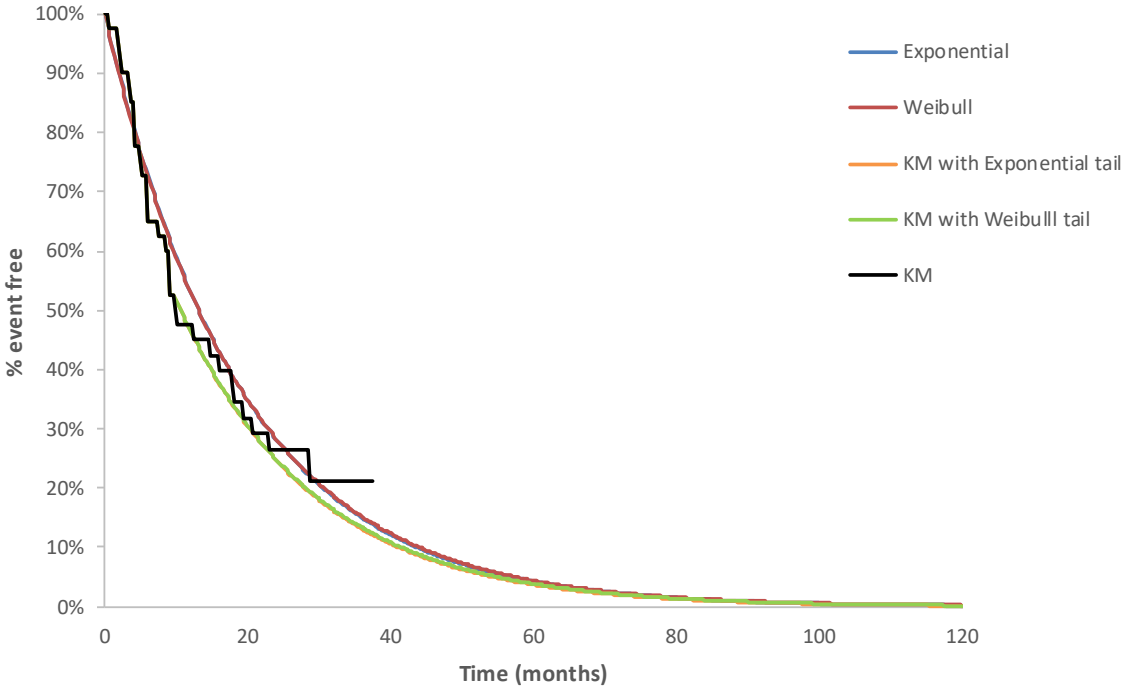
Adapted from ERG report, Section 4.1.1, Table 11, pages 33-34
KM extrapolations are given until 48% are at risk
[a] Not in a PD-L1-positive population
KM, Kaplan-Meier; OS, overall survival

Figure 1 Approaches for modelling OS for atezolizumab



KM, Kaplan-Meier; OS, overall survival; SACT, Systemic-Anti-Cancer Therapy

Figure 2 Approaches for modelling OS for platinum-based chemotherapy



KM, Kaplan-Meier; OS, overall survival

Table 2 investigates the impact of all four approaches to modelling OS on results. Scenarios have been run using assumptions from the company submission base

case with the following amendments from the company's submission base case as per the technical engagement process:

- Update of application of utilities as per response to clarification question B6
- Weibull curve to model PFS
- Subsequent treatment duration of atezolizumab of 7.9 months
- Updated company approach to estimating TTD (as per Appendix A.2)
- Updated company approach to estimating utilities (as per Appendix A.6).

Table 2 Scenarios for approaches to modelling OS

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation (updated company base case)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	32,200
Platinum-based chemotherapy	18,652	1.38	0.85	--	--	--	--	--
Kaplan-Meier curves (until 48% of patients are at risk) + Weibull extrapolation								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,411	30,970
Platinum-based chemotherapy	18,732	1.39	0.85	--	--	--	--	--
Exponential extrapolation (ERG's preferred approach)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,277	33,640
Platinum-based chemotherapy	18,382	1.50	0.92	--	--	--	--	--
Weibull extrapolation								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,505	32,617
Platinum-based chemotherapy	18,421	1.51	0.92	--	--	--	--	--

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; QALYs, quality-adjusted life years

Roche believe that all four approaches are suitable for decision making to inform this appraisal. All four approaches:

- Provide clinically plausible long-term OS in both treatment arms
- Are the most conservative choices to align closely with the SACT dataset in order to validate curve choice

- Provide a good fit to the observed data
- Do not use an unreasonably low number of patients at risk in the Kaplan-Meier curve to model an endpoint as per the precedent set in the original appraisal.

Roche feel that given all four approaches should be deemed acceptable, the full range of approaches should be considered to assess the cost-effectiveness of atezolizumab. The Weibull extrapolation has the advantage it doesn't force a constant hazard where there is some evidence of decreasing hazards in the atezolizumab arm. However, validation with SACT dataset should be seen as the most important priority in curve selection. Therefore, for the updated company base case analysis, Roche have selected the Kaplan-Meier curves + exponential extrapolation as this is the approach that most closely resembles the SACT dataset and is an approach with results falling towards the middle of the range of accepted approaches.

A.2 Key issue 5: Further TTD scenarios

As per the technical engagement response form, Roche have suggest three further approaches to modelling OS to add to the ERG's preferred approach:

- Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation
- Kaplan-Meier curves (until 48% of patients are at risk) + Weibull extrapolation
- Exponential extrapolation
- Weibull extrapolation (ERG's preferred approach).

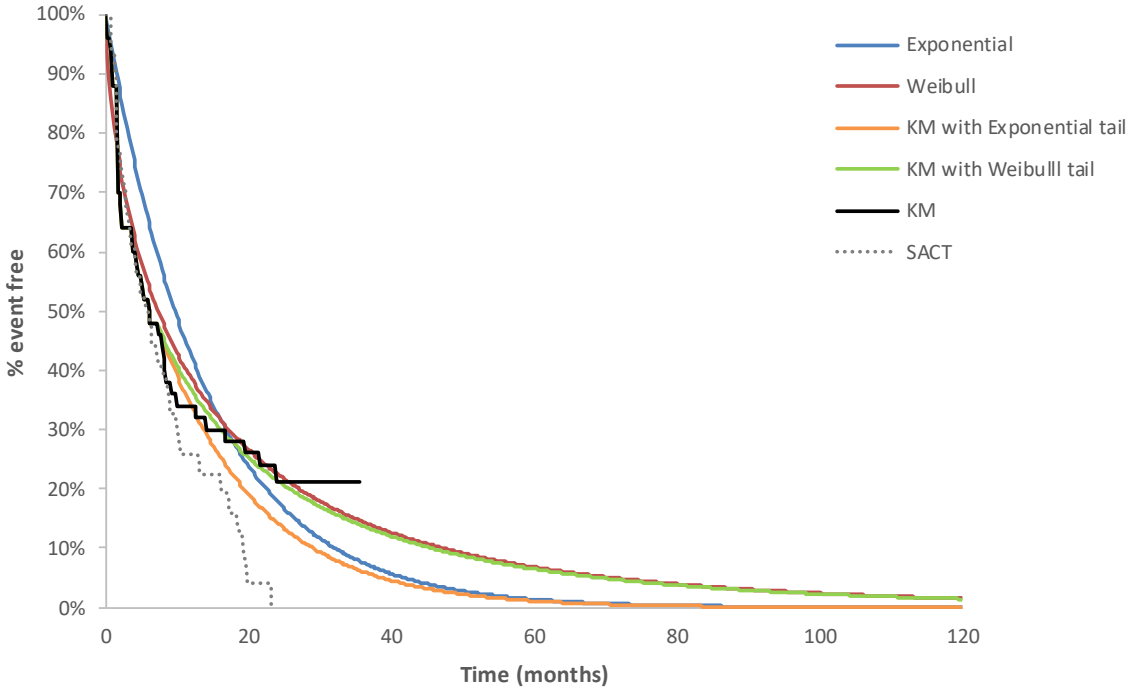
Table 3 compares trial, SACT and company expert opinion TTD for atezolizumab against the four different approaches to model TTD for atezolizumab. Figure 3 show the modelling of the approaches graphically. Digitized versions of the SACT dataset have been added for reference.

Table 3 Comparison of trial TTD KM with parametric curve extrapolation (company proposed approaches) and other sources at various time points

Treatment	Source	1 year	2 years	3 years	5 years	10 years	20 years
Atezolizumab	IMVigor130	34%	21%	--	--	--	--
	SACT cohort study	~26%	0%	--	--	--	--
	Company expert opinion	--	--	--	0-2%	0%	--
	KM + exponential	34%	14%	6%	1%	0%	0%
	KM + Weibull	37%	21%	14%	7%	1%	0%
	Exponential	42%	18%	8%	1%	0%	0%
	Weibull	39%	23%	15%	7%	2%	0%

Adapted from Company Submission Appendix, Appendix E.3, Table 39, page 87
KM extrapolations are given until 48% are at risk
KM, Kaplan-Meier; TTD, time to treatment discontinuation

Figure 3 Approaches for modelling TTD for atezolizumab



KM, Kaplan-Meier; SACT, Systemic-Anti-Cancer Therapy; TTD, time to treatment discontinuation

Table 4 investigates the impact of all four approaches to modelling TTD on results. Scenarios have been run using assumptions from the company submission base case with the following amendments from the company's submission base case as per the technical engagement process:

- Update of application of utilities as per response to clarification question B6
- Weibull curve to model PFS
- Subsequent treatment duration of atezolizumab of 7.9 months
- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model OS (updated company approach as per Appendix A.1)
- Updated company approach to estimating utilities (as per Appendix A.6).

Table 4 Scenarios for approaches to modelling TTD

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Kaplan-Meier curves (until 48% of patients are at risk) + exponential extrapolation (updated company base case)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	32,200
Platinum-based chemotherapy	18,652	1.38	0.85	--	--	--	--	--
Kaplan-Meier curves (until 48% of patients are at risk) + Weibull extrapolation								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,322	45,743
Platinum-based chemotherapy	18,566	1.38	0.85	--	--	--	--	--
Exponential extrapolation								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,542	41,549
Platinum-based chemotherapy	17,665	1.38	0.85	--	--	--	--	--
Weibull extrapolation (ERG's preferred approach)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,443	48,942
Platinum-based chemotherapy	17,927	1.38	0.85	--	--	--	--	--

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation

The Weibull and the Kaplan-Meier curves with Weibull extrapolation both predict clinically implausible long-term TTD as per clinical expert opinion and over-predict TTD observed in the SACT dataset. The exponential curve displays a poor fit to the observed data and over-predicts survival in the first 18 months. Therefore the updated company base case will be the Kaplan-Meier curve + exponential extrapolation. This curve selection:

- Provides clinically plausible long-term TTD for atezolizumab
- Is the most conservative choices to align closely with the SACT dataset in order to validate curve choice
- Provides a good fit to the observed data
- Does not use an unreasonably low number of patients at risk in the Kaplan-Meier curve to model an endpoint as per the precedent set in the original appraisal.

A.3 Key issue 5: Possible combinations of plausible OS and TTD curve choice scenarios

Appendix A.1 and Appendix A.2 each outline four possible approaches to modelling OS and TTD respectively. Table 5 outlines all possible ICERs of these 16 combinations. Scenarios have been run using assumptions from the company submission base case with the following amendments from the company's submission base case as per the technical engagement process:

- Update of application of utilities as per response to clarification question B6
- Weibull curve to model PFS
- Subsequent treatment duration of atezolizumab of 7.9 months
- Updated company approach to estimating utilities (as per Appendix A.6).

Table 5 ICERs for all possible combinations of approaches for modelling OS and TTD as outlined in Appendix A.1 and Appendix A.2

		OS (£)			
		KM + exponential	**KM + Weibull**	**Exponential**	**Weibull**
TTD (£)	**KM + exponential**	32,200	30,970	33,640	32,617
	KM + Weibull	45,793	43,766	47,101	45,535
	Exponential	41,549	39,674	42,878	41,364
	Weibull	48,942	46,762	50,270	48,551

ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; TTD, time to treatment discontinuation

Of the 16 most plausible approaches to modelling OS and TTD, only one ICER is above the £50,000 cost-effectiveness threshold associated with end-of-life treatments. The updated company base case ICER is £32,200. The ERG's preferred base case ICER is £50,270.

A.4 Key issue 6: Naïve health state utility scenario

The health state utility values used in the base case analysis (Company Submission, Section A.6.a, Table 9, page 19) were calculated using a mixed-effects model approach. Further details around this approach are provided in Appendix A.6 . Table 6 displays the “naïve” utility estimates which were not calculated using the mixed-effects model approach.

Table 6 Health state utility data from IMvigor130- naïve utilities

Treatment arm (n patient)	Health state	Mean utility	N. Obs
Pooled (91)	PF	0.807	1097
Pooled (45)	PD	0.735	177
Atezolizumab monotherapy (49)	PF	0.815	757
Atezolizumab monotherapy (21)	PD	0.755	112
Platinum-based chemotherapy (42)	PF	0.791	340
Platinum-based chemotherapy (24)	PD	0.702	65

CI, confidence intervals; PD, progressed disease; PF, progression-free; SD, standard deviation

Table 7 investigates the impact of naïve health state utility values on results compared to those used in the company submission base case and the updated company approach as per Appendix A.6 . The scenario has been run using assumptions from the company submission base case with the following amendments from the company’s submission base case as per the technical engagement process:

- Update of application of utilities as per response to clarification question B6
- Weibull curve to model PFS
- Subsequent treatment duration of atezolizumab of 7.9 months
- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model OS (updated company approach as per Appendix A.1)

- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model TTD (updated company approach as per Appendix A.2).

Results demonstrate that when using naïve health state utility values instead of the mixed-effects model approach, the ICER decreases. This scenario has been provided to demonstrate that the result of cost-effectiveness is not sensitive to the company's choice of a mixed-effects model (over naïve values) to estimate health state utility values. Roche maintains that the mixed-effects model approach is the preferred methodology for estimating utilities and continues to use the mixed-effects model in the company base case analysis. Roche's updated company base case is provided in Appendix A.6 .

Table 7 Scenario for nave utility estimates

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Company submission health state utility values (mixed-effects model approach; atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.527; pooled PD: 0.567)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	30,236
Platinum-based chemotherapy	18,652	1.38	0.76	--	--	--	--	--
Naïve health state utility values (atezolizumab PF: 0.815; platinum-based chemotherapy PF: 0.791; pooled PD: 0.735)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	26,321
Platinum-based chemotherapy	18,652	1.38	1.05	--	--	--	--	--
Updated company approach to health state utility values as per Appendix A.6 (mixed-effects model approach; atezolizumab PF: 0.648; platinum-based chemotherapy PF: 0.615; pooled PD: 0.611; updated company base case)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	32,200
Platinum-based chemotherapy	18,652	1.38	0.85	--	--	--	--	--

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PD: progressed disease, PF, progression-free; QALYs, quality-adjusted life years

A.5 Key issue 6: Alternative scenario for health state utility values

Note to reader: This section was originally provided as part of the original Appendix on 14th July 2021. However, with the updated information provided in Appendix A.6 , the scenario provided in this section is no longer relevant as the utilities in this scenario have been superseded by those provided in Appendix A.6 . Therefore, this section should no longer inform decision making for this appraisal. This section has remained included in this appendix for transparency.

The ERG have stated they do not consider it is plausible for the progression-free utility value for the platinum-based chemotherapy arm (0.527) to be lower than the value used for utility in progressed-disease (0.567). To address this issue, the ERG proposed the assumption to assume an increase in the in the platinum-based chemotherapy arm PF health state utility from 0.527 to 0.567 so that it aligns with the pooled PD health state utility value. An equally valid solution to this issue would be to assume a decrease in the pooled PD health state utility so that it aligns with the platinum-based chemotherapy arm PF health state utility from 0.567 to 0.527. It is logical to use the estimate that contains the highest number of observations (340 vs. 177).

The scenario has been run using assumptions from the company submission base case with the following amendments from the company's submission base case as per the technical engagement process:

- Update of application of utilities as per response to clarification question B6
- Weibull curve to model PFS
- Subsequent treatment duration of atezolizumab of 7.9 months
- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model OS (updated company approach as per Appendix A.1)
- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model TTD (updated company approach as per Appendix A.2).

Table 8 demonstrates the results for the alternative scenario compared to the company base case and the ERG preferred scenario.

Table 8 Scenario for alternative health state utility estimates

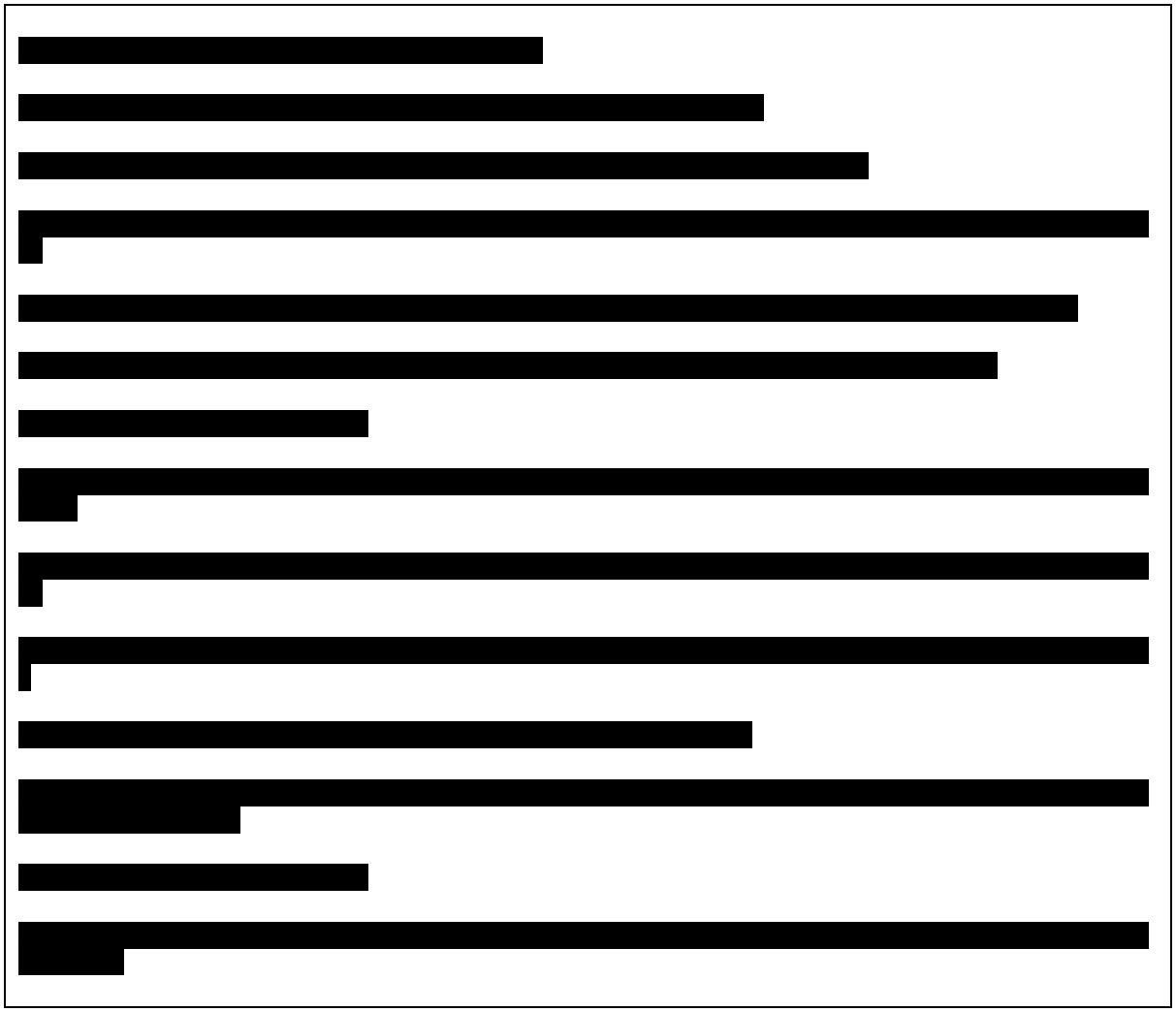
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Company submission health state utility values (atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.527; pooled PD: 0.567)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	30,236
Platinum-based chemotherapy	18,652	1.38	0.76	--	--	--	--	--
ERG health state utility values (atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.567; pooled PD: 0.567)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	31,545
Platinum-based chemotherapy	18,652	1.38	0.78	--	--	--	--	--
Alternative company scenario (atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.527; pooled PD: 0.527)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	30,707
Platinum-based chemotherapy	18,652	1.38	0.73	--	--	--	--	--

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PD: progressed disease, PF, progression-free; QALYs, quality-adjusted life years

A.6 Key issue 6: Further information on company approach to estimating utilities and updated company approach

In order to estimate health state utility values for the current appraisal, Roche ran a linear mixed-effects model on the patient level data in order to account for variables that may impact utility. Roche considered a variety of mixed-effects models. The R code of these mixed-effects models is presented in Equation 1. The variable *QSDY_M* is the time from randomization to the EQ-5D assessment in months. The variable *TRT01P* is the treatment arm variable, the variable *POSTPDFL* is the indicator variable (= 1 if the assessment is after progression, otherwise = 0). *USUBJID* is the subject identifier. Finally, *SEX*, *LIVERFL*, *BECOG* and *RACE* are respectively, gender, presence of liver metastases (yes vs no), ECOG at baseline and race (White vs. Asian).

Equation 1 R code used for mixed-effects models for estimating health state utility values

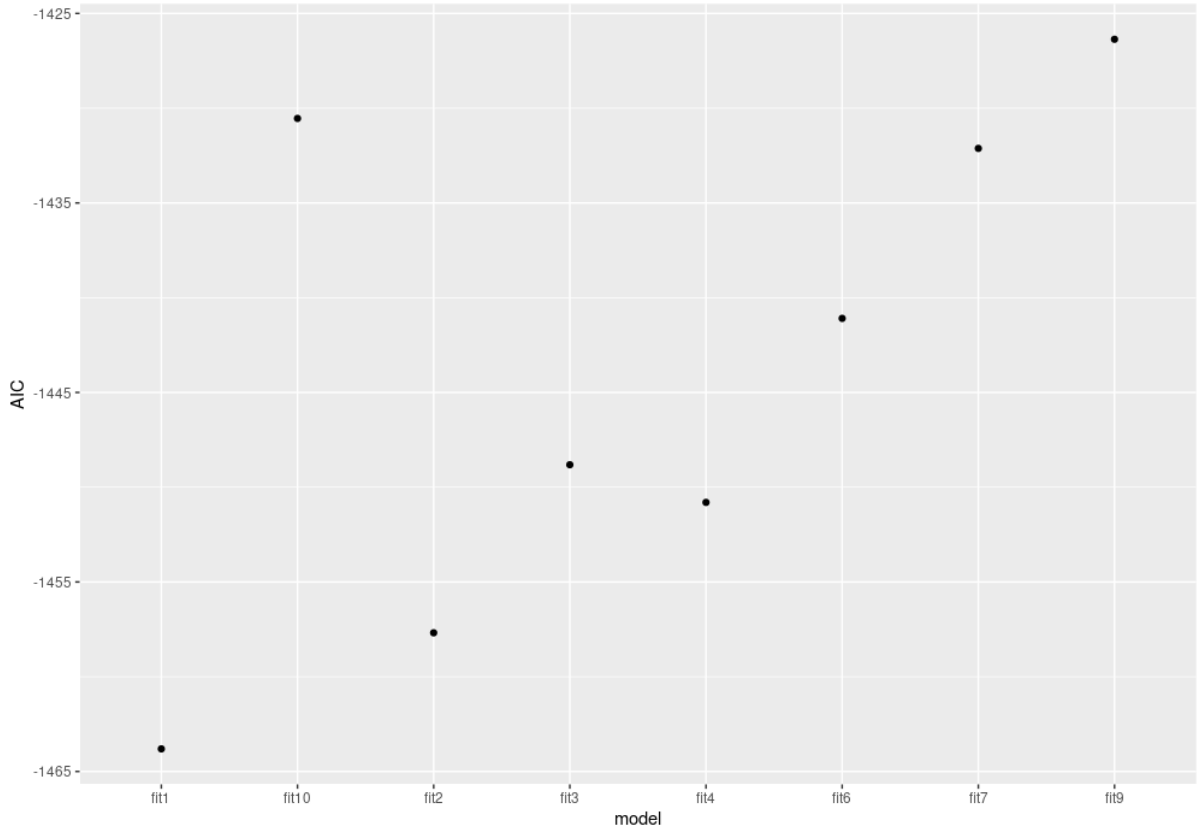


[redacted]

Note: Models fit5, fit8 and fit11 did not converge

Figure 4 provides the AIC for each of the mixed-effects models (that converged) in Equation 1.

Figure 4 AIC for mixed-effects models used to estimate health state utilities



AIC, Akaike information criterion

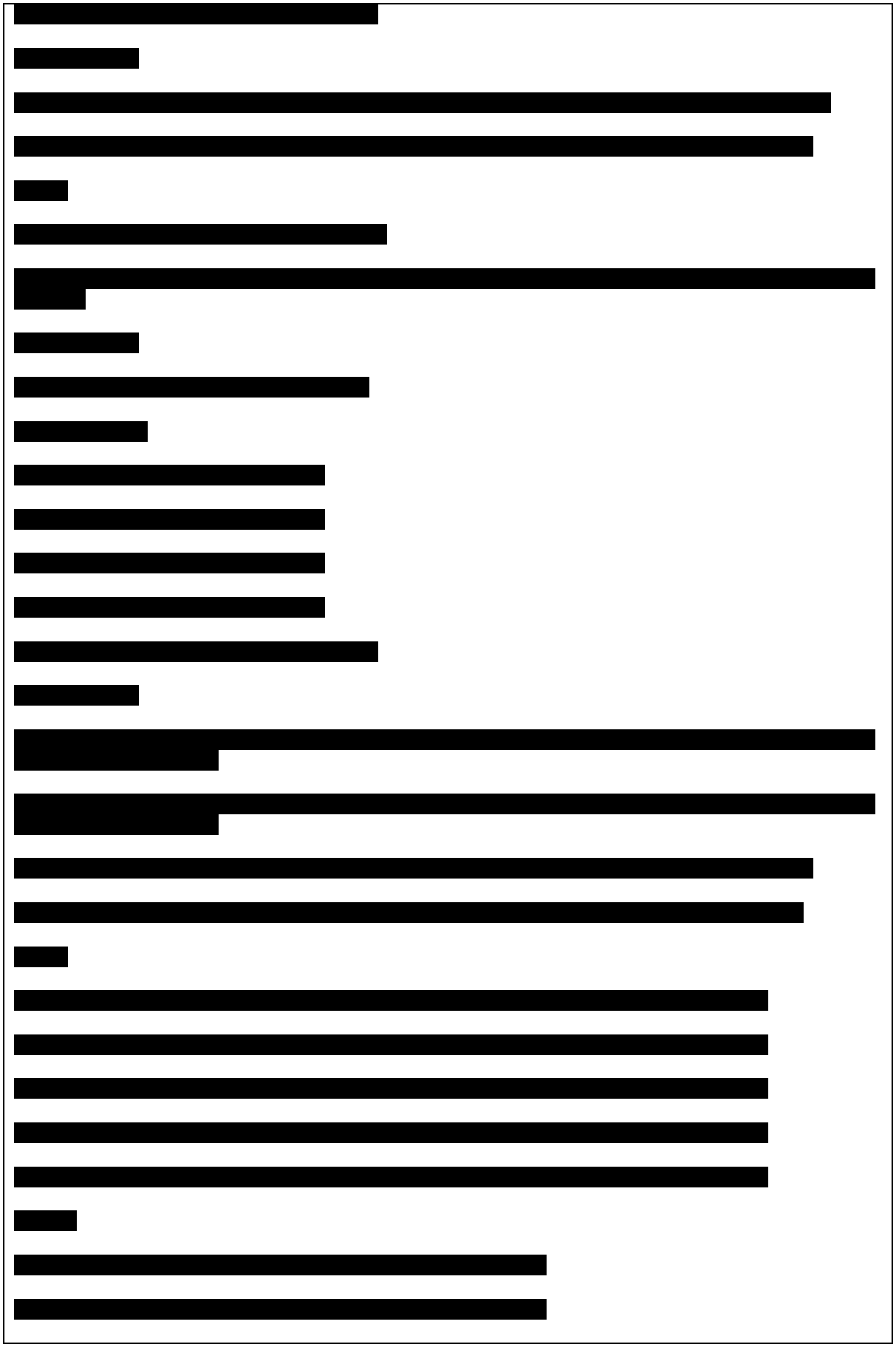
The current appraisal uses data from the treatment arm B vs. C comparison (atezolizumab monotherapy vs. platinum-based chemotherapy) cisplatin-ineligible, PD-L1-positive subgroup of IMvigor130. IMvigor130 also contained a treatment arm A vs. C comparison (atezolizumab + platinum-based chemotherapy vs. platinum-based chemotherapy) which was due to inform the evidence base of the now suspended NICE appraisal ID1206. Following the latest data cut for IMvigor130,

evidence generation and the development of mixed-effects models to estimate health state utilities for the current appraisal and ID1206 were done in parallel.

The model used in “fit7” was the model presented in the company submission. This model includes time, treatment arm, progression status, gender and liver metastases as variables. At the outset of evidence generation for this appraisal, this model was selected as the approach to inform utilities in order to maintain consistency in methodology between the current appraisal and ID1206. Upon review of the methodology for estimation of these utilities as part of the technical engagement stage of this current appraisal, this was decided to not be an appropriate justification for the selection of the model for utility estimation for this patient population.

A more appropriate model to use would be fit4. This model is reasonably simple and has a reasonably low AIC. Fit1 and fit2, although they have lower AIC than fit4, do not provide estimates of utility by both treatment arm and progression status. The inclusion of time, treatment arm, progression status variables were seen as critical to the estimation of utilities. Therefore, fit4 represents the model with the lowest AIC that includes all of these critical variables. Therefore, the model provided in fit4 is the most robust way to estimate health state utility values for the current submission and Roche have included these utilities in the updated company base case.

Equation 2 Results for fit4 and fit7 models for estimating health state utility values



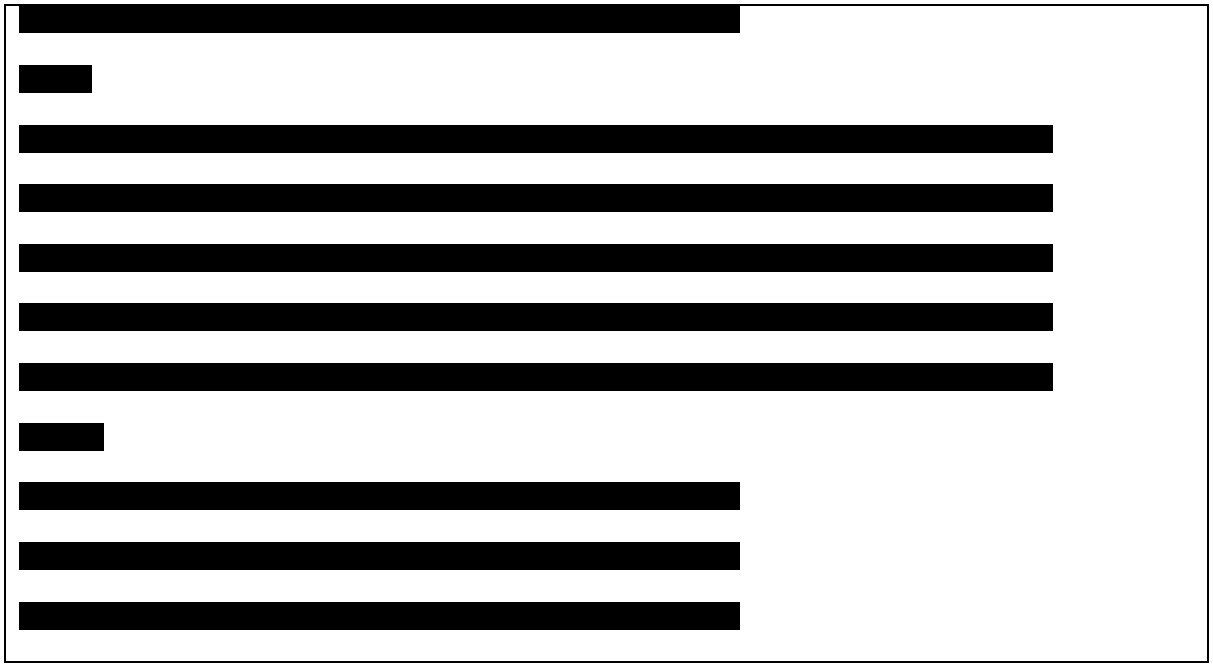


Table 9 compares the health state utility values from the original company submission (fit7) with the utility values from the updated company base case (fit4).

Table 9 Comparison of health state utility values from the original company submission (fit7) with the updated company base case (fit4)

Utilities provided in for original company submission (fit4)		
	Atezolizumab (95% CI)	**Platinum-based chemotherapy (95% CI)**
PF	0.642 (0.534, 0.750)	0.527 (0.404, 0.649)
PD	0.567 (0.481, 0.653)	
Utilities provided in updated company base case (fit7)		
	Atezolizumab (95% CI)	**Platinum-based chemotherapy (95% CI)**
PF	0.648 (0.565, 0.732)	0.615 (0.532, 0.697)
PD	0.611 (0.537, 0.686)	

Adapted from Company Submission, Section 4.8.6, Table 11, page 28

CI, confidence intervals; PD, progressed disease; PF, progression-free

The ERG Report (Section 1.3, page 9) summarises key issue 6:

> *"The ERG is unable to verify the utility values from the description and data submitted by the company. It is unclear to the ERG how the values used in the model have been obtained from the naïve patient-level values submitted in response to ERG clarification questions. We have concerns about the*

progression-free utility value for platinum-based chemotherapy being lower than the pooled estimate for progressed disease which appears implausible."

In the updated company base case (fit4), the PF health state utility value in the platinum-based chemotherapy arm (0.615) is higher than the pooled utilities in the PD health state (0.611). This was not the case for the utilities for the original company base case (fit7; 0.527 vs. 0.567) which was identified as a key issue by the ERG. By providing additional information in this appendix to detail the company's approach to estimating health state utility values and the updated values Roche believe they have addressed the ERG's concerns outlined in key issue 6.

Table 10 displays the impact of the updated company approach to estimating health state utilities (fit4) to the health state utilities used in the original submission (fit7). It should be noted there is an increase in the ICER. The scenario has been run using assumptions from the company submission base case with the following amendments from the company's submission base case as per the technical engagement process:

- Update of application of utilities as per response to clarification question B6
- Weibull curve to model PFS
- Subsequent treatment duration of atezolizumab of 7.9 months
- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model OS (updated company approach as per Appendix A.1)
- Kaplan-Meier curves (until 48% at risk) + exponential extrapolation to model TTD (updated company approach as per Appendix A.2).

Table 10 Impact of health state utility values from the original company submission (fit7) against the updated company base case (fit4) on ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Company submission health state utility values (fit7; atezolizumab PF: 0.642; platinum-based chemotherapy PF: 0.527; pooled PD: 0.567)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	30,236
Platinum-based chemotherapy	18,652	1.38	0.76	--	--	--	--	--
Updated company approach to health state utility values (fit4; atezolizumab PF: 0.648; platinum-based chemotherapy PF: 0.615; pooled PD: 0.611; updated company base case)								
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,344	32,200
Platinum-based chemotherapy	18,652	1.38	0.85	--	--	--	--	--

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PD: progressed disease, PF, progression-free; QALYs, quality-adjusted life years

All other scenarios throughout this appendix have included the updated health state utility values.

A.7 Updated eMIT drug prices

The company submission uses 2019 electronic market information tool (eMIT) prices for acquisition costs of generically available treatments.(2) As outlined on the Technical Engagement call (6th July 2021) by NICE, as of 11th March 2021, the 2020 version of eMIT prices are available.(3) Table 11 displays the difference between eMIT 2019 and 2020 prices. As eMIT prices are cheap and changes are not drastic, the impact of different eMIT pries years on overall results are negligible (<£50 impact on company submission ICER). For simplicity, eMIT 2019 prices have been used in the companies response to technical engagement.

Table 11 Comparison of eMIT 2019 and 2020 prices

Drug	Composition	Used in company base case or scenario analysis	eMIT 2019 (£, used in submission)	eMIT 2020 (£)
Gemcitabine	200mg	Base case and scenario	3.28	3.09
Carboplatin	50mg	Base case and scenario	3.75	3.37
Paclitaxel	30mg	Base case and scenario	4.69	4.41
Cisplatin	100mg	Scenario	6.66	8.73
Methotrexate	500mg	Scenario	8.70	5.94
Doxorubicin	200mg	Scenario	17.21	18.08

eMIT, electronic market information tool

A.8 Updated dosing

As a response to clarification question B1, the company provided an updated version of Table 14 (Company Submission, Section A.8.7, page 31). As part of the Technical Engagement call (6th July), NICE highlighted that there was an error with this response as the dosing in the response did not align with the economic model.

In IMvigor130, the dose for the carboplatin + gemcitabine is:

- Carboplatin will be administered at doses to achieve AUC of 4.5 mg/mL per min by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity
- Gemcitabine will be administered at a dose of 1000 mg/m^2 by IV infusion on Day 1 and Day 8 of each 21-day cycle, until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity

The dosing in the economic model is 2,000mg/m^2 which represents the dose per treatment cycle. Patients on this regimen incur two administration costs per cycle, one for carboplatin + gemcitabine on day 1 ('Subsequent treatments!AF45') and one for gemcitabine on day 8 ('Subsequent treatments!AF44').

The dosing reported for gemcitabine in the clarification response was '1,000mg/m^2 Q3W'. This has been amended to '1,000mg/m2 On Days 1 and 8 of every 21 day cycle'. This has been updated in Table 12 below. There is no impact on base case results.

Table 12 Subsequent treatment acquisition and administration costs (Updated relevant rows of Clarification Response, B1, Table 1, page 12)

Drug	Dose	List price cost (£)	Source	Unit (mg)	Admin. Cost (£)	Source
Carboplatin	400mg/m^2 Q3W	3.75	eMIT	50	199	NHS ref.
Gemcitabine	1,000mg/m^2 On Days 1 and 8 of every 21 day cycle	3.28	eMIT	200	199	NHS ref.
Gemcitabine hydrochloride	1,000mg/m^2 On Days 1 and 8 of	3.28	eMIT	200	199	NHS ref.

	every 21 day cycle					
Pembrolizumab	200mg Q3W	2,630.00	BNF	100	199	NHS ref.

BNF, British National Formulary; eMIT, electronic market information tool; NHS, National Health Service

References

1. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30(2):191-9.
2. Department of Health. Drugs and pharmaceutical electronic market information (eMit) 2020 [
3. Department of Health. Drugs and pharmaceutical electronic market information (eMit) 2021 [Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

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Clinical expert statement & technical engagement response form

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

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- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Selina Bhattarai**
2. Name of organisation	**Royal College of Pathologists**
3. Job title or position	**Consultant Histopathologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	☒ yes

submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression of disease and improve quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	NA

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, this is the only available option for patients with advanced metastatic Bladder Ca
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	NA, I am not a treating clinician to be able to answer this.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
12. Will the technology be used	Yes

(or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The use of Immunotherapy (Atezo) comes with an added cost which needs funding.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As a pathologist, I will comment on the technical investment and interpretation of the test itself. I am in a lab where the test has recently been validated. The training of technicians doing the test and pathologist who interpret the test. Both are time consuming with 4 hours to do the test and at least 30 min to interprete and provide the result. The laboratory's input needs to be recognised and funded. As these tests are few in numbers currently, a centralised service with several centres would be effective in providing a good turn around times for the test.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than	Yes

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	NA
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or	NA (see above)

monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	NA
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	NA
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	NA

• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	NA
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in	improved survival and quality of life, Yes though patient numbers were small.

the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	NA
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NA
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA492?	NA
23. How do data on real-world experience compare with the trial	comparable

data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	NA
24b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
25. In the original company submission the company identified 2 potentially relevant trials which included best supportive care (BSC). Could either of the populations in the trials be considered representative of the subgroup in this appraisal.	NA

1. NCT00315237: people with advanced transitional cell carcinoma of the urothelium (TCCU) who had experienced progression after a first-line platinum-containing regimen. 2. UMIN000003157: people with progressive bladder cancer after first-line platinum-based chemotherapy.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The IMvigor130 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.	As with any trial in the initial phase, the numbers are few but the results so far are good. We need more time and patients for a better analysis which we will have with time.
Key issue 2: There were baseline differences between trial arms in terms of sex and	It is possible but difficult to be certain.

racial characteristics, and it is unclear if these differences could have biased the treatment effects.	
Key issue 3: The overall survival estimates from the SACT dataset and the IMvigor130 trial differ substantially.	There is a difference with the IMvigor data showing a better OS and PFS but with fewer cases for a stronger statistical correlation. The true real world estimates may be somewhere between the two.
Key issue 4: No comparison was made between atezolizumab and best supportive care in the company's base case.	Going forward a system to evaluate BSC needs to be developed.
Key issue 5: The approach to modelling the long-term outcomes of overall survival, progression-free survival and time to treatment	NA

discontinuation.	
Key issue 6: The way in which the utility values were estimated and why the progression-free utility value for platinum-based chemotherapy is lower than the pooled estimate for progressed disease.	NA
Key issue 7: The approach to estimate the duration of subsequent treatments.	NA
Are there any important issues that have been missed in ERG report?	No, The ERG has done an excellent critical review of data provided.

PART 3 - Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- All published and trial data have shown an overall fair to good response to the treatment with Atezo
- Numbers less currently but will have better data with time.
- Need a more robust way of assessing BSC for comparison
- Funding for all arms of the technology from the laboratory assessment to therapy needs to be taken into consideration.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Syed A Hussain**
2. Name of organisation	**University of Sheffield (Nominated by Roche)**
3. Job title or position	**Professor of Medical Oncology and Honorary Consultant** Member NCRI-Bladder and Renal CSG Chair NCRI-Advanced Bladder cancer sub-group
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Patients with inoperable advanced urothelial cancer ineligible for cisplatin based chemotherapy remains an area of unmet need. The survival in this group of patients is disappointingly low with chemotherapy and is in the range of 8-9 months. With the use of Atezolizumab in this patient population group the survival is consistently in the range of 12-18 months. Imvigor 210 showed the survival to be 15.9 months, SACT data set showed it to be 12.5 months and the IMvigor 130 within a randomised setting among pdl+ cisplatin-ineligible patients (though within a small sample set of 50 patients on Atezlolizumab and 43 patients on chemotherapy) showed median survival of 18 months in Atezolizumab group versus 10 months in chemotherapy group. The above data within this group of patients shows the impact of atezolizumab on our patients within clinical trials and within the real world data.
9. What do you consider a clinically significant treatment	Treatment leading to improvement in survival that is clinically significant

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, this remains an area of unmet need. The impact from Atezolizumab is significant. The drug is generally well tolerated and quality of life data in previous studies comparing Atezolizumab versus chemotherapy favours the use of atezolizumab treatment.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	The drug is available on CDF currently and is used for cisplatin ineligible pdl+ patients. In some cases 3 weekly gemcitabine and carboplatin chemotherapy x 6 cycles is used
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are limited treatment options in this setting. The use of Immune check point inhibitors in cisplatin ineligible pdl+ patients is recommended.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	As above, In England some clinicians use Atezolizumab for pdl+ cisplatin ineligible patients in 1st line setting, while some clinicians may use gemcitabine plus carboplatin in younger patients with good performance status. Availability of Atezolizumab for this group of patients on CDF has led to improvement in outcome for this group of patients, even where more older patients were treated with a median age of 76 in the SACT data set, compared to a median age of 71 in IMvigor 130 dataset. Similarly there were more PS 2 patients in SACT dataset with 31% of patients with PS 2, compared to 16% PS2 patients in IMvigor 130 dataset. This will to some extent explain the difference in median overall survival of 12.5 months in SACT data set compared to 18.6 months in IMvigor 130 trial.

• What impact would the technology have on the current pathway of care?	Availability of Atezolizumab will be welcomed by clinicians and patients. This is an important drug for our patients. I have seen patients deriving clinically significant benefit from this treatment and hope this will continue to be the case in future.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	It is already in sue in current care through CDF
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be used in specialist clinics, where early identification and management of toxicity is important in getting maximum benefit for our patients.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This technology is already being used. Testing of PDL1 should be made available in more centres in improve the turnaround time of the pdl1 testing. Currently in urothelial cancer this is being done only in a limited number of sites. Increasing the number of sites geographically will help to improve the turnaround time and help initiate treatment for these patients without any delays in the pathway.
13. Do you expect the technology to provide clinically meaningful	Yes, this is already been seen and the data discussed above within this subset of patients clearly demonstrates that.

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes as above
• Do you expect the technology to increase health-related quality of life more than current care?	Yes as above
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As above
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	This is already in use routinely

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	PDL1 testing will be done for cisplatin in-eligible patient group. Treatment will be discontinued on disease progression or unacceptable toxicity.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This will result in long term improvement in disease control and survival in sub-set of patients as discussed in data
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	As above, this group of patients who are cisplatin in-eligible had poor median survival documented in clinical trials. This had not changed till the advent of immune check point inhibitors. The clinical trials data and the real world data are extremely encouraging and hopefully our patients will continue to benefit based on the data showing significant survival benefit and excellent tolerability.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	These drugs are now in routine clinical practice in different tumour sites including urothelial cancer. The toxicities are well managed by specialist hospitals in collaboration with other specialities. Industries have played an excellent role in proactively engaging with clinicians and hospitals around the country in providing educational opportunities and platforms, on line tools to asses, identify and treat toxicities without any delays.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, as above. A large number of patients within this group have been treated in UK and are represented in the data set.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Improvement in median survival
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N-A
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance TA492?	
23. How do data on real-world experience compare with the trial data?	The improvement in survival has been documented in the real world data as well. The survival is lower compared to that seen in trials but as described above, more patients with PS 2 and more older patients were part of the real world data.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	-
24b. Consider whether these issues are different from issues with current care and why.	-
Topic-specific questions	
25. In the original company submission the company identified 2 potentially relevant trials which included best supportive care (BSC). Could	Yes

either of the populations in the trials be considered representative of the subgroup in this appraisal. 1. NCT00315237: people with advanced transitional cell carcinoma of the urothelium (TCCU) who had experienced progression after a first-line platinum-containing regimen. 2. UMIN000003157: people with progressive bladder cancer after first-line platinum-based chemotherapy.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The IMvigor130 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.	I think they are the best available data for a small sub-set of patient groups that we see in our clinical practice. The improvement in survival is significant and hopefully this treatment will remain available for our patients.
Key issue 2: There were baseline differences between trial arms in terms of sex and	The numbers are small to derive any meaningful conclusions. We are still understanding the differences of these baseline characteristics and impact of immune check point inhibitors on clinical outcome and toxicities for different tumours. This remains an area of active research.

racial characteristics, and it is unclear if these differences could have biased the treatment effects.	
Key issue 3: The overall survival estimates from the SACT dataset and the IMvigor130 trial differ substantially.	As above, Availability of Atezolizumab for this group of patients on CDF has led to improvement in outcome for this group of patients, even where more older patients were treated with a median age of 76 in the SACT data set, compared to a median age of 71 in IMvigor 130 dataset. Similarly there were more PS 2 patients in SACT dataset with 31% of patients with PS 2, compared to 16% PS2 patients in IMvigor 130 dataset. This will to some extent explain the difference in median overall survival of 12.5 months in SACT data set compared to 18.6 months in IMvigor 130 trial. Of note here the median survival of 10 months in the chemotherapy in the comparator arm of IMvigor130.
Key issue 4: No comparison was made between atezolizumab and best supportive care in the company's base case.	-
Key issue 5: The approach to modelling the long-term outcomes of overall survival, progression-free survival and	-

time to treatment discontinuation.	
Key issue 6: The way in which the utility values were estimated and why the progression-free utility value for platinum-based chemotherapy is lower than the pooled estimate for progressed disease.	-
Key issue 7: The approach to estimate the duration of subsequent treatments.	-
Are there any important issues that have been missed in ERG report?	No

PART 3 - Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Clinical trial data shows significant survival benefit compared to chemotherapy within IMvigor130.
- Real world (SACT) data in patients with more unfavourable PS patients still achieved significantly better survival compared to chemotherapy data from the past.
- Overall median survival benefit seen in trials and real world data strongly support continued availability of this technology for our patients.
- Quality of life data in Immune -check point inhibitor studies strongly favour their use compared to chemotherapy.
- It is time bladder cancer is treated equally compared to other cancers like breast cancers. These exciting treatments should be made available in bladder cancer that has often been given a Cinderella status.

Professor Syed A Hussain, MBBS, MSc, MD, FRCP, Professor of Medical Oncology, University of Sheffield, & Sheffield Teaching Hospitals, Sheffield, South Yorkshire, United Kingdom.
Member: NCRI Bladder and renal group
Chair: NCRI Advanced Bladder cancer sub-group

Conflicts of interest:
Grants: CR UK, MRC/NIHR, Boehringer Ingelheim, Roche, Janssen- Cilag, Pierre Fabre.
Consulting fee: Pierre Fabre, Bayer, Janssen Oncology, Roche, Merck, Bristol-Myers Squibb, AstraZeneca, Pfizer, Astellas and GSK.
Support for attending meetings and/or travel: Janssen- Cilag, Bayer, Boehringer Ingelheim, Pierre Fabre, Pfizer, Roche, Bristol-Myers Squibb, AstraZeneca and MSD Oncology.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **14 July 2021.**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Allen Knight**
2. Are you (please tick all that apply):	☐ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Action Bladder Cancer UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: All ABC UK Trustees and staff work closely with patients, both directly and via our network of support groups. In addition, four of our trustees and many of our volunteers and fundraisers are patients or carers. It is absolutely fundamental to our work that we have a deep and current understanding of our patients, their hopes and fears and their treatment options, current and future. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	None personally, but through ABC UK I have met a survivor who responded well to this treatment and have referred knowledge of other patients. This is what patients tell us: Initial diagnosis is invariably a shock, not just because this is cancer, but because bladder cancer is so poorly known or understood. It can be difficult to talk about, as the impact can be so personal, not just with family and friends but also with clinicians. Although treatment for non-muscle invasive bladder cancer is relatively straightforward and effective, that for muscle invasive bladder cancer can be drastic, less effective, and can often recur. The particular condition for this consultation is the advanced case where platinum chemotherapy cannot be given and where survival rates are especially poor, typically measured in months.

	This group of patients has already gone through the mill. Bladder cancers are not well known or understood, so the initial diagnosis will have come as a particular shock to most patients. From often quite mild symptoms they will have already experienced a battery of tests, some of which are intrusive such as cystoscopies and/or TURBT. They will have experienced a roller coaster of emotions as they learn of the seriousness of their condition. Many experience pain and discomfort, and struggle to maintain control of their bladder function. They will know that there is no cure available, so the issue is solely how long they can remain healthy enough to enjoy what life they have left. Most patients in this group are older, in their sixties or seventies, many have other health issues. Their partners, carers and family members are often feeling pretty desperate, and both patients and their families can feel hopeless. It is not just the patient, but carers, partners and the family can all feel physically, emotionally and mentally battered.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a and b combined. Treatment of this specific condition would normally be with platinum based chemotherapy. However, due to the relatively advanced age and other illnesses present in so many patients with advanced bladder cancer, a significant number are unable or unwilling to take cisplatin. Currently, the only option is best supportive care, usually palliative, and so there is an urgent need for alternatives or improvements for this group of patients. Carers are forced to watch their love ones approach the end of life with increasing weakness, great discomfort and chronic pain. There is a great deal of physical, emotional and mental stress for both patients and their carers. **Without treatment, there is no hope.**
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how	Current NHS treatments include non platinum based chemotherapy and pain relief palliative care until end of life. This has the main disadvantage that it is not curative and therefore has all of the attendant emotional and mental stress. In addition, non

the treatment is given or taken, side effects of treatment etc) please describe these	platinum chemotherapy has severe side effects causing general sickness and increasing reliance on pain relief.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	a. Atezolizumab represents hope for many where other treatment options have been exhausted. The main benefits include: □ complete response in some cases □ prolonging life □ improved quality of life for patient, carers and family, as the drug is reasonably well tolerated as well as beneficial. ABC UK thinks a major potential benefit to both patients and those who care for them is the creation of real hope for the future where none currently exists, and has not existed for decades. b. All three advantages are equally important, however seeing a sustained and complete response in some is the ultimate goal. c. Yes, Atezolizumab overcomes some of the side effects of best supportive care (notwithstanding prolonging life or complete response) as it is better tolerated by most than non platinum based chemotherapy.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe	ABC UK is not aware of any disadvantages perceived by patients or carers. However, some may find regular attendance for treatment a challenge.

these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Currently about 5,000 patients die each year in the UK from metastatic bladder cancer. All of these could potentially benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any	None known. However, women tend to present later and therefore are more likely to have advanced disease.

groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Bladder cancer is not a rare cancer. It is the 4th most prevalent cancer in men and the 7th most prevalent overall. The five year survival rate for all stages and grades of bladder cancer is only 50%. This

	figure has not improved at all in well over 30 years. This compares very badly with any of the other ten most prevalent cancers. For instance, the five year survival statistics for breast cancer, prostate cancer and bowel cancer show that patients are two or three times more likely to survive the disease today than 30 years ago. Bladder Cancer recurs more than any other common cancer requiring long term surveillance and repeat treatments. This makes bladder cancer one of the most expensive cancers for the NHS to treat, per patient. Bladder cancer patients are among the highest of all cancer patients who present at A&E with advanced disease. And those in this group have a mean life expectancy measured in months rather than years, typically around 15 months. Despite these bleak statistics, bladder cancer receives less than 1% of the cancer research spend. In many other cancer settings, the expected impact of immunotherapy drugs may not be particularly significant at this stage of disease, compared with available alternatives. However, in the case of cancer patients with advanced disease as here, the outlook is very poor, the patient experience often dire and there are no available treatments. There is a huge unmet need for advanced bladder cancer patients, and atezolizumab offers the prospect of a step change improvement for many of the patients in this group.

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The IMvigor130 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.	No comment
Key issue 2: There were baseline differences between trial arms in terms of sex and racial characteristics, and it is unclear if these differences could have biased the treatment effects.	No comment
Key issue 3: The overall survival estimates from the SACT dataset and the	No comment

IMvigor130 trial differ substantially.	
Key issue 4: No comparison was made between atezolizumab and best supportive care in the company's base case.	The ERG acknowledge that best supportive care data is 'sparse, inconsistently defined and difficult to identify'. Given the 5 significant figures to which ICERs are calculated, it would seem churlish to make comparisons against such a soft baseline. Was this best supportive care subject to similar ERG scrutiny before it entered into NICE Guidance? If not, are we in danger of frustrating progress?
Key issue 5: The approach to modelling the long-term outcomes of overall survival, progression-free survival and time to treatment discontinuation.	In terms of modelling, the preferred ERG assumptions and extrapolation methods include: exponential for OS, and Weibull for PFS and TTD. The Executive Summary 1.3 bullet 1 says, 'based on visual fitting', yet Figures 1, 2 and 3 on pages 35, 37 and 38 all clearly show that the extrapolated data rapidly decay to zero in all cases. From the lay perspective, these ERG curves do not visually fit the data at all well. Although no raw data is shown in these graphs, ABC UK understands that the patient response is for a proportion of patients (around 20%) to show lasting and sustained OS, PFS and QoL. The mechanism of action of Atezolizumab is to induce this total response in a significant proportion of patients, and not in others, for reasons that are not yet fully understood. Our concern is that the simple mathematical curve fit models used do not account for the known behaviour of the treatment and thereby show a much poorer response over time than can be expected. This has the effect of prejudicially inflating the ICER and rendering the treatment less competitive and less likely to attract NICE approval.
Key issue 6: The way in which the utility values were estimated and why the progression-free utility value for platinum-based	No comment

chemotherapy is lower than the pooled estimate for progressed disease.	
Key issue 7: The approach to estimate the duration of subsequent treatments.	No comment
14. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

15. In up to 5 sentences, please summarise the key messages of your statement:

- There has been little or no improvements in care for these patients in over 30 years, and they are left with 'best supportive care'.
- Patients, on average, have only a few months to live, and the last months of life are particularly harrowing for both them and their carers.
- This treatment has been shown to have a positive effect, and in some cases a dramatic effect, on life expectancy, and is relatively well tolerated.
- Atezolizumab gives hope to many for whom other treatment options have been exhausted, and for whom there is no alternative.

- ABC UK strongly supports the licensing and use of the treatment within the NHS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

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- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Lydia Makaroff**
2. Are you (please tick all that apply):	☐ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Fight Bladder Cancer
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I have collated patient and carer experiences of advanced bladder cancer and atezolizumab ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	What is it like to live with the condition? Advanced urothelial cancer has a very poor prognosis. At this point in the pathway there is currently limited choice on treatments. Most current treatments are also very invasive, have significant side effects and often have quite serious side effects that significantly reduce the quality of life for the final months. It is a constant battle to delay the further growth and spread of the cancer. The condition is physically and emotionally tough with a regime of chemotherapy, a known low survival rate, and the understanding that the battle is to "prolong life" rather than resulting in a cure. Patients report that this condition has a substantial impact on their ability to work, ability to travel, and ability to exercise. "It's like a gun to my head every single minute of the day and night"

	"Everything I do is tinged with a sadness and a sorrow of "will this be the last time I do this?"." "It's totally all consuming" What do carers experience when caring for someone with the condition? For carers, the pressure is on them, from day one, to help support and care for their loved ones. Carers report that it has a substantial impact on their ability to work, ability to travel ,and ability to spend time with family and friends. "Caring for her means constant worry and constant vigilance. I wish we could go back to the time before 2020 when we were free of all this and could enjoy life. I have nothing to look forward to but the eventual end of her life, and then having to go on after she has left me behind."
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	For advanced/metastatic urothelial cancer, prognosis is very poor with very limited treatments being available. In addition to the chemotherapy treatments, the patients are likely to need other treatments such as radiotherapy to the part of the body where the cancer has spread, surgery to remove the cancer, surgery to unblock the ureters or urethra, and drugs to strengthen the bones. "There's a lack of understanding of bladder cancer by medical staff. Our dad's bladder cancer has taken over our whole life - even when we pretend things are normal, the next scan, the next treatment, fear of the future never goes away. The physiological impact on patients and their families is truly underestimated. Supporting my dad leaves me little time or energy for much else!" "Nearly 7 years with advanced bladder cancer, 40+ operations, 3 rounds of

	chemotherapy, radiotherapy minus a kidney and the one remaining will have to go too. Life is different, I'm different, but I'm still here. I would not be if it wasn't for the NHS, good or bad, and I've had both experiences. They have saved my life many times and I will be forever grateful"
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Urothelial cancer has come near the bottom of the annual NHS cancer patient experience survey since its launch. The new technology offers a ray of hope for a step change in treatment for this much ignored cancer. The high risk of recurrence and progression has led to this cancer seeing one of the highest associated suicide rates for cancer patients due to the emotional strains of the treatment and quality of life issues. Over the past 20 years in England and Wales, there has only been two innovative treatments funded for bladder cancer. Earlier this year pembrolizumab was removed from the Cancer Drugs Fund [ID1536], and atezolizumab is under threat of the same fate [ID3777]. There is also a chance that NICE will not recommend avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]. The existing treatments for urothelial cancer have limited effectiveness which results in the poor prognosis for those with advanced/metastatic cancer. There is a substantial unmet need for treatment options that can meaningfully improve survival and quality of life in patients with advanced bladder cancer following chemotherapy. "I would love a wonder pill, even if it could just get rid of the fatigue that comes with the procedures and stress" "Every ache or twinge makes me feel uneasy. It really does suck, especially with Covid-19 all over the place. My life consists of the internet, writing, and TV."

Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	We spoke with patients who had experienced atezolizumab. "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." "My cancer started in the bladder and then spread to the prostate and then 4 months later had spread to the base of my spine and in the bones, so therefore inoperable and incurable. Speaking personally, in my opinion it's given me extended life. I call the drug my life saver, as I honestly believe that's what it is. I can't praise this drug enough. I know immunotherapy doesn't work for everyone and I had to wait 3 months to see if my body accepted it, or not. In my case I've been extremely lucky, as back in 2017 I was given about 10 months to live." "I've been on it now for 20 months. I've another 4 months. It's been great for me."
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential	Patients report minimal side effects, but note that while the treatment is life-extending for many, it is not a cure. Out of the patients we spoke with, 3/4 stated that they responded well to the treatment, while 1/4 stated that the drug did not work for them. "I had Tecentriq infusions for metastatic bladder cancer and it did not work. A good surgeon and a sharp knife was my cure." "The only side effect I experienced was profuse perspiration."

side affects you have heard about, please describe them and explain why.	"Some fatigue and tinnitus and that's it."
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	NICE should examine the evidence to see if it still supports the assertion that PD-L1 should be used as a biomarker to identify a population that is more likely to respond to atezolizumab, or whether it is merely a prognostic marker that is associated with higher survival rates overall. NICE should examine the evidence to see if atezolizumab is also cost-effective for all types of untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable, regardless of PD-L1 status
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	Women with bladder cancer have worse outcomes compared to men. Women tend to present with advanced stage, experience differences in quality-of-life following treatment and suffer worse cancer-specific mortality (Hart ST, Woods ME, Quek ML. Gender disparities in bladder cancer management. Urology Times, February 20, 2019, Volume: 47, Issue: 2)

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The IMvigor130 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.	
Key issue 2: There were baseline differences between trial arms in terms of sex and racial characteristics, and it is unclear if these differences	

could have biased the treatment effects.	
Key issue 3: The overall survival estimates from the SACT dataset and the IMvigor130 trial differ substantially.	
Key issue 4: No comparison was made between atezolizumab and best supportive care in the company's base case.	
Key issue 5: The approach to modelling the long-term outcomes of overall survival, progression-free survival and time to treatment discontinuation.	

Key issue 6: The way in which the utility values were estimated and why the progression-free utility value for platinum-based chemotherapy is lower than the pooled estimate for progressed disease.	
Key issue 7: The approach to estimate the duration of subsequent treatments.	
14. Are there any important issues that have been missed in ERG report?	Over the past 20 years in England and Wales, there has only been two innovative treatments funded for bladder cancer. Earlier this year pembrolizumab was removed from the Cancer Drugs Fund [ID1536], and atezolizumab is under threat of the same fate [ID3777]. There is also a chance that NICE will not recommend avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735].
PART 3 -Key messages	
15. In up to 5 sentences, please summarise the key messages of your statement:	

- Advanced bladder cancer is physically and emotionally tough with a known low survival rate, and the understanding that the battle is to prolong life rather than resulting in a cure
- Advanced cancer has an impact on the ability to enjoy daily life, work, ability to travel, and ability to exercise of both the patient and their family
- In cisplatin-ineligible patients, atezolizumab has demonstrated durable response rates, survival, and tolerability
- There are very few treatment options for cisplatin-ineligible patients with advanced bladder cancer
- Patients who have experienced this drug overwhelmingly call for it to be available for others on the NHS

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (CDF Review of TA492) [ID3777]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **14 July 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Clinical effectiveness issues		
Key issue 1 The IMvigor130 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.	**No**	These data were not available at the time of the initial submission, so they are new.
Key issue 2: There were baseline differences between trial arms in terms of sex and racial characteristics, and it is unclear if these differences could have biased the treatment effects.	**No**	There is no reasonable hypothesis to suggest that these imbalances would impact on the conclusions.
Key issue 3: The overall survival estimates from the SACT dataset and the IMvigor130 trial differ substantially.	**No**	Our experts note that this is not surprising and the magnitude of the difference is in line with previous differences between trial populations and real world populations. Furthermore, as patients enrolling in IMvigor130 were potentially randomised to receive chemotherapy, there would be a further selection bias for patients with good prognostic features compared to the SACT database (where patients were not necessarily suitable for chemotherapy).

Key issue 4: No comparison was made between atezolizumab and best supportive care in the company's base case.	**No**	
Cost effectiveness issues		
Key issue 5: The approach to modelling the long-term outcomes of overall survival, progression-free survival and time to treatment discontinuation.	**No**	Our experts agree that the ERG approach to modelling the extreme 'tail of the curve' has more face validity than the approach used by the company.
Key issue 6: The utility values.	**No**	The ERG approach seems reasonable.
Key issue 7: The approach to estimate the duration of subsequent treatments.	**No**	

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

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Evidence Review Group Report commissioned by the
NIHR Systematic Reviews Programme on behalf of NICE

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

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	26th July 2021

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1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Roche Products Limited, to the key issues for technical engagement (TE) proposed in the ERG report for this appraisal. The ERG received the company's response on 15th July 2021.

The company's TE response form contains the following information:

- A written response to each of the six key issues, two of which include new analyses (see Table 1).
- A set of updated cost-effectiveness results, incorporating:
    - Additional analyses provided by the company in response to some of the key issues for TE.

In this report we present the following:

- Our critique of the company's response to each of the issues for technical engagement (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of an updated ERG base case and scenario analyses (Section 3)

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Uncertainty of IMVigor 130 trial treatment estimates	No
2	Baseline differences between trial arm characteristics	No
3	Differences in OS estimates between SACT dataset and the IMVigor 130 trial	No
4	Lack of a comparison between atezolizumab and best supportive care in the company's base case.	No
5	The approach to modelling the long-term outcomes of overall survival, progression-free survival and time to treatment discontinuation.	Yes
6	The methodology used to estimate utility values	Yes

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Uncertainty of IMVigor 130 trial treatment estimates

The ERG report stated that the IMvigor 130 trial treatment effect estimates (e.g. OS and PFS) are uncertain because they are based on an interim data analysis of a small subgroup of PD-L1 positive, cisplatin ineligible patients (n=93). In response, the company reiterates that the subgroup was necessary to inform this NICE CDF review due to the restriction placed on the marketing authorisation by the EMA. The ERG acknowledges that a consequence of this restriction is a reduction in the sample of patients available for analysis, from 760 in the intention-to-treat population to 93 in the subgroup. As enrolment in the trial completed in 2018, there is no opportunity to increase this sample size.

The company also states that the confidence intervals around the HR do not cross 1 and that this is "robust enough" evidence to inform decision making. The ERG notes that the OS and PFS HR confidence intervals are, nonetheless, wide (OS= 0.50, 95% CI 0.29 to 0.87; PFS= 0.56, 95% CI 0.34 to 0.93) based on the interim analyses and thus uncertainty in the treatment effects is still an issue.

The company does not comment on any uncertainty due to the interim status of the results (data cutoff of 14th June 2020). The ERG notes that that at this cutoff, 579 of the 667 deaths required for the final data analysis had occurred (86.8%), and that median OS had been reached in both of the relevant trial arms. Although final results from the trial are not yet available to inform this appraisal, the relative maturity of the current survival data helps to reduce overall uncertainty.

In summary, there is inherent uncertainty in treatment effects due to the small sample of patients in the relevant trial subgroup. Survival data are reasonably mature and the final results, expected in Q2-3 2022, may increase precision of effects, albeit slightly.

2.2 Issue 2 – Baseline differences between trial arm characteristics

The ERG noted baseline imbalances between the IMvigor 130 trial arms, in terms of patients' sex and racial characteristics and concluded that the magnitude and direction of bias on treatment effects is uncertain. The company, in response, acknowledge these differences, and suggest that the bias would favour atezolizumab. In addition, the company cite baseline imbalances in two other variables - patient Bajorin risk factor scores and ECOG performance status - and posit that these may bias in favour of platinum-based chemotherapy. They conclude that the "opposing differences" in bias from the above

baseline characteristics, coupled with the small sample size, makes it impossible to determine the direction or magnitude of potential bias.

We note that Bajorin risk factor/liver metastasis scores (0 vs.1 vs. 2 or patients with liver metastasis) was one of a small number of variables stratified across trial arms at randomisation. Our understanding is that stratification was intended to achieve a balanced distribution of selected patient characteristics between randomised trial arms for the whole trial population. It cannot necessarily be assumed, however, that stratification would achieve a balanced distribution of these patient characteristics in trial subgroups. This is apparent from examination of the magnitude of the imbalance in Bajorin risk factor/liver metastasis scores between the atezolizumab arm and the platinum based chemotherapy arm in the subgroup of PD-L1 positive, cisplatin ineligible patients (36.0% vs 53.5% (score = 0), 34.0% vs 32.6% (score = 1), 30.0% vs 14.0% (score = 2), respectively). These imbalances are likely to increase the potential for selection bias favouring platinum-based chemotherapy.

Regarding baseline ECOG performance status, it is our understanding that imbalances in the distribution of higher scoring patients (ECOG 2, associated with some impairment in functional status) would more likely bias outcomes than those with lower scores (ECOG 0 to 1, associated with no or mild impairment). We note that 16.0% of the atezolizumab arm and 16.3% of the platinum-based chemotherapy arm had an ECOG score of 2. Therefore, we consider it unlikely that imbalances in the lower ECOG scores would have impacted the outcomes of the trial.

In summary, some of the imbalances in the aforementioned baseline characteristics between trial arms are likely to bias treatment effects. For some characteristics the bias appears to favour atezolizumab, and for others it is likely to favour platinum-based chemotherapy. The ERG concludes that the combined impact of the imbalances on treatment effects, in terms of direction and magnitude of bias, is unclear.

2.3 Issue 3 – Differences in OS estimates between SACT dataset and the IMVigor 130 trial

In the ERG report we noted substantial differences in the median OS estimates for atezolizumab monotherapy between the SACT dataset and the IMVigor 130 trial (12.4 months versus 18.6 months, respectively). We speculated this could be due to people in the SACT dataset being older and having a poorer performance status. In the ERG's opinion,

the SACT cohort is more representative of the population who would typically be seen in the NHS.

At the clarification question stage of this appraisal our invitation to the company to conduct an exploratory OS scenario analysis using data from both the SACT dataset and the IMvigor130 trial was declined. We did not repeat this recommendation or propose any other scenarios in the ERG report for technical engagement, but we did conduct our own exploratory scenario analysis (see below).

In their response, the company acknowledge the difference in OS estimates, but do not discuss likely explanations. They reiterate the Terms of Engagement of this appraisal, which states that the IMvigor130 trial should be the primary source of evidence to inform OS estimates in the economic evaluation. We concur that the trial should inform the base case, and our suggestion to incorporate SACT OS data was always intended to inform exploratory scenario analysis. The company could, therefore, have explored this scenario without compromising the Terms of Engagement.

The company cites the ERG's exploratory OS scenario analysis (based on the SACT dataset, and the IMvigor130 trial), and they note that atezolizumab was shown to be more cost-effective than in the company's and the ERG's base cases (both of which used only IMvigor130 OS estimates). The ERG would like to point out that our scenario assumes the same treatment effect (i.e. the difference in OS between atezolizumab and platinum-based chemotherapy) as seen in the IMVigor 130 trial (i.e. a stratified HR of 0.5). As the SACT dataset did not include a platinum-based chemotherapy comparator arm it is unclear whether the same treatment effect would be observed in practice. In the absence of data to support this assumption, we reiterate that this should be considered an exploratory analysis.

2.4 Issue 4 – No comparison was made between atezolizumab and best supportive care in the company's base case.

The company states that, due to the absence of available suitable data, they "do not intend to include further analyses on best supportive care". The ERG has no further comment to make on this issue, but as stated in the ERG report, we are aware of at least two randomised trials (which do not appear to have been identified by the company in their systematic review search) of treatments for urothelial cancer which included best supportive care as a comparator. However, these trials may not include untreated PD-L1-positive cisplatin-ineligible patients with locally advanced or metastatic disease, and thus it may not

be feasible to perform an indirect comparison with atezolizumab using the relevant subgroup from the IMVigor 130 trial.

2.5 Issue 5 – The approach to modelling the long-term outcomes of overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (TTD)

In their response, the company accept the ERG's approach to modelling PFS and update their base case accordingly. However, they disagree with the ERG's approach to modelling OS and TTD, as discussed below.

2.5.1 Overall survival

To inform their base case the company's model uses data from the IMVigor 130 trial Kaplan-Meier (KM) curves until 20% of patients remain at risk, at which point a parametric survival curve (exponential) is fitted for the remainder of the survival observation period. As discussed in the ERG report, section 4.1.1, we consider it more appropriate to fit the parametric survival extrapolation over the whole survival period since there is uncertainty in survival estimates associated with the small sample size of the PD-L1-positive cisplatin-ineligible patient subgroup.

The company's response to TE includes a set of 4 further scenarios for OS. In two of these they increase the number of patients remaining at risk in the KM curve to 48% before fitting the survival curve (one an exponential curve and the other a Weibull curve). The change to the point at which the curve is fitted is intended to offset uncertainty caused by sparse data at the tail of the KM curve. A limitation, however, is that it discards almost half of the observed data. In the ERG's opinion there is inherent uncertainty in survival estimates due to the small sample size. We therefore retain our approach of fitting a survival curve for the entire observational period. The other two company scenarios follow the ERG's preferred approach to curve fitting (one an exponential curve and the other a Weibull curve). The results of all 4 scenarios, in terms of ICERs, are similar.

The company state all four scenarios "Are the most conservative choices to align closely with the SACT dataset in order to validate curve choice". It is not clear to the ERG exactly how the SACT dataset has been used for this purpose. Whilst the company's view is that the OS estimates from the two studies are aligned, the ERG's interpretation is that they result in quite different survival estimates (Table 1, TE appendix A.1).

2.5.2 Time to treatment discontinuation

The company considers that the Weibull extrapolation for TTD, as favoured by the ERG, predict clinically implausibly long-term TTD, and results in over-predicted TTD compared to the SACT dataset. Furthermore, they state that the exponential curve displays a poor fit to the observed data and over-predicts survival in the first 18 months. Therefore, the updated company base case uses the KM TTD curve with an exponential extrapolation.

Clinical experts to the company estimated that after 5 years 0-2% of patients would still be on treatment with atezolizumab (vs. 7% predicted by the Weibull model). The experts also suggested that after 10 years no patients were likely to remain on treatment with atezolizumab (vs 2% predicted by the Weibull model). The ERG notes that the Weibull model predicts that 0.9% of patients remain on atezolizumab treatment after 10 years (rather than 2% as stated by the company).

As discussed in the ERG report section 4.1.1.3, we prefer the Weibull distribution because the hazard for TTD in the IMVigor 130 trial decreases over time and this favours the Weibull distribution over the exponential distribution. In addition, as stated by the company, the exponential distribution provides a poor fit to the KM data in the first 18 months. Similarly, when using the KM data with an exponential tail, this assumes a constant probability of treatment discontinuation over time, whereas as stated above this probability is decreasing in the trial KM data. We consider that using the KM data with an exponential tail would overestimate the probability of treatment discontinuation, and therefore underestimate treatment costs for atezolizumab.

We consider it problematic to use the SACT data to inform the choice of the TTD curve selection for the IMVigor 130 trial as there are differences between these two studies in patient population characteristics (as we discussed earlier in section 2.3, people in the SACT dataset were older and had a poorer performance status). Also, the SACT dataset does not have a longer duration of follow-up than the IMVigor 130 trial.

2.6 Issue 6 – The methodology used to estimate utility values

The company addressed the ERG's key issue regarding the lack of clarity over the approach to estimating health state utility values by providing a more detailed explanation of the methodology used.

In brief, the company updated the mixed effects model used to estimate utility values. The updated model uses time, treatment arm and progression status as variables (gender and liver metastases variables were also included in the original mixed-effects model used in the original CS). The company notes that the updated model has the lowest AIC of all models that included these variables.

The updated company base case health state utility values are shown in Table 2 (Table 3 in the company response). The company notes that updated utility value for the platinum - based chemotherapy progression-free health state (0.615) is now higher than the pooled utilities estimates for the progressed health state (0.611). (This was not the case for the original company base case and was raised a concern by the ERG).

Table 2 Updated company base case health state utility values

Utilities provided in updated company base case		
	Atezolizumab (95% CI)	**Platinum-based chemotherapy (95% CI)**
PF	0.648 (0.565, 0.732)	0.615 (0.532, 0.697)
PD	0.611 (0.537, 0.686)	
Reproduced from the company response to TE Table 3. PF progression free; PD progressed disease		

The ERG welcomes the further explanation provided by the company on the methodology of deriving the utility values. Further, we agree that the updated values provided have better face validity than the original utility values provided by the company, in the regard that the difference between the progression-free utility values for atezolizumab and platinum-based chemotherapy are more similar to those seen in the naïve utility values and, in addition, the progression-free utility value for platinum-based chemotherapy is higher than that for progressed disease. We have therefore updated the ERG base case with these utility values.

We note that the utility values derived are still considerably lower than the naïve values and the company has not provided an explanation for this. However, the company provided a scenario using the naïve values (Company response appendix Table 7) in which the ICER reduces. Therefore, we consider it is reasonable to use the updated utility values as these are conservative compared to the naïve utility values.

2.7 The approach to estimate the duration of subsequent treatments

The company has accepted the ERG's approach to estimating the duration of subsequent treatments and included this amendment in the updated company base case. The ERG has no further comments on this issue.

3. Updated cost-effectiveness results - ERG summary and critique

In their response to TE, the company provided the results of their updated base case analysis, in which they incorporate some of the ERG's preferred assumptions. The company's updated base case includes the following:

- **PFS extrapolation**: use of Weibull (*as per ERG's preferred assumptions).*
- **OS extrapolation**: use of KM + exponential.
- **TTD extrapolation**: use of KM + exponential.
- **Subsequent treatment duration of atezolizumab**: duration of 7.9 months in platinum-based chemotherapy arm (*as per ERG's preferred assumptions*).
- **Utilities**: updated approach to health state utilities, described above in section 2.6 (atezolizumab PF: 0.648, platinum-based chemotherapy PF: 0.615, and pooled PD: 0.611).

3.1 Company's updated base case cost-effectiveness results

The ERG found a minor difference in some of the ICER results reported in the company's response to technical engagement (differences <£100). Table 3 shows the ERG corrected version of the company's updated base case results. The results show that atezolizumab offers a mean QALY gain of [redacted] for an additional mean cost of [redacted] compared with platinum-based chemotherapy, giving an ICER of £32,235 per QALY gained.

Table 3 Company updated base case results, deterministic analysis (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,235
Platinum-based chemotherapy	£18,652	1.38	0.85				
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							

3.2 ERG's revised preferred assumptions

We maintain all our preferred model assumptions (previously discussed in the ERG report). We have only revised the ERG base case to incorporate the updated health state utilities provided by the company in their response to TE (atezolizumab PF: 0.648, platinum-based chemotherapy PF: 0.615, pooled PD: 0.611).

3.3 Cost-effectiveness results based on ERG-preferred model assumptions

Table 4**Error! Reference source not found.** shows the cumulative cost-effectiveness results of applying the ERG's revised preferred model assumptions. The ICER increases from £49,301 per QALY to £50,324 per QALY versus platinum-based chemotherapy.

Table 4 ERG's preferred model assumptions (discounted, PAS price for atezolizumab)

Preferred assumption	Cumulative ICER £/QALY
ERG previous base case	£49,301
+ Updated health state utilities (atezolizumab PF: 0.648, platinum-based chemotherapy PF: 0.615, pooled PD: 0.611)	£50,324
ERG revised base case	£50,324
OS, overall survival; PF, progression free; PFS, progression free survival; TTD, time to treatment discontinuation	

3.4 Scenario analyses conducted on the ERG's revised preferred assumptions

Table 5 summarises the results of the scenario analyses considered most relevant for technical engagement (those related to the company's new analyses). In addition, a scenario using the naïve health state utilities was added (atezolizumab PF: 0.815; platinum-based chemotherapy PF: 0.791; pooled PD: 0.735).

The other scenarios and exploratory analyses that were in the ERG report (section 6) have been updated with the ERG's revised base case and these are presented in Appendix 4.1.

- Using KM + exponential to extrapolate TTD with 48% of patients at risk decreases the ICER to £33,676 per QALY.
- Applying the naïve health state utility values decreases the ICER to £41,100 per QALY.

- The remaining scenarios change the ICER to a lesser extent.

Table 5 Main scenario analyses using the ERG's revised model assumptions (discounted, PAS price for atezolizumab)

Scenario	ICER (£/QALY)
ERG revised base case	£50,324
OS extrapolation: Weibull	£48,602
OS extrapolation: KM (48% at risk) + Weibull	£46,810
OS extrapolation: KM (48% at risk) + exponential	£48,995
TTD extrapolation: exponential	£49,924
TTD extrapolation: KM (48% at risk) + Weibull	£47,152
TTD extrapolation: KM (48% at risk) + exponential	£33,676
Utilities: naïve health state utilities from IMVigor130	£41,100
ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; OS, overall survival; QALY, quality-adjusted life years; TTD, time to treatment discontinuation.	

4. Appendices

Appendix 4.1 Results of scenario and exploratory analyses

In this section we update the scenario analyses presented in the ERG report and also the exploratory analyses with the ERG's revised preferred assumptions.

Scenario analyses

Changing the magnitude of the treatment effect (OS hazard ratio) changes the ICER considerably: from £36,778 to £113,009 per QALY. We suggest that these ICERs are interpreted with caution as the platinum-based chemotherapy OS curve was varied rather than the atezolizumab curve. Using KM + exponential to extrapolate TTD with 20% of patients at risk has a significant impact on the cost-effectiveness results (£38,438 per QALY). The remaining scenarios change the ICER to a lesser extent.

Table 6 Scenario analyses using the ERG's revised model assumptions (discounted, PAS price for atezolizumab)

Scenario	ICER (£/QALY)
ERG revised base case	£50,324
PFS extrapolation: exponential	£51,378
PFS extrapolation: KM (20% at risk) + Weibull	£49,382
PFS extrapolation: KM (48% at risk) + Weibull	£50,140
PFS extrapolation: KM (20% at risk) + exponential	£50,528

PFS extrapolation: KM (48% at risk) + exponential	£52,208
OS extrapolation: KM (20% at risk) + exponential	£46,308
OS hazard ratio: 0.29	£36,778
OS hazard ratio: 0.87	£113,009
OS hazard ratio: 0.5	£44,931
TTD extrapolation: KM (20% at risk) + Weibull	£47,966
TTD extrapolation: KM (20% at risk) + exponential	£38,438
Subsequent treatment costs: excluded	£53,350
Distribution of subsequent treatments: adjusted to match IO use	£52,273
Duration of subsequent IO treatment: as per IMvigor 130	£52,997
IO, immunotherapy; KM, Kaplan Meier; OS, overall survival; PAS, patient access scheme; PD, progressive disease; PF, progression free; PFS, progression free survival; QALY, quality-adjusted life years; TTD, time to treatment discontinuation.	

Exploratory analyses

We digitised the SACT OS and TTD curves (CS Figure 5 and 6) and fitted exponential parametric curves to the KM data. For the platinum-based chemotherapy arm, we assumed the same treatment effect as seen in the IMVigor 130 trial (hazard ratio 0.5).

Best supportive care was assumed to be equivalent to platinum-based chemotherapy in terms of effectiveness while no costs were incurred for drug acquisition and administration and for treating adverse events. In addition, it was assumed that i) subsequent treatment costs were not incurred for both arms (analysis 1, as per company's scenario); ii) utility of best supportive care was equal to the utility of atezolizumab and subsequent treatment costs were incurred for atezolizumab only (analysis 2); and iii) utility of best supportive care was equal to the utility of atezolizumab and subsequent treatment costs were incurred for both arms (analysis 3).

The results are shown in Table 7. These show that using the SACT data with the ERG revised base case assumptions produces an ICER of £31,955 per QALY and comparing atezolizumab to best supportive care produces an ICER of £59,816 per QALY when no subsequent treatment costs and equal utilities are included, £62,701 per QALY when including same utilities and subsequent treatment costs for atezolizumab only and £58,915 per QALY when including same utilities and subsequent treatment costs for both arms.

Table 7 ERG exploratory analyses using the ERG revised base case assumptions (discounted, PAS price for atezolizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			
				Costs (£)	LYG	QALYs	ICER (£/QALY)
Exploratory analysis using the SACT data							
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,955
Platinum-based chemotherapy	£9,634	0.81	0.50				
Exploratory analysis comparing atezolizumab with best supportive care – analysis 1							
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59,816
Best supportive care	£11,630	1.50	0.92				
Exploratory analysis comparing atezolizumab with best supportive care – analysis 2							
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,701
Best supportive care	£11,630	1.50	0.94				
Exploratory analysis comparing atezolizumab with best supportive care – analysis 3							
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,915
Best supportive care	£13,804	1.50	0.94				
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.							