AURORA

Atezolizumab in patients with urinary tract squamous cell carcinoma: a single arm, open label, multicentre, phase II clinical trial

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Protocol Information

This protocol describes the AURORA trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
GCP	Good Clinical Practice
IB	Investigator Brochure
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SCTU	Southampton Clinical Trials Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UTSCC	Urinary Tract Squamous Cell Carcinoma

KEYWORDS
Bladder cancer; urinary tract cancer; squamous cell carcinoma; immunotherapy; atezolizumab, phase 2

TRIAL SYNOPSIS

Trial Name	AURORA
Full Title	Atezolizumab in patients with urinary tract squamous cell carcinoma: a single arm, open label, multicentre, phase II clinical trial

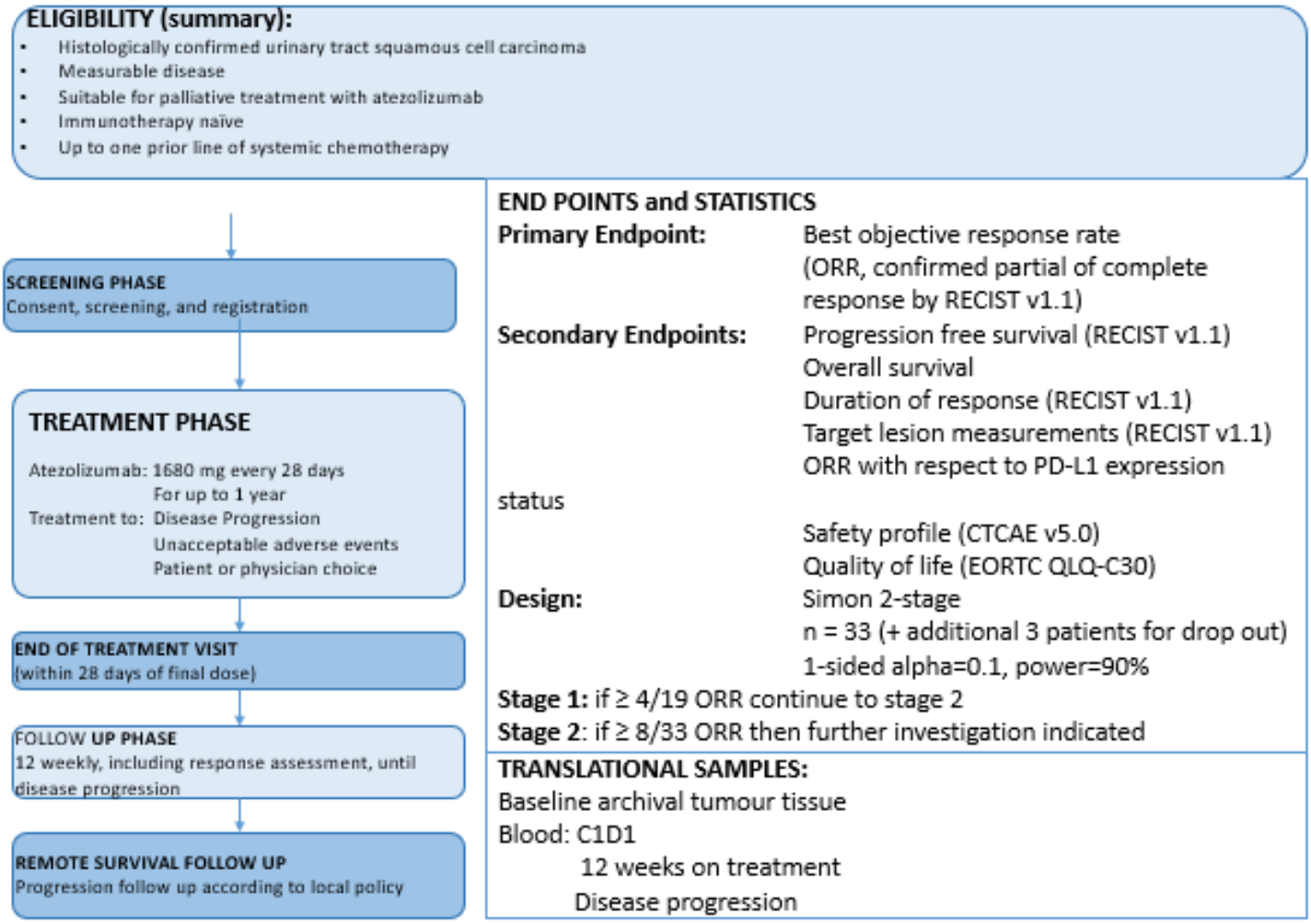
Population	**INCLUSION CRITERIA** 1. Histologically confirmed cancer of the urinary tract with squamous cell carcinoma (UTSCC) histology and without any TCC component. Mixed non-TCC histology is allowed if squamous cell carcinoma is the predominant histology 2. Newly diagnosed or progressive measurable disease as defined by RECIST version 1.1. To be considered measurable (and to be designated as a target lesion), a lesion must not have been treated with prior radiotherapy or focal ablation techniques 3. Suitable, in the judgment of the local investigator, for treatment with atezolizumab, with palliative intent 4. Adequate haematologic and end-organ function within 28 days prior to the first study treatment including: a. Absolute neutrophil count ≥ 1.5 $x10^9$/L b. Platelet count ≥ 100 $x10^9$/L c. Haemoglobin ≥ 90 g/L d. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the institutional upper limit of normal (ULN) e. Total bilirubin ≤ 1.5 times ULN (or ≤ 3 ULN in patients with Gilbert's syndrome) f. Calculated creatinine clearance ≥ 20 mL/min (Cockcroft-Gault formula) 5. Up to one prior line of systemic chemotherapy for UTSCC 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 7. Life expectancy ≥ 12 weeks 8. Representative formalin-fixed paraffin embedded (FFPE) tumour sample with an associated linked-anonymised pathology report that is available for central use in translational studies 9. Able to comply with all trial procedures and processes 10. Age ≥ 18 at time of signed inform consent form 11. Provision of written informed consent **EXCLUSION CRITERIA** 1. Any component of TCC histology 2. Planned for treatment with curative intent 3. Prior systemic immunotherapy (prior intra-vesical treatments are allowed) 4. Major surgery within 30 days prior to enrolment 5. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins 6. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation 7. Use of oral or IV steroids for 14 days prior to enrolment. Use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for

	adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed 8. Administration of a live or attenuated vaccine within 4 weeks prior to enrolment (COVID-19 vaccination is allowed) 9. Treatment with any other investigational agent within 4 weeks prior to enrolment 10. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable arrhythmias, unstable angina or congestive cardiac failure (New York Heart Association ≥ grade 2) within 6 months prior to enrolment 11. Patients with known HIV infection or with active tuberculosis 12. Patients with known active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test) or hepatitis C. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and the absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA 13. Autoimmune disease including myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone or with controlled Type I diabetes mellitus on a stable dose of an insulin regimen are eligible for this study 14. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. A history of radiation pneumonitis in the radiation field (fibrosis) is permitted 15. Prior allogeneic stem cell or solid organ transplant 16. Patients who are pregnant or breast feeding 17. Patients of child-bearing potential who are not able to use a highly effective method of contraception (as detailed in section 3.7) 18. A recent or current other cancer. Current non-melanoma skin cancer, cervical carcinoma in situ or localized prostate cancer not requiring current treatment are permissible, as is a history of a separate other malignancy having completed all active treatment ≥2 years previously	
Primary Objective and Endpoint	To determine the clinical activity of atezolizumab in patients with incurable histologically confirmed, immunotherapy naïve UTSCC	Best overall objective response rate (ORR; the percentage with confirmed partial (PR) or complete (CR) response) by RECIST v1.1
Secondary Objectives and Endpoints	1. To determine the safety and tolerability of atezolizumab in this clinical setting 2. To determine the overall survival (OS) of patients treated with atezolizumab in this clinical setting 3. To determine the progression-free survival (PFS) of patients treated	Adverse events using CTCAE v5.0 Defined as time from enrolment to death from any cause. Censored at the last follow-up if event free Defined as time from enrolment to disease progression (by RECIST v1.1) or

	with atezolizumab in this clinical setting	death from any cause. Censored at the last follow-up if event free
	4. To determine the duration of response of patients treated with atezolizumab in this clinical setting	Duration of objective response, as time from enrolment, by RECIST v1.1
	5. To determine tumour burden changes of individual patients treated with atezolizumab in this clinical setting	Waterfall plots of RESIST v1.1 summed target lesion measurements at 12 weeks and at best response
	6. To determine the impact on quality of life of the atezolizumab in this clinical setting	Measured using the EORTC QLQ-C30 Tool
	7. To determine the impact of PD-L1 expression status on clinical response	Best overall objective response rate (the percentage with confirmed partial (PR) or complete (CR) response) by RECIST v1.1 in PD-L1 'positive' and 'negative' subgroups
Translational Objectives	Tumour samples: 1. PD-L1 expression in tumour and immune cell infiltrate 2. Tumour infiltrating lymphocytes (TILs) percentage 3. Gene expression analysis 4. Intra-tumoral T-Cell receptor repertoire 5. Morphological evaluation of tumour infiltrating immune cells and their spatial distribution 6. Tumour mutational burden (TMB) Blood samples: 1. Circulating immune cell profiles 2. Peripheral T-Cell receptor clonality	(See the trial laboratory manual for endpoint assessment methods for translational objectives)
Sample Size	We will recruit up to 36 patients with UTSCC. If 4 or more, of the first 19 patients (Stage 1), achieve an objective radiological response (confirmed partial or complete response by RECIST v1.1) then the trial will continue with recruitment to stage 2	

	(recruitment will not pause between Stage 1 and 2) where 8 or more responses in 33 patients will meet the criteria to indicate further investigation is warranted.
Investigational Medicinal Product	Atezolizumab (PD-L1 inhibitor)
Treatment Regimen	Treatment will consist of atezolizumab, by IV infusion, at a dose of 1680 mg, every 28 days, for up to one year (13 doses) unless discontinued for disease progression (RECIST v1.1) or unacceptable toxicity or patient/investigator choice

TRIAL SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit	**Screening Phase**	**Treatment Phase[1]**			**End of Treatment Visit**	**Follow Up Phase**	**Remote Survival Follow Up[2]**
		Cycle 1 Day 1	**Cycle 2 Day 1**	**Cycle 3 to 13 Day 1**	**28 days from final dose**	**12 weekly[3]**	**As per local policy**
Week	**Day -28 to 1**	**1**	**5**	**9 +**			
Window			**+/- 3 days**	**+/- 3 days**	**+/- 1 week**	**+/- 1 week**	
Informed consent[4]	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Targeted physical exam	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	
CT chest/abdomen/pelvis[5]	X			X		X	
Biochemistry[6]	X		X	X	X		
Haematology[7]	X		X	X	X		
Archival tumour material	X						
Translational blood samples[8]		X		X[8]	X[8]	X[8]	
Concomitant medications	X	X	X	X	X	X	
Adverse event assessment		X	X	X	X	X	
QOL questionnaire[9]	X			X[9]		X[9]	
Atezolizumab		X	X	X			
Pregnancy Testing (WOCBP)	X[10]	X	X	X			
Patient survival status							X

[1] 28-day treatment cycle

[2] Follow up as per local policy

[3] 12 weekly, until disease progression. Assessment points during the Follow Up Phase should be timed such that they continue seamlessly with the 12-weekly schedule of CT scans during the Treatment Phase

[4] Consent may be taken up to 2 months prior to Cycle 1 Day 1

[5] To include cross-sectional imaging of chest, abdomen and pelvis by CT scan during the screening period including response assessment by RECIST, and then every 12 weeks (+/-1 week) from enrolment during the Treatment Phase and Follow Up phase until disease progression. (MRI is acceptable if local practice would substitute this, or in cases of renal impairment)
[6] Serum biochemistry including renal, liver (including ALT, AST, ALP and bilirubin), bone (including serum albumin and calcium) and thyroid profiles, and random cortisol and glucose levels
[7] Including Hb, WCC, neutrophil count, platelet count and differential
[8] Translational blood sample at C1D1, C4D1 (12 weeks on treatment) and at disease progression only
[9] Quality of life questionnaire (EORTC QLQ-C30) to be completed during screening and every 12 week to disease progression
[10] Pregnancy test at Screening must be serum test. All pregnancy testing following this can be urine testing.

1 INTRODUCTION

1.1 BACKGROUND

Overview

There are few data available to guide treatment decisions for urinary tract squamous cell carcinoma (UTSCC). The AURORA trial will test the hypothesis that PD-L1 inhibition with atezolizumab immunotherapy is clinically effective, tolerable and safe, in patients with UTSCC. Translational endpoints will aim to determine characteristics for responsiveness to this treatment. AURORA was developed on behalf of the International Rare Cancers Initiative (IRCI) and the National Cancer Research Institute (NCRI) Bladder and Renal Group.

Urinary tract cancers

Urinary tract cancers account for approximately 10,000 new diagnoses and 5,000 deaths annually in the UK.[1] Approximately 90% are composed of transitional cell carcinoma (TCC) histology and are treated with platinum based chemotherapy in each of the neoadjuvant, adjuvant and palliative settings.[2] Data also support the use of PD-1/PD-L1 directed immunotherapy for selected patients with TCC in the first line, maintenance and second line palliative settings.[2-7] Outcomes for TCC remain poor however. About 50% of potentially curable muscle invasive bladder cancers relapse and the median survival for advanced metastatic TCC is under 2 years.[2-10]

The remaining non-TCC histology urinary tract cancers include squamous cell carcinoma, large cell carcinoma, small cell and neuroendocrine carcinoma, adenocarcinomas (including urachal/mullerian cancers) and clear cell carcinoma.[11] The approximate incidence of non-TCC urinary tract cancers in the UK is 1.7/100,000/year. Urinary tract cancers may also present with mixed histological components.

Urinary tract squamous cell carcinoma (UTSCC)

UTSCC is the most common of the rare urinary tract cancer histologies, comprising between 2.1–6.7% of urinary tract cancers overall. Risk factors include smoking, long-term catheterisation (e.g., in spinal cord injury), chronic inflammation due to bacterial infections, urinary tract foreign bodies, bladder calculi and schistosomiasis infection in relevant parts of the world.

Patients with UTSCC have more advanced disease stage at diagnosis, on average, than TCC, with approximately 70% having muscle invasive disease. If bladder confined, 5-year disease-free survival following radical cystectomy is 43–57%.[11] Compared to TCC, patients with UTSCC are more likely to be female and (in a US series) African American. UTSCC appears to carry a worse prognosis overall, and on a stage by stage basis.[12] In part, this may reflect more limited, and substantially less researched, treatment options.

Treatment of UTSCC

Radical cystectomy is the mainstay of treatment for UTSCC, where the disease remains localised.[13,14] Radiotherapy alone appears to be less effective based on a Surveillance, Epidemiology, and End Results (SEER) database analysis of 5018 UTSCC cases, although these retrospective and non-randomised data available limit firm conclusions.[14,15] Available data do not support the use of peri-operative chemotherapy for patients with pure UTSCC (unlike for TCC).[14]

We have yet to establish a definitive systemic treatment approach for UTSCC. These patients are commonly disadvantaged as a result of explicit exclusion from urinary tract cancer clinical trials. This includes every registration phase III study of PD1/PD-L1 directed immunotherapy to date. UTSCC is conventionally considered to respond poorly to chemotherapy. The sole example of a dedicated, prospective, UTSCC clinical trial, to our knowledge, was a single arm phase II clinical trial conducted in the 1990s (BA08) of cisplatin, methotrexate and vinblastine

chemotherapy (CMV) for advanced UTSCC. In 38 patients, CMV induced a 9 week objective response rate of 39% (95% CI 24%, 55%) with a median overall survival of 7.8 months (95% CI 3.4, 12.6).[16]

More recently, the SAUL single arm phase IIIb safety study has provided data on atezolizumab immunotherapy in 1004 urinary tract cancer patients in the second line, post chemotherapy, setting. Efficacy and tolerability were broadly comparable with registration phase III studies for TCC. SAUL included 41 patients with non-TCC histology, including 18 UTSCC patients. However, no data were provided relating specifically to outcomes within these rare histological subtypes including for the UTSCC subset. Furthermore, there was neither a formal statistical hypothesis for the trial overall, nor any pre-specified analysis proposed for the UTSCC subset. As such, this post licensing 'experience' was not designed to formally assess the efficacy of atezolizumab for UTSCC.[17]

The phase II PURE-01 trial that evaluated pembrolizumab, a PD-1 inhibitor immunotherapy, as a neoadjuvant treatment for T2-4a N0 M0 bladder cancer.[18] Seven of 114 patients had UTSCC. Of these, six had down staging to pT<1, with one patient achieving a complete pathological response. This apparently high response rate needs to be treated with some caution. Firstly, in relation to the sample size of UTSCC patients which was not a primary focus of this trial. Secondly, the lack of randomisation to determine the down staging rate without immunotherapy (following trans-urethral resection alone). Accepting these limitations however, these data are consistent with a hypothesis predicting clinical efficacy for PD-1/PD-L1 directed immunotherapy in UTSCC. Furthermore, the mean tumour mutational burden (TMB) and PD-L1 expression were associated with response overall and were higher on average for UTSCC (and lymphoepithelioma-like) cases than for other rare histologies.

Biology of UTSCC

Reflecting its rarity, there are relatively limited data on the biology of UTSCC. HPV infection rates are low, for example 18% in pure UTSCC in one series.[19] UTSCCs have been shown to exhibit similarities to other non-HPV infection related squamous cell carcinoma entities, including lung, head and neck and oesophageal SCCs, where immunotherapy has an established role.[20]

High PD-L1 expression has been described in around two thirds of UTSCC cases, for example in 6 of 17 cases in a recently reported pure UTSCC cohort, in contrast to lower expression rates reported for TCC at around 20%.[21-23] Somatic variants in this study included *TP53*, *PIK3CA*, *FBXW7*, and *CDKN2A*. Copy number alterations included gains in *MYC*, *BIRC3*, and *EGFR*, and loss of *CDKN2A*. *CDKN2A* alterations were significantly more frequent in PD-L1–positive tumours. Gene expression analysis indicated correlation between high *CD274/PD-L1* expression and relative overexpression of basal subtyping genes.[23]

The prognostic implication of PD-L1 expression status was assessed in 151 pure UTSCCs treated with radical cystectomy in Egypt between 1997 and 2004. Low PD-L1 expression was associated with higher pathologic stage, higher grade, presence of lymphovascular invasion, and worse progression free and cancer specific survival outcomes.[22] (The 81% rate of schistosomiasis in this cohort might confound extrapolation to other settings, although there was no association to tumoral PD-L1 expression.)

From the literature on non-schistosomal related UTSCC, identification of rational experimental therapeutic targets, that might currently be realistically actionable, indicates the PD1/PD-L1 immune checkpoint, in addition to PI3K/AKT, HER2, EGFR and FGFR mediated signalling.[18,20,23,24]

Preliminary translational data on UTSCC

We have investigated (S. Crabb, Southampton Experimental Cancer Medicine Centre, unpublished data) immunohistochemistry (IHC) for PD-L1 and tumour infiltrating lymphocyte (TIL) density, together with gene expression analysis on FFPE samples from 16 systemic therapy naïve patients with UTSCC. Results are as follows.

PD-L1 expression was 'high' in 7 of 16 samples using the established 5% cut point for infiltrating immune cell expression used clinically for atezolizumab for TCC histology urinary tract cancers. Tumour infiltrating lymphocyte (TIL) percentage was 'high' in 10 of 16 samples using a cut point of 10%.

We interrogated gene expression patterns using the HTG PIOP gene expression panel and grouped samples according to either PD-L1 protein expression or TIL percentage. Using conservative statistical criteria, we determined a list of differentially expressed genes between these groups, some of which are implicated with urinary tract cancers and response to immunotherapy in other settings. Preliminary signalling pathway analysis indicated gene expression alterations consistent with upregulated interferon γ signalling in PD-L1 high versus low expressing UTSCC samples.

Immunotherapy targeting the PD-1/PD-L1 checkpoint for urinary tract cancer

Programmed death 1 (PD-1) protein is a co-inhibitory receptor expressed on activated T cells, which when bound to its ligand PD-L1, limits T cell activity within the immune microenvironment. Tumours expressing PD-L1 utilise this pathway to evade the anti-tumour activity of T cells within the tumour microenvironment and so prevent activation and migration of tumour-infiltrating lymphocytes to the tumour site. PD-1/PD-L1 checkpoint inhibitors are therefore intended to activate the immune response against cancer cells.[3]

Atezolizumab, avelumab (anti-PD-L1), pembrolizumab and nivolumab (anti-PD-1), are approved for use in Europe in patients with advanced TCC histology urinary tract cancer supported by phase III second line and single arm phase II first line data.[3-7] NICE currently (June 2021) supports the use of atezolizumab for TCC, via the Cancer Drugs Fund,

- as second line treatment after platinum based chemotherapy
- as first line treatment 'cisplatin ineligible' patients with high PD-L1 expressing tumours
- and, as an interim measure during the COVID-19 pandemic, for a wider group of patients as first line treatment irrespective of either PD-L1 status or cisplatin eligibility

UTSCC patients are not included within these NICE approvals, or those within the devolved nations, and so do not have access to immunotherapy.

Biomarkers for PD-1/PD-L1 directed immunotherapy for urinary tract cancer

We currently lack validated predictive biomarkers for immunotherapy benefit for urinary tract cancers. Potential candidates for TCC histology urinary tract cancer include tumour or infiltrating immune cell PD-L1 expression, CD8+ T-cell infiltration, tumour mutational burden, an interferon-γ gene expression signature and the presence of DNA damage response and repair gene alterations.[(2, 3, 23)]

To date, the only practical application in the clinic has been to use PD-L1 expression to indicate less favourable outcome for immunotherapy (atezolizumab or pembrolizumab) compared to chemotherapy for first line treatment in cisplatin ineligible patients with urinary tract TCC. Within the IMvigor130 trial, which tested first line atezolizumab monotherapy or in combination with chemotherapy, PD-L1 expression status appeared to distinguish benefit for atezolizumab over chemotherapy alone for cancers with high PD-L1 protein expression. Specifically, this biomarker is 'positive' in the presence of ≥5% PD-L1 expression, on tumour infiltrating immune cells, using the SP142 PD-L1 IHC assay (Ventana Medical Systems, Tucson, AZ). This test is established for use within the NHS for selection of first line atezolizumab for high PD-L1 expressing TCC.[5]

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

UTSCC is a rare disease with no established systemic treatment options and poor outcomes. Patients have been explicitly denied access to most of the clinical trials done for bladder cancer/urinary tract cancer. Where such patients have been included (PURE-01, SAUL), analysis of this subset was not pre-specified and the outcomes were either not separately reported, or are on a sample size that makes interpretation highly challenging.[17,18] However, there are pre-clinical and translational data, and early clinical data, that support a hypothesis that UTSCC would be responsive to PD-1/PD-L1 checkpoint inhibitor immunotherapy. Furthermore, these data support avenues for predictive biomarker studies. Atezolizumab is an established treatment for TCC and in other cancer settings. Clinical

development and post-marketing experience with atezolizumab indicate a tolerable and predictable safety profile.[3,5,6] AURORA will be the first dedicated clinical trial of immunotherapy for advanced UTSCC and only the second ever undertaken for systemic therapy.

In the setting of the COVID-19 pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19 related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms. There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination, and it is recognised that human immune responses are highly regulated and that immune modifying therapies may positively or negatively impact the efficacy and safety of SARS-CoV-2 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Cancer Comprehensive Network (NCCN) COVID 19 Vaccination Advisory Committee, SARS-CoV-2 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of SARS-CoV-2 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive SARS-CoV-2 vaccination include the following: the risk of SARS–CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID 19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering SARS-CoV-2 vaccines. When administered, SARS–CoV-2 vaccines must be given in accordance with the approved or authorised vaccine label. Receipt of the SARS–CoV-2 vaccine is considered a concomitant medication and should be documented as such.

2 TRIAL DESIGN, OBJECTIVES AND ENDPOINTS

2.1 TRIAL DESIGN

AURORA is a single arm, open label, multicentre, phase II clinical trial of atezolizumab immunotherapy, in immunotherapy naive patients with urinary tract squamous cell carcinoma (UTSCC).

Recruitment is intended to occur over approximately 2 years and will follow a two-stage statistical design (see section 7). However, the intention is to allow continuous recruitment between Stage 1 and Stage 2.

Following a Screening Phase of up to 28 days, eligible patients will be registered and will then commence atezolizumab immunotherapy, every 28 days, within a Treatment Phase of up to 1 year. On treatment discontinuation, patients will be reviewed in an End of Treatment Visit, and then 12 weekly (timed such as to continue with the 12 weekly schedule of CT scans from the Treatment Phase) until disease progression. Following disease progression, patients will revert to routine local follow up processes.

Consent will be obtained for long term collection of overall survival status.

2.2 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint to evaluate
Primary:	To determine the clinical activity of atezolizumab in patients with incurable histologically confirmed, immunotherapy naïve UTSCC	Best overall objective response rate (ORR; the percentage with confirmed partial (PR) or complete (CR) response by RECIST v1.1
Secondary:	1. To determine the safety and tolerability of atezolizumab in this clinical setting	Adverse events using CTCAE v5.0
	2. To determine the overall survival (OS) of patients treated with atezolizumab in this clinical setting	Defined as time from enrolment to death from any cause. Censored at the last follow-up if event free
	3. To determine the progression-free survival (PFS) of patients treated with atezolizumab in this clinical setting	Defined as time from enrolment to disease progression (by RECIST v1.1) or death from any cause. Censored at the last follow-up if event free
	4. To determine the duration of objective response of patients treated with atezolizumab in this clinical setting	Duration of objective response, as time from enrolment, by RECIST v1.1
	5. To determine tumour burden changes of individual patients treated with atezolizumab in this clinical setting	Waterfall plots of RESIST v1.1 summed target lesion measurements at 12 weeks and at best response
	6. To determine the impact on quality of life of the atezolizumab in this clinical setting	Measured using the EORTC QLQ-C30 Tool
	7. To determine the impact of PD-L1 expression status on clinical response	Best overall objective response rate (the percentage with confirmed partial (PR) or complete (CR) response) by RECIST v1.1 in PD-L1 ‘positive’ and ‘negative’ subgroups

Translational:	Tumour samples: 1. PD-L1 expression in tumour and immune cell infiltrate 2. Tumour infiltrating lymphocytes (TILs) percentage 3. Gene expression analysis 4. Intra-tumoral T-Cell receptor repertoire 5. Morphological evaluation of tumour infiltrating immune cells and their spatial distribution 6. Tumour mutational burden (TMB) Blood samples: 1. Circulating immune cell profiles 2. Peripheral T-Cell receptor clonality	(See the trial laboratory manual for endpoint assessment methods for translational objectives)

*Designation of a partial of complete response will require confirmation of this response at a subsequent scan point ≥4 weeks later according to RECIST v1.1 (Appendix **B**)

2.3 **DEFINITION OF END OF TRIAL**

All patients will be followed up for a minimum of 12 months after the last patient is recruited (or all patients have experienced disease progression if this happens sooner). If the trial ceases recruitment after Stage 1 due to inadequate clinical efficacy (based on the criteria in Section 7), then the Trial Management Group (TMG), in consultation with the Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC), will have the option to halt follow up at an earlier stage once all patients have completed the Treatment Phase of the trial.

End of Trial is defined as when the last patient has had their last trial visit and all data to answer the research objectives have been collected.

3 SELECTION AND ENROLMENT OF PARTICIPANTS

3.1 CONSENT

Prior to any study specific procedures, each patient must provide written informed consent, which should be signed by an Investigator and the patient. Patients will keep a copy of the Participant Information Sheet and signed consent form.

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Participant Information Sheet provided and sufficient time allowed for consideration (a minimum of 24 hours) and for participants to have had the opportunity to have any questions addressed. Signed participant consent must be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes and the original filed in the site trial file A copy of the consent form be sent to the SCTU via email to uhs.sctu@nhs.net using a secure nhs.net email address to allow for central monitoring.

3.2 INCLUSION CRITERIA

1. Histologically confirmed cancer of the urinary tract with squamous cell carcinoma histology and without any TCC component. Mixed non-TCC histology is allowed if squamous cell carcinoma is the predominant histology
2. Newly diagnosed or progressive measurable disease as defined by RECIST version 1.1. To be considered measurable (and to be designated as a target lesion), a lesion must not have been treated with prior radiotherapy or focal ablation techniques
3. Suitable, in the judgment of the local investigator, for treatment with atezolizumab, with palliative intent
4. Adequate haematologic and end-organ function within 28 days prior to the first study treatment including:
    a. Absolute neutrophil count ≥ 1.5 $x10^9$/L
    b. Platelet count ≥ 100 $x10^9$/L
    c. Haemoglobin ≥ 90 g/L
    d. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the institutional upper limit of normal (ULN)
    e. Total bilirubin ≤ 1.5 times ULN (or ≤ 3 ULN in patients with Gilbert's syndrome)
    f. Calculated creatinine clearance ≥ 20 mL/min (Cockcroft-Gault formula)
5. Up to one prior line of systemic chemotherapy for UTSCC
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
7. Life expectancy ≥ 12 weeks
8. Representative formalin-fixed paraffin embedded (FFPE) tumour sample with an associated linked-anonymised pathology report that is available for central use in translational studies
9. Able to comply with all trial procedures and processes
10. Age ≥ 18 at time of signed inform consent form
11. Provision of written informed consent

3.3 EXCLUSION CRITERIA

1. Any component of TCC histology
2. Planned for treatment with curative intent
3. Prior systemic immunotherapy (prior intra-vesical treatments are allowed)

4. Major surgery within 30 days prior to enrolment
5. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
6. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
7. Use of oral or IV steroids for 14 days prior to enrolment. Use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed
8. Administration of a live or attenuated vaccine within 4 weeks prior to enrolment (COVID-19 vaccination is allowed)
9. Treatment with any other investigational agent within 4 weeks prior to enrolment
10. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable arrhythmias, unstable angina or congestive cardiac failure (New York Heart Association ≥ grade 2) within 6 months prior to enrolment
11. Patients with known HIV infection or with active tuberculosis
12. Patients with known active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test) or hepatitis C. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and the absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
13. Autoimmune disease including myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone or with controlled Type I diabetes mellitus on a stable dose of an insulin regimen are eligible for this study
14. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. A history of radiation pneumonitis in the radiation field (fibrosis) is permitted
15. Prior allogeneic stem cell or solid organ transplant
16. Patients who are pregnant or breast feeding
17. Patients of child-bearing potential who are not able to use a highly effective method of contraception (as detailed in section 3.7)
18. A recent or current other cancer. Current non-melanoma skin cancer, cervical carcinoma in situ or localized prostate cancer not requiring current treatment are permissible, as is a history of a separate other malignancy having completed all active treatment ≥2 years previously

3.4 **SCREEN FAILURES**

Patients who are found to be screen failures will have their initials, year of birth and reasons for failure recorded on a screening form. The screening log should be scanned and emailed to the SCTU trial specific email address on a monthly basis.

3.5 **ENROLMENT PROCEDURES**

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Participant Information Sheet offered, and time allowed for consideration. Signed participant consent must be obtained. The right of the participant to refuse to participate without giving reasons must be respected, After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the trial for the purposes of

follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes and the original filed in the site trial file. Only if informed consent has been provided for the SCTU to receive this information should a copy of the consent form be sent to the SCTU either by email to uhs.sctu@nhs.net using a secure nhs.net email address, safesend or encrypted mail to allow for central monitoring.

3.6 REGISTRATION PROCEDURES

Patients will undergo screening assessments where required and be registered on the trial specific RAVE database, within 28 days prior to starting treatment.

3.7 CONTRACEPTION

Requirements for adequate contraception in patients of child-bearing potential are as follows:

- Female patients must agree to use two highly effective forms of contraception for example; combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, sexual abstinence(effective from the first administration of all study drugs, throughout the trial and for six months afterwards are considered eligible.
- Male patients with partners of child-bearing potential who agree to take measures not to father children by using one form of highly effective contraception for example; combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, sexual abstinence effective from the first administration of all study drugs, throughout the trial and for six months afterwards are considered eligible. Male participants must also refrain from donating sperm during this period.
- Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate

Where appropriate, and according to local institutional policy, investigators should discuss with and advise patients on the need for cryopreservation of sperm or oocytes for future fertility.

4 TRIAL OBSERVATIONS AND PROCEDURES

Trial observations and procedures are described below. Use of remote or face-to-face approaches to completing these is left to the discretion of the local investigator and institutional policy.

4.1 SCREENING PHASE PROCEDURES

4.1.1 Day -28 – Day 1

- Informed consent (consent may be taken up to 2 months prior to Cycle 1 Day 1)
- Inclusion/exclusion criteria
- Medical history
- Targeted physical exam
- ECOG performance status
- Pregnancy testing (WOCBP)
- CT chest/abdomen/pelvis including response assessment by RECIST. (MRI is acceptable if local practice would substitute this, or in cases of renal impairment)
- Biochemistry including renal (including sodium, potassium, urea, creatinine), liver (including ALT, AST, ALP and bilirubin), bone (including serum albumin and calcium) and thyroid profiles, and random cortisol and glucose levels
- Full blood count including Hb, WCC, neutrophil count, platelet count and differential
- Archival tumour sample with a linked-anonymised pathology report shipped to the Southampton HTA licensed tissue bank during the trial screening period
- Concomitant medications
- Quality of life questionnaire (EORTC QLQ-C30) to be completed during screening and every 12 weeks to disease progression

4.2 TREATMENT PHASE PROCEDURES

Treatment cycles are according to a 28-day cycle (+/- 3 days after the previous cycle). If treatment is precluded due to treatment related adverse events, then doses are omitted rather than delayed. Patients should continue to be reviewed according to the schedule of events (or more frequently if clinically indicated).

4.2.1 Treatment Cycle 1, day 1

- Targeted physical exam
- ECOG performance status
- Pregnancy testing (WOCBP)
- Translational blood sample
- Concomitant medications
- Adverse event assessment
- Atezolizumab administration

4.2.2 Treatment Cycle 2, Day 1 (+/- 3 days), week 5

- Targeted physical exam
- ECOG performance status
- Pregnancy testing (WOCBP)
- Biochemistry including renal (including sodium, potassium, urea, creatinine), liver (including ALT, AST, ALP and bilirubin), bone (including serum albumin and calcium) and thyroid profiles, and random cortisol and glucose levels
- Full blood count including Hb, WCC, neutrophil count, platelet count and differential

- Concomitant medications
- Adverse event assessment
- Atezolizumab administration

4.2.3 Cycles 3 to 13, day 1 (+/- 3 days), week 9 onwards

- Targeted physical exam
- ECOG performance status
- Pregnancy testing (WOCBP)
- CT chest/abdomen/pelvis including response assessment by RECIST. (MRI is acceptable if local practice would substitute this, or in cases of renal impairment). Undertaken every 12 weeks (+/- 1 week) from enrolment. Scanning should continue on this schedule regardless of treatment administration
- Biochemistry including renal (including sodium, potassium, urea, creatinine), liver (including ALT, AST, ALP and bilirubin), bone (including serum albumin and calcium) and thyroid profiles, and random cortisol and glucose levels
- Full blood count including Hb, WCC, neutrophil count, platelet count and differential
- Translational blood sample, collected at cycle 4 day 1 only (irrespective of whether treatment is administered)
- Concomitant medications
- Quality of life questionnaire (EORTC QLQ-C30) to be completed during screening and every 12 weeks to disease progression
- Adverse event assessment
- Atezolizumab administration

4.2.4 End of Treatment Visit, 28 days (+/- 1 week) from final dose

- Targeted physical exam
- ECOG performance status
- Biochemistry including renal (including sodium, potassium, urea, creatinine), liver (including ALT, AST, ALP and bilirubin), bone (including serum albumin and calcium) and thyroid profiles, and random cortisol and glucose levels
- Full blood count including Hb, WCC, neutrophil count, platelet count and differential
- Translational blood sample, collected only if disease progression has occurred
- Concomitant medications
- Adverse event assessment

4.3 **FOLLOW UP PHASE PROCEDURES**

4.3.1 Follow up 12 weekly (+/- 1 week), timed such that they continue seamlessly with the 12-weekly schedule of CT scans from the Treatment Phase, until disease progression

- Targeted physical exam
- ECOG performance status
- CT chest/abdomen/pelvis including response assessment by RECIST. (MRI is acceptable if local practice would substitute this, or in cases of renal impairment). Undertaken every 12 weeks (+/- 1 week). Assessment points during the Follow Up Phase should be timed such that they continue seamlessly with the 12-weekly schedule of CT scans during the Treatment Phase
- Translational blood sample, collected only if disease progression has occurred (if not taken at End of Treatment visit already)
- Concomitant medications
- Quality of life questionnaire (EORTC QLQ-C30) to be completed during screening and every 12 weeks to disease progression

- Adverse event assessment

4.3.2 Survival follow up

- Patient survival status. Follow up as per local policy with remote recording of survival status

4.4 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

4.5 TRIAL TREATMENT DISCONTINUATION

In consenting to the trial, participants have consented to the trial intervention, follow-up and data collection. If the participant discontinues trial treatment, they will continue to be followed up for adverse events, progression and survival in line with the follow up schedule unless they withdraw consent.

Reasons for trial discontinuation

A participant may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Participant choice
- Intolerance to treatment: Any clinical adverse event (AE), laboratory abnormality or intercurrent illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Clinician's decision
- Termination of the study by Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Pregnancy

*In the case of pregnancy, the investigator must immediately notify the Sponsor of this event. In all cases, the study drug will be permanently discontinued in an appropriate manner.

Full details of the reason for trial discontinuation should be recorded in the eCRF and medical record.

4.6 WITHDRAWAL

The participant/legal representative is free to withdraw consent from the trial at any time without providing a reason.

Investigators should explain to participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If participants additionally withdraw consent for follow-up, they should revert to standard clinical care as deemed by the responsible clinician.

Details of trial discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

5 TREATMENT

5.1 ATEZOLIZUMAB TREATMENT DOSE AND SCHEDULE

Treatment will consist of atezolizumab, by IV infusion, at a fixed dose of 1680 mg, every 28 days (day 1 of each cycle, +/- 3 days), for up to one year. Each participant will receive up to 13 doses in total.

Infusion parameters, prophylaxis for infusion reactions, other supportive medications and monitoring of vital signs should follow local institutional protocols for administration of this agent and Investigator's Brochure.

Administration of atezolizumab will be performed in a clinical setting in which there is immediate access to trained personnel and adequate equipment and capacity to manage potentially serious reactions according to local institutional standard protocols.

5.2 ATEZOLIZUMAB SUPPLY

Atezolizumab will be supplied as commercial packs of Tecentriq 840 mg concentrate for solution for infusion and will consist of enough product for 2 cycles per shipment. Pharmacies are responsible for ordering of stock from Roche, who will supply directly to the site.

Only pharmacists who have been registered as site specific contacts will be able to request initial supply and re-supply.

Drug supply can be requested using trial supply forms supplied by Roche.

On receipt of drug supply, pharmacy should send the Certificate of Clinical Trial Supply (CoCTS) to Roche and Sponsor, confirming receipt.

Pharmacy should then either segregate the stock or apply local Annex 13 compliant labels. These local labels will be approved by the Sponsor before the site is open to recruitment. These labels should not obscure the drug name, strength, batch number or expiry date stated on the original packaging.

Atezolizumab will be supplied in single use vials and prepared at site according to the Investigator Brochure. Study drug must be kept secure at site at stored between 2°C - 8°C, protected from light and not frozen or shaken.

Reordering will be done via Roche. Please see the AURORA Pharmacy Manual for further details.

5.3 DRUG ACCOUNTABILITY LOGS

Accountability and dispensing logs will be required for the IMP (atezolizumab) supplied for this trial. These logs will be supplied to sites by SCTU.

5.4 CONCOMITANT MEDICATIONS

Information on any treatment received by the participant, along with dose, frequency and therapeutic indication, from prior to starting trial treatment up to the point of disease progression will be recorded in the electronic case report form (eCRF).

5.5 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

Cytochrome P450 enzymes and conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. There are no known interactions with other medicinal products. There are no known dietary restrictions for patients receiving atezolizumab.

If there is a clinical indication for any medication or vaccination specifically prohibited during the trial then discontinuation from trial therapy may be required. The investigator should discuss any questions regarding

this with the Sponsor. The final decision regarding medication or vaccination rests with the investigator and/or subject's primary physician. Decision for the participant to continue on the trial therapy requires mutual agreement of the investigator, sponsor and the subject.

Prohibited concomitant medication:

- Immunotherapy other than atezolizumab
- Systemic cancer therapy not specified in the protocol
- Investigational agents not specified in the protocol
- Radiation therapy – need for palliative radiation therapy should be discussed with the Sponsor. In general this would be likely to require discontinuation of atezolizumab on the grounds of disease progression
- Glucocorticoids for purposes other than to modulate symptoms from an adverse event related to suspected immunological aetiology, or for cancer complications (e.g., for spinal cord compression), should be discussed with the sponsor. Need for glucocorticoids for cancer complications would be likely to require discontinuation of atezolizumab on the grounds of disease progression. Use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed

Guidance on vaccines, including for COVID-19:

- Administration of a live, attenuated vaccine within the four weeks prior to enrolment or for five months after the last dose of atezolizumab is prohibited (COVID-19 vaccination is allowed)
- The benefit of using the currently authorized COVID-19 vaccines is likely to outweigh any potential risk
- It is the investigator's decision on whether to administer COVID-19 vaccines based on the risk of COVID-19 infection/complications and potential benefit from vaccination, general condition of the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label
- Institutional guidelines should be considered in the decision making
- Vaccines are considered concomitant medication and must be reported on the Concomitant Medication eCRF as per protocol instructions
- Where available, details regarding COVID-19 vaccination (such as vaccination date, anatomic site, laterality, and manufacturer) should be captured in the patient's case notes

5.6 TREATMENT RELATED TOXICITY MANAGEMENT AND ATEZOLIZUMAB DOSE OMISSION

All treatment related toxicities should be recorded (in line with MedDRA) and graded according to NCI CTCAE, version 5.0.

Please see section 6.7 Management of Atezolizumab-specific adverse events of the Atezolizumab IB v18 for further guidance.
Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Immune-related adverse reactions that cannot be controlled with systemic

corticosteroid use should be reviewed for consideration of administration of other systemic immunosuppressants.

Toxicities associated, or possibly associated, with atezolizumab treatment should be managed according to standard procedures for administration of this agent at the treating site. Guidance on dose modification in relation to specific treatment related toxicities is also provided within the IB (Appendix D).

Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.

There will be no dose reductions for atezolizumab.

Where required, excessive treatment related toxicity will be managed by periods of dose omission rather than dose delay. As such, there will be no extension to the planned total duration of treatment of 1 year (up to 13 doses at 28-day intervals).

If corticosteroids are initiated for treatment of toxicity, it is recommended that they are tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisolone before atezolizumab is resumed. Atezolizumab may be omitted for ≤12 weeks to allow for improvement in toxicity and for patients to taper off corticosteroids prior to resuming treatment.

If atezolizumab is withheld for >12 weeks after event onset, the patient will be permanently discontinued from atezolizumab irrespective of toxicity severity.

6 SAFETY

6.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered.
All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure (IB) for an unapproved investigational product.
When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB which occur in a more severe form than anticipated are also considered to be unexpected. Reports which add significant information on specificity or severity of a known documented adverse event are to be considered unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** *
- **Requires hospitalisation, or prolongation of existing hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: *It is the responsibility of the PI or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).*

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

6.2 SERIOUSNESS

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the principal investigator.

All adverse events that fulfil the criteria definition of 'serious' in protocol section 6.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

All SAEs must be reported immediately by the PI or delegate at the participating centre to the SCTU.

6.2.1 Exceptions:

For the purposes of this trial, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Death due to UTSCC
- UTSCC disease progression
- Hospitalisation for elective treatment of a pre-existing condition

6.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the principal investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the MHRA will be informed of both parties' points of view.

Relationship	Description	Denoted
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant treatments).	SAR/ SUSAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

6.4 EXPECTEDNESS

Expectedness assessments are made against the approved Reference Safety Information (RSI). The RSI for this trial is specified within the document version listed in the table below:

Name of Product	IB	Section /Table No.	Manufacturer	Date of text revision DD-MMM-YYYY
Atezolizumab	IB v18	Table 42	Roche	July 2021
For information purposes only:				
Atezolizumab	IB v18 Addendum 1		Roche	July 2021

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AE should be recorded as 'unexpected'.

6.5 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the SCTU in the first instance.

6.5.1 Reporting Details

For all SAEs, SARs and SUSARs an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

Or

Contact SCTU by phone for advice and then email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

The SAE report form asks for nature of event, date of onset, severity, outcome, causality and expectedness. The responsible investigator (or delegate) should assign the seriousness, causality and expectedness of the event with reference to the approved IMP IB and provide version used for the assessment.

The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the NCI CTCAE v5.0.

Additional information should be provided as soon as possible if all information was not included at the time of reporting, but no more than 7 days after initial report.

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Elevations in liver biochemistry that meet Hy's Law criteria are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

6.5.2 Time Frame for Reporting, Follow Up and Post-trial SAEs

The reporting requirement for AEs and SAEs affecting participants applies:

- Between provision of informed consent, and the first dose of atezolizumab: for all AEs and SAEs that are considered by the investigator to be related to trial procedures
- Between the first dose, and 30 days after the last dose of atezolizumab for AEs and SAEs and 90 days after the last does for SAEs

All unresolved adverse events should be followed by the investigator until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

6.5.3 Non-serious AEs

All adverse events (unless specified as exceptions in this protocol) should be recorded in the relevant eCRF and submitted to SCTU.

6.5.4 Adverse Events of Special Interest (AESI)

Atezolizumab's mechanism of action against cancer cells is through enhancing the immune response through binding PD-L1. A number of adverse drug reactions will be considered adverse events of specialist interest (AESI). These are listed below. Please also refer to the atezolizumab Investigator Brochure. AESIs will be reported within 24 hours of discovery to SCTU.

- Infusion related reactions (IRR)
- Cytokine release syndrome (CRS)
- Immune-mediated ocular inflammatory toxicity
- Immune-mediated nephritis
- Immune-mediated vasculitis
- Immune-mediated severe cutaneous reaction
- Autoimmune hemolytic anaemia
- Systemic lupus erythematosus (SLE)
- Hypersensitivity
- Grade >=2 cardiac disorders e.g. atrial fibrillation, myocarditis, pericarditis
- Haemophagocytic lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS)

6.5.5 Accidental Overdose or Medication Error (Special Situations)

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug. In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria or qualifies as an AESI, the event should be reported to the Sponsor according to the rules for SAE or AESI reporting within this protocol. For atezolizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

6.5.6 Pre-existing Conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the condition worsens during the trial. The condition, however, must be reported on the Medical History eCRF. Any adverse events that occur after Informed Consent should be recorded on the AE eCRF as per safety reporting section.

6.5.7 Pregnancy

If a participant or their partner becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP (up to six months following IMP administration), the investigator must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy.

The investigator must immediately notify SCTU of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be completed.

Follow-up is, of course, dependent on obtaining informed consent for this from the participant (or their partner in the case of male trial subjects). Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to SCTU. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

If the participant leaves the area, their new healthcare professional should also be informed.

6.6 **RISKS ASSOCIATED WITH ATEZOLIZUMAB**

Atezolizumab has been associated with risks that include the following: infusion-related reactions, immune mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis,

meningoencephalitis, myocarditis, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome which are considered to be potential risks for atezolizumab.

6.7 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the necessary REC of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU will submit all safety information to the REC in an annual progress report and in the annual Development Safety Update Report.

6.8 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit the Developmental Safety Update Reports to MHRA annually.

7 STATISTICS AND DATA ANALYSES

7.1 SAMPLE SIZE

This study uses a modified Simon's 2-Stage optimal design with best ORR (% with confirmed partial or complete response by RECIST v1.1) at a minimum of 12 weeks from commencing treatment as the primary endpoint. We propose that an ORR of <15% would not warrant further investigation, and an ORR ≥35% would warrant further investigation in a randomised trial. With a one-sided Type I error rate of 0.1, 90% power, p1=15% and p2=35%, up to 19 patients will be recruited into Stage 1. If 4 or more patients out of the 19 in Stage 1 (with a minimum of 12 weeks from commencing treatment) have an objective response (confirmed PR or CR by RECIST v1.1) then the trial will continue with ongoing recruitment to Stage 2 recruiting a maximum of 14 further patients or 33 patients overall. (There is no pause in recruitment whilst the Stage 1 analysis is undertaken.) Otherwise, accrual will close. If 8 or more patients overall have a best objective response by RECIST (confirmed PR or CR) then this intervention will be considered to have clinical activity that warrants further investigation. To account for drop out, up to an additional 3 patients will be recruited, making the final sample size to be a maximum of 36 patients.

7.2 INTERIM ANALYSIS

The IDMC will review the emergent response data from the trial as recruitment progresses, which will be used to make a recommendation on whether to transition from Stage 1 to Stage 2. The Stage 1 interim analysis will occur once 19 patients are recruited and each have reached at least the first 12-week on-treatment response assessment (CT scan) point, or have unequivocal disease progression at an earlier point. Patients withdrawing earlier than the planned week-12 response assessment will be assessed as non-responders for the interim analysis. To allow for late responses occurring beyond 12 weeks, the IDMC will have the option to defer a decision on proceeding from Stage 1 to Stage 2 until all Stage 1 patients have completed 12 months of follow up if this would potentially alter this decision.

The trial will continue recruitment during the Stage 1 interim analysis period to optimise the recruitment rate to the trial. The justification for this is that atezolizumab has a well-established safety and toxicity profile and this is a disease setting with no established alternative treatment options. Patients will be informed of this approach as part of the informed consent process. The IDMC and Trial Management Group will have the option to integrate a recruitment pause between Stage 1 and Stage 2 if they deem this appropriate based on emergent results.

7.3 STATISTICAL ANALYSIS PLAN (SAP)

The trial will be analysed according to the principles of the ICH E9 guidelines and reported using the 'Consolidation Standard of Reporting Trials' (CONSORT) guidelines. A full statistical analysis plan will be developed prior to the final analysis of the trial.

The primary analysis of best ORR will be based on the evaluable population defined as those who have received at least one dose of study treatment. Those who do not receive any treatment will be excluded from the analysis and will be replaced. The best ORR will be calculated as the percentage of patients who achieve either PR or CR according to RECIST v1.1. Patients who do not have a 12-week on-treatment response assessment due to drop out will be considered as treatment failure. A 95% confidence interval for the proportion will be calculated. A secondary analysis will be performed on the ITT population.

For the secondary endpoints, a PFS and OS Kaplan-Meier analysis curve for the ITT population will be displayed. The 95% confidence intervals for median survival will be computed using the method of Brookmeyer and Crowley. Response data will be presented using Waterfall, spider and swimmers plots with all other analyses being descriptive (i.e., medians and IQRs, means and 95% CI and proportions with 95% CI). All adverse events (AEs) and serious adverse events (SAEs) by relatedness will be listed and summarised by system/organ class, grade (CTCAE v5.0) and term (MedDRA) on the safety population (those receiving at least one dose of study drug). Analysis of PD-L1 and other translational parameters are described in Section 8.

8 TRANSLATIONAL RESEARCH

8.1 TRANSLATIONAL RESEARCH SAMPLES

Sites will be provided with an AURORA Trial Laboratory Manual for detailed description of sample collection, handling and shipment processes.

1. **Archival FFPE tumour samples:** will be collected at baseline on all patients. Availability of an archival tumour sample, with an associated linked-anonymised pathology report, for transfer for use in the AURORA trial will be an eligibility requirement for trial entry
2. **Blood samples:** These will be taken at baseline (cycle 2, day 1), at 12 weeks on treatment (cycle 4, day 1) and at the point of disease progression in all patients

Central blood and tumour sample storage will be at the Human Tissue Authority (HTA) licensed Southampton Tissue Bank. All samples will be identified via a unique trial ID number, with linked anonymisation.

8.2 TRANSLATIONAL RESEARCH ANALYSES

Translational endpoint work will address the over-arching hypotheses that markers of immune cell infiltration or activation, or tumour mutational burden, will predict for treatment response to atezolizumab in UTSCC.

Translational objectives are listed in Section 2.2. Analysis plans for translational endpoints to achieve these objectives are described within the AURORA Trial Laboratory Manual.

Analysis of PD-L1 expression is described below. All other translational analyses will be considered exploratory and will be reported as such with descriptive statistics.

Immunohistochemistry will occur within the Department of Histopathology at University Hospital Southampton. The Southampton Experimental Cancer Medicine Centre (ECMC), hosted within the Wessex Investigational Sciences Hub Laboratory, will undertake all other translational endpoints.

In addition, patients will also be asked to sign consent for transfer of samples for use in future analyses, as yet to be defined, linked to the overall objectives of the AURORA trial with collaborators in other research groups who may be in the UK or abroad and in either the academic or commercial sector. All such work would maintain patient confidentiality and anonymisation in presentation of data.

8.3 PD-L1 EXPRESSION STATUS ANALYSIS

The primary translational analysis endpoint within the AURORA trial will assess PD-L1 expression with a cut point of ≥5% PD-L1 positivity by immunohistochemistry (IHC) on tumour-infiltrating immune cells using the Ventana SP142 PD-L1 IHC assay (Ventana Medical Systems, Tucson, AZ). This pragmatic choice was made to be consistent with the approach to selection for clinical use of atezolizumab in urinary tract TCC.5

Sample Size
PD-L1 with a ≥5% cut point for 'high' classification will be considered as the translational analysis of primary interest. Previous studies, looking specifically at UTSCC, have reported PD-L1 'high' rates up to 67% and our preliminary data suggested a rate of 44%. Therefore, for the purpose of demonstrating statistical power estimates for the PD-L1 'high' group, both scenarios are presented. As test failure rates are generally very low (<1%), it is assumed that the full 33 patients will have a PD-L1 result by IHC.

Based on an A'Hern approach, assessing the performance of the PD-L1 groups using the same assumptions for best ORR as used in the modified Simon 2-stage optimal design (i.e. p1=15% and p2=0.35%), with a 20% one-sided alpha (deemed appropriate given the likely smaller sample size):

- A PD-L1 'high' sample size of 21 patients, as in the first scenario, would require 5 or more CR or PR responses to conclude that the minimum required efficacy of 35% is plausible and warrants further investigation, and that the efficacy also exceeds 15% (the ineffective level of activity) with 90% power and 20% one-sided significance
- Similarly, for a sample size of 15 (scenario 2), 4 or more CR or PR responses would have 80% power for 20% one-sided alpha.

Analysis: For the final analysis, given that the final sample size is unknown a priori, the proportion of best ORR in both the PD-L1 'high' and 'low' patients will be presented along with the 90% and 80% one-sided CI for the proportions (based on the exact binomial distribution). If the lower boundary of the CI exceeds 15%, then it will be concluded that the ineffective level of activity has been excluded with 10% or 20% one-sided significance and if also greater than 35% that the minimally effective criteria has also been exceeded.

For descriptive purposes, the odds ratio and corresponding 95% 2-sided CI will also be presented for the difference between the high and low PD-L1 groups.

9 REGULATORY

9.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

10 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

10.1 SPECIFIC ETHICAL CONSIDERATIONS

The SCTU uses the electronic data capture tool called RAVE, which will be used in the AURORA trial for sites to input anonymised trial data. The servers that this database will be held on are based in the USA and therefore being stored outside of the UK and EEA. The Patient Information Sheet and Informed Consent Form shall highlight to patients where the data shall be held.

10.2 ETHICAL APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

10.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

10.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

11 SPONSOR

SCTU, the Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

11.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.2 FUNDING

The AURORA trial is funded by Cancer Research UK with provision of atezolizumab by Roche.

11.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

This study is adopted onto the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

11.4 PARTICIPANT PAYMENTS

Participants will not be paid for participation in this trial.

12 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the TMG, the TSC and the IDMC.

12.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the trial, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the trial.

The AURORA TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The AURORA TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)/ DATA MONITORING AND ETHICS COMMITTEE (DMEC)

(NB for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).

The aim of the IDMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

The AURORA IDMC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other trial committees.

13 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). ECRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

14 DATA SHARING REQUESTS

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

15 MONITORING

15.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU within the required timeframe. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

For central monitoring, Informed Consent Forms will be scanned and sent to SCTU via secure electronic means; to the nhs.net secure account for SCTU, by SafeSend or by encrypted email to a University email account with limited access. Drug accountability forms will be sent electronically to SCTU to allow for review prior to onsite monitoring.

15.2 CLINICAL SITE MONITORING

Sites will be monitored as per the AURORA Trial Monitoring Plan. Sites will be contacted by the SCTU Trial Team/ Monitoring Team to arrange a monitoring visit and request that patient records to be reviewed be made available. Where on-site monitoring is not permitted due to the COVD-19 pandemic, alternative strategies such as remote monitoring will be deployed. These will be fully described in the Trial Monitoring Plan. Clinical site monitoring frequency will be determined by the recruitment figures at each participating centre as detailed in the Trial Monitoring Plan. Triggered site monitoring will occur where required.

15.2.1 Source Data Verification

Upon receipt of a request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

15.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

15.4 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust (UHS) (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, UK Policy Framework for Health & Social Care Research, applicable contracts/agreements and national regulations.

16 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 25 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

17 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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19 APPENDICES

19.1 APPENDIX A: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE V5.0)

Please go to the following website to access the CTCAE Version 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

19.2 **APPENDIX B: RECIST**

Please go to the following website to access RECIST Version 1.1:

https://recist.eortc.org/

19.3 **APPENDIX C: ECOG PERFORMANCE STATUS**

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

19.4 **APPENDIX D: MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS**

Expected side effects – Expected Adverse Events are recorded in the IB as per the versions specified in section 6.4. Please refer to these approved documents for full list of expected side effects.

20 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V1 26-NOV-2021	Initial Submission
V2 03-MAY-2022	**Changes to the contraception changes as per MHRA review**
V3 21-JUL-2022	Changes to the RSI section – update to IB version and clarification of definition of evaluable patient population.
V4 03-MAY-2023	Additional wording added to section 5.2 regarding handling of stock