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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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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

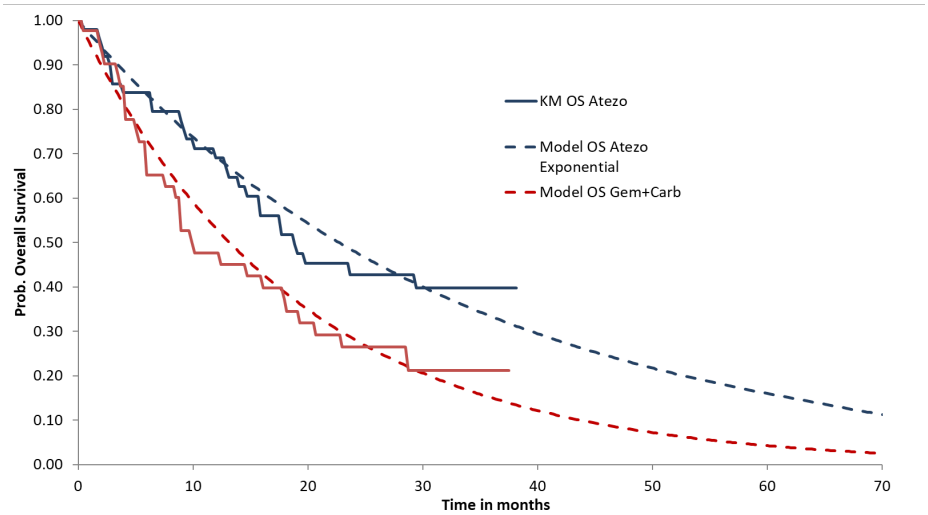
Treatment	Source	1 year	2 years	3 years	5 years	10 years	20 years
Atezolizumab	IMVigor 130	69%	43%	40%	--	--	--
	SACT cohort study	~54%	~36%	--	--	--	--
	Company expert opinion	--	--	--	5-30%	1-20%	1-6%
	KM + exponential	69%	43%	35%	17%	3%	0%

	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.

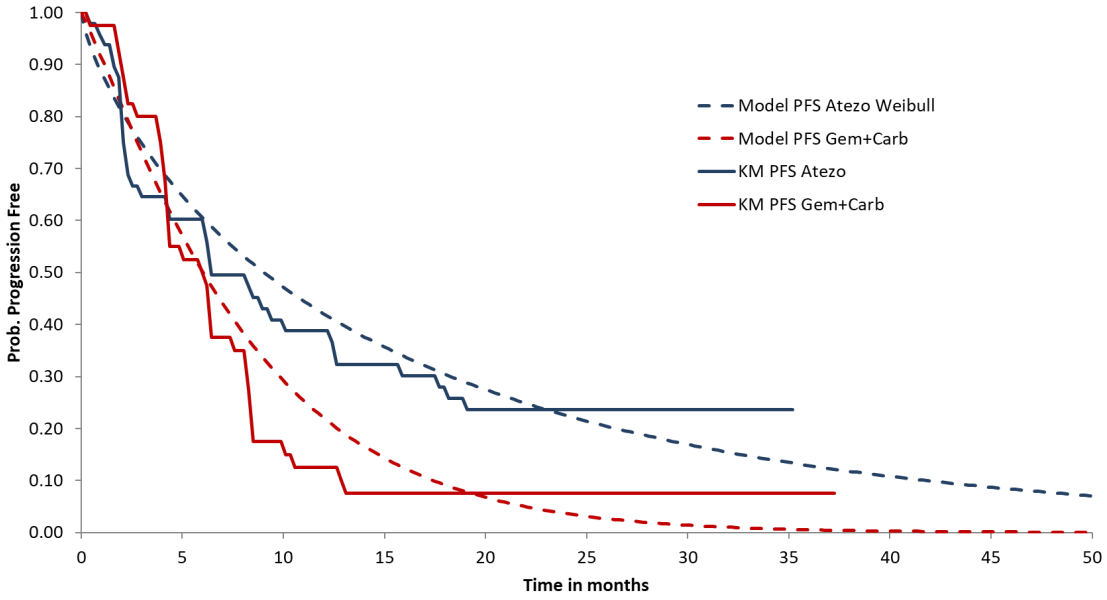
Table 12 Comparison of trial PFS KM with parametric curve extrapolation (Company and ERG base case and scenarios) and other sources at various time points

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

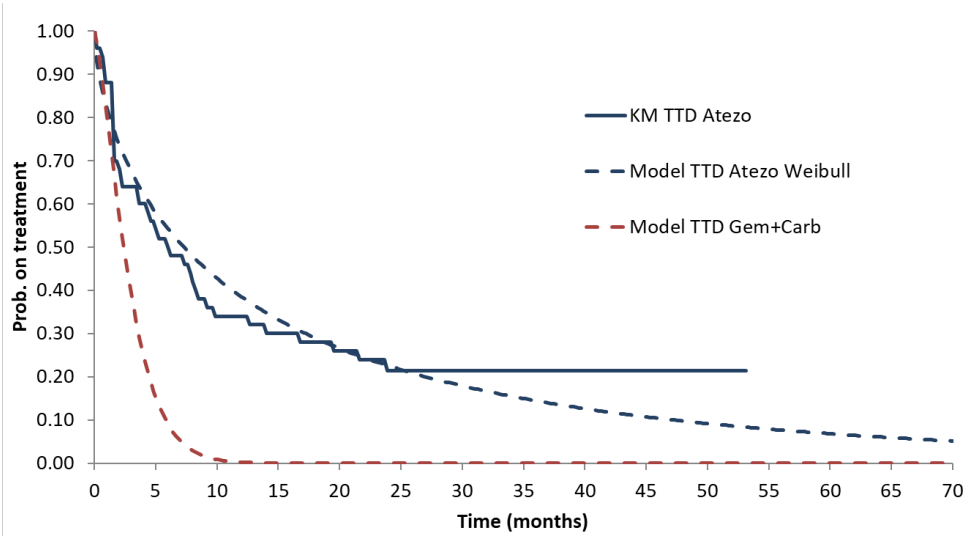
The company did not consider it relevant to assess proportional hazards for TTD, since the chemotherapy was based on an 18-week capped dosing schedule. Parametric curves were fitted to the observed TTD data from the IMVigor 130 trial and then assessed for goodness of fit using Akaike information criteria / 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

1. Patterson K, Prabhu V, Xu R, et al. Cost-effectiveness of Pembrolizumab for Patients with Advanced, Unresectable, or Metastatic Urothelial Cancer Ineligible for Cisplatin-based Therapy. *Eur Urol Oncol* 2019;2(5):565-71. doi: 10.1016/j.euo.2018.09.009 [published Online First: 2019/08/15]
2. European Medicines Agency. Atezolizumab Summary of Product Characteristics, 2021.
3. Electronic Medicines Compendium (EMC). Tecentriq 1,200 mg concentrate for solution for infusion 2021 [Available from: https://www.medicines.org.uk/emc/product/8442/smpc#gref accessed 16 June 2021.
4. 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 accessed 16 Mar 2021.
5. Galsky MD, Arija JÁ A, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2020;395(10236):1547-57. doi: 10.1016/s0140-6736(20)30230-0 [published Online First: 2020/05/18]
6. F Hoffmann-La Roche Ltd. (Data on File). IMvigor130 Clinical Study Report, 2020.
7. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *The Lancet Oncology* 2011;12(3):211-4. doi: 10.1016/s1470-2045(10)70275-8 [published Online First: 2011/03/08]
8. Public Health England. Atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable – data review. London: Public Health England, 2021.
9. Zafar SY, Currow D, Abernethy AP. Defining Best Supportive Care. *J Clin Oncol* 2008;26(31):5139-40. doi: 10.1200/jco.2008.19.7491
10. Bellmunt J, Fougeray R, Rosenberg JE, et al. Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based

chemotherapy. *Ann Oncol* 2013;24(6):1466-72. doi: 10.1093/annonc/mdt007 [published Online First: 2013/02/20]

11. Bellmunt J, Théodore C, Demkov T, et al. Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract. *J Clin Oncol* 2009;27(27):4454-61. doi: 10.1200/jco.2008.20.5534
12. Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med* 2020;383(13):1218-30. doi: 10.1056/NEJMoa2002788 [published Online First: 2020/09/19]
13. De Santis M, Bellmunt J, Mead G, 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. doi: 10.1200/jco.2011.37.3571 [published Online First: 2011/12/14]
14. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2012;15(5):708-15. doi: 10.1016/j.jval.2012.02.008 [published Online First: 2012/08/08]
15. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525] - Committee discussion 2018 [Available from: https://www.nice.org.uk/guidance/ta525/chapter/3-Committee-discussion accessed 16 Mar 2021.

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				