WINGMEN Protocol

Full title: Windows trial of INsulin-like Growth factor neutralising antibody Xentuzumab in MEN scheduled for radical prostatectomy

Short title: IGF inhibition with xentuzumab prior to radical prostatectomy

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Conflict of Interest statement

Details of potential conflicts of interest are given on page 3.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Trial Office, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee unless authorised to do so.

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Professor Macaulay is a Consultancy Board member for Boehringer Ingelheim. The other authors have no conflict of interest to declare.

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PROTOCOL SYNOPSIS

Full Title of study:	Windows trial of INsulin-like Growth factor neutralising antibody Xentuzumab in MEN scheduled for radical prostatectomy	
Short Title:	IGF inhibition with xentuzumab prior to radical prostatectomy	
Trial Acronym:	WINGMEN	
Clinical Phase:	Phase 0	
Study Design:	Open label, 'window of opportunity' study	
Number of Centres	Single centre	
	Objectives	Endpoints
Primary Endpoint:	Assess the amount of IGF pathway inhibition induced by xentuzumab	Phospho-IGF-1R and phospho-AKT (or downstream target) immunohistochemistry on tissue from biopsy and prostatectomy
Secondary Endpoints:	1. Feasibility of treatment in pre-operative setting 2. Assess safety and tolerability of xentuzumab administered in the pre-prostatectomy setting	1. Number of patients whose radical prostatectomy is performed on schedule after 3 doses of xentuzumab (patients can receive up to 10 doses of xentuzumab if surgery is delayed) 2. Treatment-related adverse events scored using CTCAE v5.0
Tertiary/exploratory Endpoints	1. Assess change in PSA following administration of xentuzumab in the pre-prostatectomy setting 2. Assess changes in tissue markers following administration of xentuzumab in the pre-prostatectomy setting 3. Assess changes in circulating markers following administration of xentuzumab in the pre-prostatectomy setting 4. Correlate changes in IGF-1R expression, IGF axis activity with baseline and post-treatment cancer profile, which may include PTEN status by IHC, tumour mutation status, transcriptional, immune and phospho-proteomic profile	1. Change in serum PSA 2. Changes by IHC and/or immunofluorescence on FFPE tissues in tissue markers e.g. Ki67 index, IGF-1R, RRM2, CD31, immune markers PD-L1, CD4, CD8, FoxP3 3. Changes in circulating markers of response to IGF blockade e.g. IGF-1, insulin, IGFBPs, serum IGF bioactivity, metabolomic profile, PBMC immunoprofilingTumour profiling eg by gene mutation panel, IHC for PTEN, FISH for TMPRSS2-ERG, transcriptional and phospho-proteomic profile, quantification of immune cell infiltration.
Planned enrolment:	20-30 patients	
Target Population:	Men with localised biopsy proven prostate adenocarcinoma, scheduled to be treated by radical prostatectomy.	
Investigational Medicinal Product(s)	Name of drug	Formulation, dose, route of administration
	Xentuzumab	Solution for infusion, 1000mg weekly, IV
Dates for planned trial period	Aug 2021- Apr 2023	
Treatment Duration	3.5-4 weeks (may be 3-10 weeks if standard of care surgery is early/delayed unexpectedly)	
Follow-up duration	6 weeks from date of surgery	

End of study	Last Patient Last Visit

SUMMARY SCHEDULE OF EVENTS

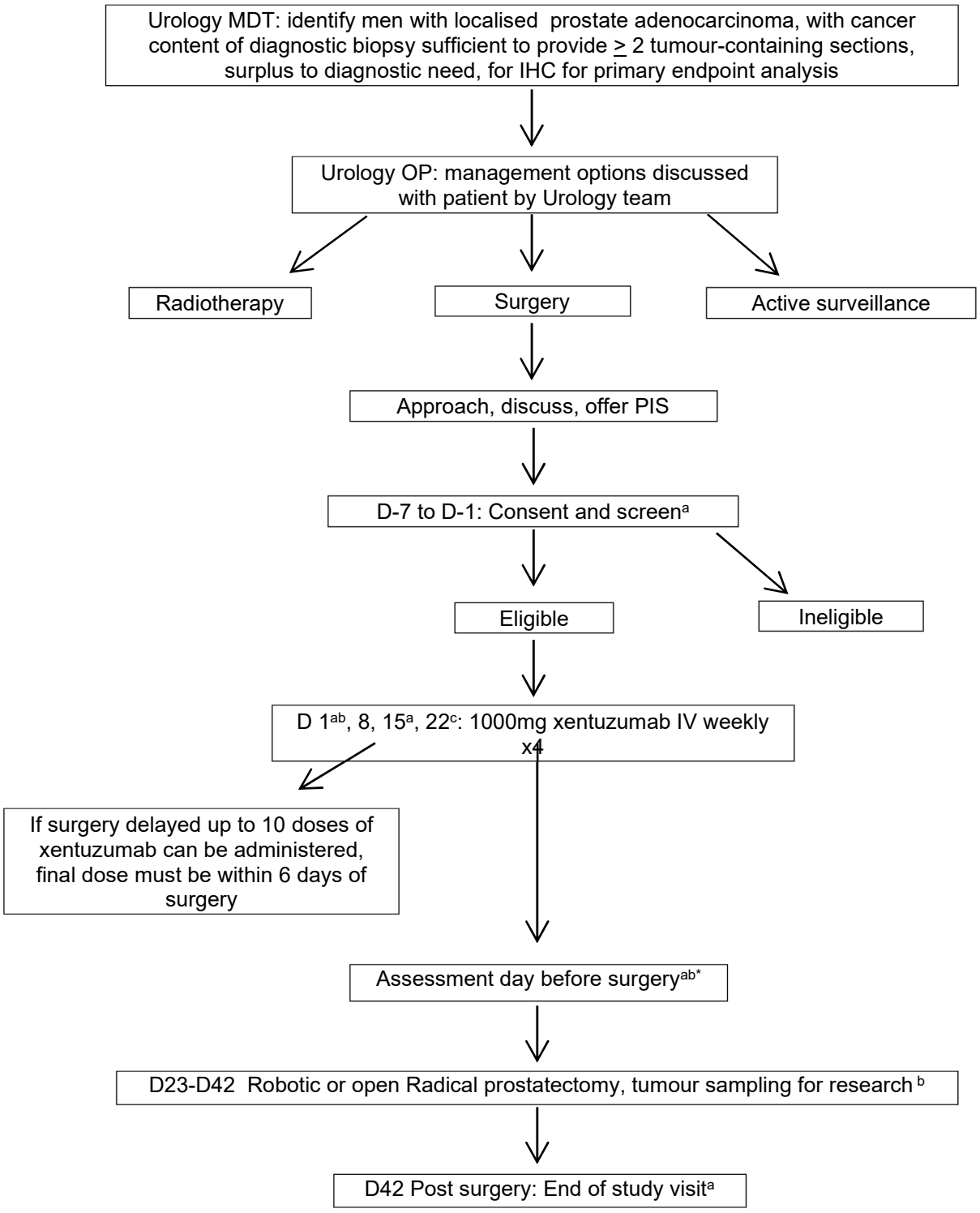
	Initial approach	Consent and screen (day –7 to 0)[b]	Day 1	Day 8	Day 15	Day 22[c]	Day 29 *(participants with surgery delayed beyond day 29 only)*	Day 36 *(and subsequent weeks in participants with surgery delayed only) maximum 10 doses*	Day before surgery (& Early withdrawal)	Surgery (day 24-42 unless surgery has been delayed)	End of study visit (6 weeks after surgery +/- 7 days)
Demographic details		X									
Patient Information sheet	X										
Consent		X									
Medical history		X									
Concomitant medications		X	X	X	X	X[C]	X	X	X		X
Symptoms/Adverse events		X	X	X	X	X[C]	X	X	X		X
Height		X									
Weight		X			X				X		
Physical examination		X	X		X				X		X
ECOG performance status		X			X				X		X
Vital signs (pulse, BP, temperature)		X	X	X	X	X[C]	X	X	X		X
Haematology & biochemistry [a]		X	X[b]	X	X	X	X	X	X		X
Blood PSA, insulin, HbA1c, IGF-1		X	X[b]		X				X		X
ECG		X			X				X		
Retrieval of surplus tissue from diagnostic biopsy for research		X									
Research blood sample(s)			X						X	X	
Xentuzumab infusion			X	X	X	X[C]	X	X			
Radical prostatectomy with tissue collection										X	

[a] **Haematology:** Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets **Biochemistry:** sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose.Patients will have had appropriate standard of care imaging assessments, usually MRI staging, and prostate biopsy, prior to being considered for the trial nb. The red X correspond to research activities

[b] Same day visit results are not required before treatment

[c] Visit not required if only 3 treatments are to be given

Study Flow Chart



[a] Blood PSA, insulin, HbA1, IGF-1 taken
[b] Research blood sample(s) taken
[c] Visit not required if only 3 treatments are to be given [*] Assessment pre-surgery can take place up to 3 days prior to surgery
D=Day OP= Outpatients

Abbreviations

ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse events of special interest
AKT	Protein Kinase B
ANC	Absolute Neutrophil Count
ALT	Alanine Transaminase
AR	Androgen receptor
AST	Aspartate Transaminase
BCT	Blood collection tubes
BrCa	Breast Cancer
CD4	Immune marker
CD8	Immune marker
CDK 4/6	Immune marker
CI	Chief Investigator
CRF	Case Report form
CRPC	Castrate Resistant Prostate Cancer
CTC	Circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumour DNA
D	Day
dATP	Deoxyadenosine triphosphate
DLT	Dose Limiting toxicity
DSMC	Data and Safety Monitoring Committee
EGFR	epidermal growth factor receptor
EoS	End of Study
ES	Ewing Sarcoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
FFPE	Formalin-fixed paraffin-embedded
FOXP3	Forkhead box P3 (Immune protein)
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HbA1c	Glycosylated Haemoglobin
HR	Hazard Ratio
HR+	Hormone Receptor positive
HRA	Health Research authority
IB	Investigator Brochure
IC	Informed consent
IEPTOC	Independent Early Phase Trials Oversight Committee
IGF	Insulin-like Growth Factor
IGF-1R	Type 1 insulin-like Growth Factor Receptor
IGFBP	Insulin-like Growth Factor Binding Protein
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product

INSR-A	Insulin receptor isoform A
INSR-B	Insulin receptor isoform B
IUD	Intrauterine device
IV	Intravenous
KG	Kilogram
LATP	Local Anaesthetic Transperineal biopsy
LRP	Laparoscopic radical prostatectomy
LDH	Lactate Dehydrogenase
LPLV	last visit of the last patient undergoing the trial
MA	Marketing Authorisation
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products regulatory agency
MRI	Magnetic Resonance Imaging
MTD	Maximal tolerated dose
n	Number
NCI	National Cancer institute
NE	Neuroendocrine
NPC	Nasopharyngeal carcinoma
OCTO	Oncology Clinical Trials Office
OP	Outpatients
PBMCs	Peripheral blood mononuclear cells
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PI	Principal Investigator
PIS	Patient Information sheet
PR	Partial Remission
ProMPT	Prostate Cancer mechanisms of response to treatment
PSA	Prostate Specific Antigen
PTEN	Phosphatase and tensin homolog
R & D	Research and Development
RARP	Robot-assisted radical prostatectomy
REC	Research ethics committee
RNA	Ribonucleic Acid
RNR	Ribonucleotide reductase
RP	Radical Prostatectomy
RRM2	Regulatory subunit of ribonucleotide reductase
RSI	Reference safety information
SAR	Serious Adverse Reaction
SD	Standard deviation
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TKI	Tyrosine kinase inhibitor
TMG	Trial management group
TRANSLATE	A randomised controlled trial of TRANSrectal biopsy versus Local Anaesthetic Transperineal biopsy Evaluation (TRANSLATE) of potential clinically significant prostate cancer

TRUS	Transrectal Ultrasound Biopsy
ULN	Upper limit of normal
WBC	White Blood Cells

1 INTRODUCTION

1.1 Background

Prostate cancer is the commonest cancer in men, and is diagnosed in 1 in 8 men in the UK, with over 47,000 men diagnosed annually. Men aged 50 and over, black men and those with a family history of prostate cancer are most at risk. Of men newly-diagnosed with prostate adenocarcinoma, ~55% present with localised (stage T1-T3) disease (1). Under current standard of care, and depending on stage and grade, these patients are offered a choice of active surveillance or radical treatment with radiotherapy or prostatectomy. Radical radiotherapy is delivered with androgen deprivation therapy via external beam or brachytherapy via an implanted radiation source (2). Radical prostatectomy (RP) may be via an open operation, or more often now as laparoscopic (LRP) or robot-assisted radical prostatectomy (RARP). These 3 approaches appear to generate similar outcomes although with shorter hospital stays and reduced blood transfusion requirement after LRP and RARP (3). Radical radiotherapy and RP have side effects that can impair quality of life, including erectile dysfunction, urinary incontinence and bowel symptoms.

Patients on active surveillance are monitored with PSA testing, digital rectal examination and MRI, and are offered radical treatment for rising PSA, upstaging on imaging or Gleason score progression (to 4+3 or greater) on biopsy (4). In the large randomised ProtecT study of mainly low/intermediate risk disease, the incidence of prostate cancer-specific deaths was low (~1%) and similar between treatments, although twice as many men on active surveillance developed disease progression and metastatic disease compared with the RP and radiotherapy groups (5). Of men assigned to active surveillance, ~25-30% require radical treatment within 3 years, and over half by 10 years (4,5). The conversion rate to active treatment may be reduced by incorporation of multi-parametric MRI (6).

While some prostate cancers are indolent and do not threaten life, many are aggressive, and despite treatment, deaths due to prostate cancer remain high. In a survey of >50,000 men diagnosed with prostate cancer in the UK between 1997 and 2006, 49.8% died of prostate cancer (1). New data indicate that prostate cancer kills more men in the UK (11,819 per year) than the number of women killed by breast cancer (https://prostatecanceruk.org/about-us/news-and-views/2018/2/). Therefore, there is a clear need for new treatments, particularly approaches to prevent progression of small indolent prostate tumours to aggressive life-threatening cancers. This could potentially enable more patients to remain safely on active surveillance, avoiding radical treatment. If effective in the active surveillance setting, such approaches may have potential as preventive measures in high risk men.

Insulin-like growth factors (IGFs) -1 and -2 activate type 1 IGF receptors (IGF-1Rs) to promote tumour growth, metastasis and treatment resistance (7). We have identified IGF-1R upregulation in primary and metastatic prostate cancer, showed that IGF-1R associates with radioresistance in prostate cancer cells and clinical cancers, and reported that IGF-1R translocates to the nucleus, upregulating genes that contribute to tumour cell survival and motility (8-13). IGFs cross-talk with androgen receptor (AR) signaling, and mediate resistance to endocrine therapy in prostate cancer (14,15). These properties make the IGF axis an attractive treatment target. However, trials of IGF-1R inhibitory drugs had mixed or negative results, likely due to co-inhibition of the metabolic insulin receptor (INSR-B) causing dose-limiting hyperglycaemia, and compensatory signaling via IGF-2-

mediated activation of variant insulin receptor, INSR-A (16). These problems have been circumvented by antibodies that block the IGF ligands without perturbing insulin actions (17). Dr Macaulay is Oxford Principal Investigator for the BI 836845 trial of IGF neutralising antibody xentuzumab (BI 835845) with enzalutamide in advanced prostate cancer (NCT02204072).

In addition to contributing to advanced disease, IGFs also have an important role at earlier stages in the natural history of cancer. Subjects with rare conditions causing low circulating IGF-1 are almost completely protected from cancer and diabetes (18-20). Conversely, people with high circulating IGF-1 are at increased risk of cancer. This has been shown most robustly for prostate cancer: men with IGF-1 levels in the highest vs lowest quintiles have ~1.4 fold-increased prostate cancer risk (21). IGFs are also implicated in the link between height and aggressive, lethal prostate cancer (22). There is compelling preclinical and clinical evidence that IGF-1 is not just an associated factor, but causative (20,23), although the molecular basis of this association is not understood.

The WINGMEN trial will explore links between IGF-1 and prostate cancer progression. This is a Phase 0 study of IGF antibody xentuzumab in men with prostate cancer in the 3-4-week window prior to radical prostatectomy. The trial will test the feasibility of recruiting men with early prostate cancer, the tolerability of xentuzumab in the pre-operative setting, and will provide pre- and post-treatment samples for assessment of circulating and tissue markers of prostate cancer progression. If effective at downregulating mediators of high IGF-1, this approach has potential to be tested for its ability to reduce the need for radical treatment in men with small cancers on active surveillance. The long-term aims are to prevent prostate cancer progression, identify biomarkers to predict who will benefit from IGF blockade, and identify key mediators that may be targets for risk reduction.

1.2 Investigational Medicinal Product used in the study

The study IMP is xentuzumab, a humanised IgG1 monoclonal antibody that neutralises the IGF ligands to inhibit activation of IGF-1R and INSR-A, suppressing IGF-mediated proliferation, invasion and therapy resistance. Xentuzumab binds IGF-1 and IGF-2 with very high affinity (0.07 and 0.8 nmol/L respectively), with no detectable binding to insulin, and IC_{50} values for inhibition of IGF-1R phosphorylation in response to IGF-1 of 0.6 nmol/L and IGF-2 of 7.5 nmol/L (24). The antibody cross-reacts with murine IGFs, allowing preclinical *in vivo* assessment and revealing anticancer activity in rodent models in combination with rapamycin (24,25). Xentuzumab currently has no marketing authorisation, but in Phase I trials showed evidence of clinical activity with 2 confirmed partial responses at 800 and 1050 mg by weekly intravenous infusion, and 12/48 patients (25%) with confirmed stable disease. At doses of up to 1800 mg xentuxumab was well-tolerated, with no evidence of drug-related hyperglycaemia, and the maximum tolerated dose was not reached. Based on a terminal half-life of ~6 days and ability to inhibit circulating IGF bioactivity, the dose of 1000 mg weekly was selected for Phase II evaluation (26,27).

Xentuzumab is being evaluated in Phase Ib/II trials in EGFR-mutant non-small cell lung cancer with afatinib (NCT02191891), prostate cancer with enzalutamide (NCT02204072) and oestrogen receptor/progesterone receptor positive (ER+/PR+), HER2 negative breast cancer with everolimus and exemestane (NCT02123823). The latter trial reported activity in patients with predominant bone metastases (28), which may reflect preclinical evidence that tumour cells are primed for bone metastasis by high IGF-1 secretion by stromal components of the primary tumour, suggesting that bone metastases may reflect IGF dependency (29,30). These results have prompted a further Phase II trial of xentuzumab with everolimus and exemestane in breast cancer patients with non-visceral disease (NCT03659136). Xentuzumab is also being tested in patients with lung, breast and other solid tumours with CDK4/6 inhibitor abemaciclib (NCT03099174). Initial outcomes of the

randomised Phase II component of the xentuzumab trial in prostate cancer (31) are discussed below.

In light of evidence linking IGF bioactivity with risk and progression of early cancer, WINGMEN is a phase 0 window of opportunity study in men with localised prostate cancer. Xentuzumab will be delivered intravenously at the recommended phase II dose of 1,000 mg/week, administered weekly over 3.5 - 4 weeks on days 1, 8, 15 and 22. This duration has been selected based on three criteria. Firstly, 3 weeks depletion of hepatic IGF-1 supply was shown to modify immune cell phenotypes towards an anti-tumour profile and inhibit metastatic tumour growth *in vivo* (32,33). Secondly, our preclinical data show that xentuzumab has significant anti-tumour activity *in vivo* following 3 weeks' treatment of tumour-bearing mice (30). Thirdly, the current interval between informing patients of their cancer diagnosis and their suitability for surgery and their date of radical prostatectomy is ~5 weeks (personal communication from Professor Hamdy, Nuffield Professor of Surgical Sciences, and Mr Ben Wright, Operational Service Manager, Renal, Transplant and Urology, Surgery and Oncology Division, Oxford University Hospitals NHS Foundation Trust). Therefore, allowing 2-3 days for discussion, consent and screening, this will enable 4 doses of xentuzumab to be administered within a 3.5 – 4 week treatment window, without altering the standard of care surgery dates for trial participants. In the event that a participant's surgery date is earlier than day 29, 3 treatments is sufficient. Equally, if it is later than day 29 a 5th dose of xentuzumab will be given on day 29. In the unlikely event that the participants surgery is further delayed patients can receive up to 10 doses of xentuzumab, the radical prostatectomy surgery must take place within 6 days of the final dose. Participants on the WINGMEN study can have a maximum of 10 doses of Xentuzumab.

1.3 Other research interventions

There are no other research interventions. The surgery received by participants is standard of care.

1.4 Rationale for the study

Non-clinical

Xentuzumab inhibits proliferation of human cancer cells *in vitro*, and increases anti-proliferative effects of exemestane in aromatase overexpressing breast cancer cells, of enzalutamide in prostate cancer cells, and everolimus and rapamycin in Ewing Sarcoma (ES) cells; the combination effects were also demonstrated *in vivo* in ES and prostate cancer xenografts (24) (Xentuzumab IB v11). Xentuzumab also enhances anti-proliferative effects of CDK4/6 inhibitor abemaciclib in breast, pancreatic and non-small cell lung cancer cells (34) (Xentuzumab IB v11). Xentuzumab has comparable affinities for human, rodent and Cynomolgus IGFs, allowing characterization of pharmacodynamic properties and toxicity *in vivo*. After dosing of mice, the majority of serum IGF-1 was bound to xentuzumab, suggesting preferential complex formation over binding to IGFBPs, with increased circulating IGF-1 and GH, consistent with compensation for IGF blockade at the pituitary level (25). After repeated intravenous dosing of rats and Cynomolgus monkeys at up to ~32 mg/kg human equivalent dose, xentuzumab toxicity included weight loss and increase in blood glucose up to but not beyond the upper limit of normal. In rats only, there were dose-related changes in liver function, reduction in reticulocyte, lymphocyte and neutrophil counts, reduction in femoral and tibial trabecular bone, and atrophic changes in the incisors, spleen, thymus, adrenal cortex, ovaries and seminal vesicles (Xentuzumab IB v11). In young (7-8 weeks) rats, xentuzumab induced growth retardation with reduction in weight gain and tail length (Xentuzumab IB v11).

This trial is underpinned by three recent preclinical findings from our group. Firstly, on the basis that effects of IGF-1 are likely to be mediated via its principal receptor, IGF-1R, we studied IGF-1R expression in men undergoing radical prostatectomy who were recruited into the ProMPT study

(NCT00967889, PI Prof Hamdy). We found that high serum IGF-1 associated with IGF-1R up-regulation in malignant but not benign prostatic epithelium, and a trend to association with increased nuclear IGF-1R (Aleksic, Macaulay, unpublished). These data represent the first tissue-level changes associated with circulating IGF-1, and suggest that IGF-1 influences the malignant epithelium of small cancers to drive their progression. Supporting a link between epithelial IGF-1R and cancer risk, investigation of the protective effects of pregnancy on breast cancer risk found prolonged post-partum *Igf1r* hypermethylation in murine mammary epithelium (35).

Secondly, we showed that IGFs regulate expression of RRM2, the regulatory subunit of ribonucleotide reductase (RNR), consistent with reports that RRM2 is a component of a transcriptional signature induced by IGF-1 in breast cancer cells (36). RNR is the rate-limiting step for dNTP production, and when we treat cancer cells with IGF-1, RRM2 is upregulated, leading to 2-3-fold increase in intracellular dATP and dTTP. Conversely, IGF-1R depletion or IGF inhibition with xentuzumab results in significant reduction in RRM2 expression and dATP supply, delaying replication fork progression and inducing replication stress (30). This new finding may contribute to the association of high serum IGF-1 with risk of developing cancer, given the dNTP pool imbalance we identify in IGF-treated cancer cells (30). Balanced dNTP supply is required for the fidelity of DNA replication and genome stability, and dNTP imbalance of the scale we identify upon manipulation of IGF signalling has been shown to be mutagenic in other models (37-39). Therefore, we predict that tumours arising in a high IGF-1 environment will harbour increased mutational load.

Finally, we are investigating whether IGF-1 also promotes cancer progression by influencing metabolism and components of the tumour microenvironment. Our recent data show that IGF-1 upregulates immune checkpoint PD-L1 in human prostate cancer cells (Nandakumar and Macaulay, unpublished), consistent with reported upregulation of PD-L1 by EGFR activation (40). Indeed, there is evidence that IGFs have profound effects on metabolism, tumour vascularization and components of the immune system, promoting the function of immunosuppressive FoxP3+ T regulatory cells (Tregs) and cytokines (41-43). In a murine model, liver-specific IGF-1 depletion for 3 weeks downregulated IGF-1R and suppressed pro-tumorigenic profiles of tumour-infiltrating neutrophils and hepatic stellate cells, inhibiting growth of induced liver metastases (32). Taken together with effects of IGF-1 on RRM2 and dNTP supply that we report (30), we speculate that a high IGF environment influences expression of RRM2 and other pro-mutagenic mediators while suppressing the ability to mount an effective anti-tumour immune response. Investigating this hypothesis will be the focus of this trial. We propose to test this hypothesis by analysing the effect of IGF blockade on tumour and circulating markers in men with early prostate cancer.

Clinical

Table 1 summarises completed and ongoing xentuzumab trials, and toxicities reported in Phase I trials. The drug is well-tolerated and an MTD was not determined in Phase I studies 1280.1 and 1280.2 (26,27). A relevant biological dose of 1000 mg weekly was selected for Phase Ib/II studies based on preclinical and clinical safety data, and anti-tumour activity in studies 1280.1, 1280.2 and 1280.15. Dose selection was also informed by PK/PD data: plasma IGF bioactivity was suppressed down to the detection limits of the assay by xentuzumab 450 mg weekly, and dose-dependent increase in total plasma IGF-1 was found to plateau at ~1000 mg weekly (Xentuzumab IB v11).

Outcomes of the randomised Phase II trials in breast cancer (1280.4, NCT02123823; (28) and prostate cancer (1280.8, NCT02204072; (31) have been recently reported (Table 1). The prostate cancer data are of particular relevance here. In 1280.8, patients with disease progression post abiraterone and docetaxel were randomised to xentuzumab plus enzalutamide vs enzalutamide alone. The most frequent adverse events (AEs) in the xentuzumab plus enzalutamide vs enzalutamide alone arms were: fatigue (67% v 49%); decreased appetite (56% v 54%), weight

reduction (37% v 12%), anaemia (33% v 44%), and back pain (30% v 37%) (31). Therefore, xentuzumab was generally well-tolerated in this population with advanced disease, although AEs in excess in the xentuzumab plus enzalutamide arm were fatigue and weight reduction.

In this Phase II trial there was no overall benefit from addition of xentuzumab, although patients in the enzalutamide arm had more favourable baseline performance status and Gleason score. After post-hoc adjustment for these imbalances there was still no significant benefit from addition of xentuzumab in the overall population (HR 0.86, 95% confidence intervals 0.47 – 1.55, p=0.6113). Subgroup analysis suggested benefit from xentuzumab in patients whose tumours contained high *IGF1* mRNA (HR 0.48 95% CI 0.20 – 1.16) but not low *IGF1* (HR 4.44, 95% CI 1.20 – 16.48; interaction p=0.0123), albeit in a small (n=25) sample (31). There was also a trend to benefit in patients whose tumours contained moderate/high PTEN on immunohistochemistry (p=0.1352; Hussain, de Bono, unpublished). Outcomes have not yet been reported for the non-randomised Phase Ib component, in which xentuzumab was added to enzalutamide on PSA progression.

Table 1: Clinical studies of xentuzumab

Trial/Ref.	Phase	Disease type or indication	No. of pts	Main Toxicities	Outcome
1280.1 NCT01403974 (26)	Phase I	Solid tumours	62	Lymphocyte decrease, no hyperglycaemia, MTD not reached	Weekly 10-1800 mg. Two PRs (NPC at 800 mg; primitive NE tumour 1050 mg) 12 pts (25%) had SD.
1280.2 NCT01317420 (27)	Phase I	Solid tumours	64	Grade 1-2 abdominal pain, constipation, fatigue, reduced appetite, nausea, lethargy. No DLTs, MTD not reached.	Three-weekly 10-3600mg. Four patients had SD; no objective responses.
1280.15 NCT02145741	Phase I	Solid tumours	21		Weekly 750-1400mg.
1280.4 NCT02123823 (28)	Phase Ib/II	HR+ BrCa + everolimus + exemestane (Xe+Ev+Ex) vs Ev+Ex alone.	163	AEs similar between arms Xen+Ev+Ex v Ev+Ex: diarrhoea (44 v 33%), mucositis (39 v 32%), rash (34 v 33%), stomatitis (34 v 38%); most grade 1/2.	Median PFS: Xen+Ev+Ex v Ev+Ex, 7.3 v 5.6 months (HR 0.97, p=0.91). In pts without visceral metastases Xen+Ev +Ex had favourable PFS v Ev+Ex (HR 0.21, p=0.0141).
1280.8 NCT02204072 (31)	Phase Ib/II	CRPC with enzalutamide (Xe+En) vs En alone.	120	AEs in Xe+En vs En: fatigue 67% v 49%; reduced appetite 56% v 54%; weight loss 37% v 12%; anaemia 33% v 44%; back pain 30% v 37%.	Median PFS Xe+En 3.6m v En 6.2m (HR 1.22, p=0.48). PSA response 21% v 19%; max PSA decline -20 v -9 µg/L; max CTC count decline -52% v -35%; CTC response 16% v 11%. Favourable PFS with high tumour *IGF1* mRNA (HR 0.48), not low *IGF1* (HR 4.44; interaction p=0.0123).
1280.16 NCT02191891	Phase Ib/II	NSCLC with mutant EGFR, progression post-TKI, plus afatinib	32		Recruitment completed, results not yet available.
1280.18 NCT03099174	Phase I	Solid tumours, breast cancer, NSCLC, plus abemaciclib	148		Ongoing
1280-0022 NCT03659136	Phase II	HR+ BrCa. non-visceral disease	80		Ongoing

MTD, maximal tolerated dose; PR, partial response; SD, stable disease; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; HR+, hormone receptor positive; AE, adverse event; PFS, progression-free survival; BrCa, breast cancer; CRPC, castrate resistant prostate cancer; NPC, nasopharyngeal carcinoma; NE, neuroendocrine; HR, hazard ratio; CI, confidence intervals; CTC, circulating tumour cells, EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor. Source: (26-28,31), Xentuzumab IB v11.

Covid-19 Risk/Benefit Balance

Cancer remains a fatal disease that continues to kill far more patients daily than COVID-19. The need to identify better treatments through clinical research is not affected by the presence of the pandemic. Pausing such research for months, if not years, until the pandemic subsides will likely result in more deaths as improvements in care are delayed. Nevertheless we have put in place significant mitigations. The COVID-19 risk for potential patients has been minimised as much as possible. The WINGMEN recruitment site, Churchill Hospital, is nominally COVID-19 free, and infected or potentially infected patients are treated at a geographically distinct site (the John Radcliffe Hospital). The following procedures have also been put in place at site:

- All patients (in and outpatients) are screened upon entry to the Churchill site
- Human traffic at the Churchill site is minimal with face to face appointments avoided and staff working from home, whenever possible.
- Face masks/social distancing/level 1 PPE for patient examinations and other protective measures are mandatory for staff at the Churchill site

Furthermore, this trial requires only 6 extra patient visits: screening, 4 treatment visits (unless surgery is unexpectedly delayed) and one visit after completion of treatment and before surgery, for post-treatment blood tests. The post-treatment End-of-Study trial assessment will be held on the same day as the routine 6-week post-operative assessment, and so will not involve an extra hospital visit. There is no evidence that treatment with an IGF inhibitory drug will cause patients to be immunosuppressed. Indeed, given experimental evidence that IGFs themselves can suppress the immune system, it is possible that treatment with xentuzumab could enhance immune responses. Therefore , we accept that extra hospital visits may confer additional COVID risk, but the treatment itself should not increase this risk.

Covid 19 Vaccination Considerations

There is no contraindication to having a COVID-19 vaccination before, during or after the study and participants will be encouraged to do so.

2 TRIAL DESIGN

This is an open label, 'window of opportunity' study investigating whether xentuzumab inhibits IGF signalling and proliferation in patients with localised prostate cancer scheduled for radical prostatectomy. The study is a Phase 0 trial because of the window of opportunity design where treatment-naïve patients are exposed to agent for a very short period of time, and the endpoints are related not to disease outcome but rather to provide a within-patient comparison to quantify IGF axis inhibition and identify mediators of high IGF supply that promote cancer progression. Thirty participants will be recruited at a single trial centre (Oxford University Hospitals NHS Foundation Trust).

Following successful completion of screening, participants will receive 4 weekly intravenous doses of xentuzumab prior to their standard of care prostatectomy, at which samples will be collected for comparison with the participant's diagnostic biopsy. Participants whose surgery is early, may receive only 3 doses, equally if surgery is delayed participants can receive up to 10 xentuzumab doses, patients must receive their prostatectomy within 6 days of their final dose of xentuzumab to be evaluable. Refer to the schedule of events and flow chart for details of the study visits and procedures.

2.1 Duration of patient participation

Participants will be in the study for approximately 12 weeks (if surgery is not delayed) from start of screening to the last follow-up protocol visit 6 weeks after surgery.

2.2 Post-trial care and follow-up

Following radical prostatectomy an end of study visit will be completed and patients will receive standard care.

3 OBJECTIVES AND ENDPOINTS

Primary Objective	**Endpoints/ Outcome measures**	**Time point(s) of evaluation of this end point**
Assess the amount of IGF pathway blockade induced by xentuzumab	Phospho-IGF-1R and phospho-AKT (or downstream target) immunohistochemistry	Baseline diagnostic biopsy vs. tissues from standard of care surgery after xentuzumab. Tissue will be formalin fixed and analysis will take place in batches.
Secondary Objectives	**Endpoints**	
Assess feasibility of treatment in the pre-prostatectomy setting	Number of patients whose radical prostatectomy is performed on schedule after 3 doses of xentuzumab.	Date of surgery
Assess safety and tolerability of xentuzumab administered in the pre-prostatectomy setting	Treatment-related adverse events scored using CTCAE v5.0	AEs reported from study entry to end of study visit
Tertiary/Exploratory Objectives	**Endpoints**	
Assess change in PSA following administration of xentuzumab in the pre-prostatectomy setting	Change in serum PSA	Baseline, day 15, day 29 (if completed), on day before surgery and at end of study visit
Assess changes in tissue markers following administration of xentuzumab in the pre-prostatectomy setting	Changes by IHC and/or immunofluorescence on FFPE tissues in tissue markers e.g. Ki67 index, IGF-1R, RRM2, CD31, immune markers PD-L1, CD4, CD8, FoxP3.	Baseline diagnostic biopsy vs. tissues from standard of care surgery after xentuzumab treatment
Assess changes in circulating markers following administration of xentuzumab in the pre-prostatectomy setting	Changes in circulating markers of response to IGF blockade e.g. IGF-1, insulin, IGFBPs, serum IGF bioactivity, metabolomic profile, PBMC immunoprofiling	Baseline samples vs. samples taken prior to standard of care surgery after xentuzumab treatment
Correlate changes in IGF-1R expression, IGF axis activity with baseline and post-treatment cancer	Tumour mutation profiling by IHC for PTEN and gene mutation panel.	Tissues from standard of care surgery after xentuzumab treatment

profile, which may include PTEN status by IHC, tumour mutation status, transcriptional, immune and phospho-proteomic profile	Tumour profiling eg by gene mutation panel, IHC for PTEN, FISH for TMPRSS2-ERG, transcriptional and phospho-proteomic profile, quantification of immune cell infiltration.Phospho-proteomic profiling of index tumour	Tissue samples taken at standard of care surgery after xentuzumab treatment, with matched historical controls

4 PATIENT SELECTION

Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria. Men with localised prostate adenocarcinoma who are due to undergo a radical prostatectomy will be identified through information provided from the medical records at the weekly Urology Multi-Disciplinary Team (MDT) meeting. An additional check will be made at the MDT to assess the tumour content of the diagnostic biopsy, to ensure that patients are approached only if they have sufficient diagnostic biopsy material, surplus to diagnostic need, for the primary endpoint analysis.

Patients in this study may be co-enrolled on the TRANSLATE diagnostic trial comparing Local Anaesthetic Transperineal biopsy (LATP) to Transrectal Ultrasound (TRUS) biopsy of the prostate. TRANSLATE has a 4-month follow up period and would therefore overlap with the WINGMEN trial. Men will be approached about the TRANSLATE trial before their diagnostic biopsy; those who are subsequently found to be suitable for radical prostatectomy surgery will be approached about the WINGMEN study. Follow-up data collection for men co-enrolled to the TRANSLATE trial would continue; patients co-enrolled in the TRANSLATE trial would still receive questionnaires to complete (relating to Health-Related Quality of Life, symptom, and biopsy-related outcomes) at 7 days, 35 days and 4 months post-biopsy, to complete their post-biopsy follow up. This should not be too burdensome for the patients, and would not compromise recruitment to the WINGMEN study.

4.1 Eligibility criteria for entry into the study

Inclusion criteria:

A patient will be eligible for inclusion in this study if all of the following criteria apply.
1. Men with prostate adenocarcinoma confirmed on prostate biopsy and with sufficient cancer-containing biopsy tissue surplus to diagnostic need to provide ≥2 sections for primary endpoint analysis.
2. Scheduled for open or robotic radical prostatectomy
3. Age ≥ 18 years
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix 1)
5. The patient is willing and able to comply with the protocol scheduled follow-up visits and examinations for the duration of the study
6. Participant is willing and able to give informed consent.
7. Participants whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception during the trial and for 70 days thereafter.
8. Adequate haematologic, renal and hepatic function, defined as follows:

Laboratory Test	Value required
Haemoglobin (Hb)	≥90g/L

White Blood Count (WBC)	>2.5 x 10^9/L
Absolute Neutrophil Count (ANC)	≥ 1.5 x10^9/L
Platelet count	≥ 100 x 10^9/L
AST, ALT, and alkaline phosphatase	≤ 2.5 x upper limit of normal
eGFR*	≥30ml/min

*eGFR calculated by Cockcroft & Gault formula, see appendix 2

Exclusion criteria:

A patient will not be eligible for the trial if any of the following apply:
1. Treated with systemic corticosteroids, insulin, metformin, other oral hypoglycemic agent, or anti-androgens in the 28 days prior to first dose of study drug
2. Diabetes mellitus
3. Previous prostate radiotherapy
4. Current or previous treatment with xentuzumab or other IGF or GH -modifying therapy
5. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV
6. Treatment with any other investigational agent, or treatment in another interventional clinical trial within 28 days prior to enrolment
7. Other psychological, social or medical condition, physical examination finding or a laboratory abnormality that the Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results.

4.2 Protocol deviations and waivers to entry criteria

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements.

Protocol adherence is a fundamental part of the conduct of a clinical study. Changes to the approved protocol need prior approval unless for urgent safety reasons.

Investigators must contact OCTO to obtain guidance and/or clarification as necessary if unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion. OCTO will contact the chief investigator or clinical coordinators as necessary. Investigators should not request a protocol waiver to enter a patient who does not satisfy the selection criteria.

The investigator must document and explain any deviations/violations from the approved protocol. The investigator should promptly report any important violations that might impact patient safety, data integrity or be a possible serious breach (see 19.7 below) to the trial office.

4.3 Re-screening if patient does not meet inclusion/exclusion criteria first time around

If a patient does not meet the inclusion/exclusion criteria initially he can be re-screened, provided it is still possible to complete re-screening and study treatment before the patient's standard of care prostatectomy.

4.4 Patient registration procedure

Potential participants will be identified from patients referred to the Oxford University Hospitals Urology MDT for the management of localised prostate adenocarcinoma, and will be given a recruitment flyer. Patients opting for surgical management will be considered for the trial with an initial approach made to the patient by the patients clinical care team.

Following the initial approach and confirmation of interest in the study, patients will be informed of the aims of the trial, and will be given a Patient Information Sheet (PIS) and have the opportunity to ask questions. Patients who express interest will be contacted e.g. by telephone approximately 24 hours later by a member of the clinical care team and if still interested will be scheduled to attend to provide written informed consent and conduct screening procedures. If potential participants do not meet the screening criteria they will not be able to continue on the study and this will be communicated to them.

A screening log must be kept of all patients considered for the trial including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without patient identifiers. The original must be retained on site.

Before entering a patient onto the study the Principal Investigator or designee will confirm eligibility. If in any doubt the Chief Investigator must be consulted before entering the patient. Details of the query and outcome of the decision must be documented on the registration/ eligibility checklist.
On completion of consent and screen procedures (i.e. before first xentuzumab treatment), site staff will complete the trial registration form and email this to the trial office to confirm the patient's eligibility: octo-WINGMEN@oncology.ox.ac.uk

The trial office will check the information provided and register the patient on the trial. The patient's trial number will then be confirmed by return email to the trial site staff.

4.5 Trial assessments and procedures

Please refer to the Schedule of Events given at the front of this protocol. Details of all protocol evaluations and investigations must be recorded in the patient's medical record for extraction onto the CRF. All study visits will take approximately 2-3 hours, comfort breaks will be provided during this time.

4.6 Informed consent

Potential participants will be given a current, approved version of the Patient Information Sheet and consent form. They will also receive clear verbal information about the study detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have at least 24 hours to consider the information provided and the opportunity to question the Investigator, their GP or other independent parties before deciding whether to participate.

The Investigator who obtains consent must be suitably qualified and experienced. All delegates must be authorised by the Principal Investigator to obtain consent. The Investigator is responsible for ensuring that the trial consent procedures comply with current applicable GCP Regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be satisfied that the patient has made an informed decision before taking consent. The patient and the Investigator must personally sign and date the current approved version of the informed consent form in each other's presence. A copy of the information and signed consent form will be given to the participant. When completed 4 copies of the consent form are required: 1 for the patient; 1 for Investigator Site File and 1 (original) to be kept in the patient's medical notes (at the discretion of the treating hospital) and 1 for the Biobank.

Contraceptive/ Pregnancy counselling

All participants must be advised on the need to use reliable methods of contraception during the study. The advice should include:

(1) The acceptable methods, required for trial subjects with premenopausal female partners, include: condom plus spermicide for the participating male plus another acceptable form of birth control for female partners e.g. female sterilization, implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs). Abstinence is an acceptable method only when this is in line with the preferred and usual lifestyle of the subject.
(2) These precautions should be continued for minimum 3 months after the last dose of study drug.
(3) That any pregnancy in female partners of male trial subjects occurring within 70 days of the last administration of study drug should be notified by the trial participant to the study team. The outcome (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be reported and followed up even if the participant is discontinued from the study.

4.7 Pre-dosing evaluations

The following screening and eligibility assessments must be performed/obtained within the 7 days before the patient receives the first study dose, except where indicated otherwise below.

- Written informed consent
- Demographic details (age, sex, smoking status and self-reported race/ethnicity)
- Medical History: to include current symptoms, cancer history, prior cancer therapies and procedures, reproductive status, smoking history, and clinically significant disease history and concomitant diseases
- Concomitant medications
- Physical examination, which should be symptom driven and include general appearance, examination of cardiovascular system, chest and abdomen. Any abnormality identified at baseline should be recorded
- Height, weight, ECOG performance status (to confirm eligibility) (Appendix 1)
- Vital signs: systolic /diastolic blood pressure (BP), pulse rate and temperature
- Haematology: Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Blood PSA, insulin, HbA1c and IGF-1

- Electrocardiogram (ECG) to confirm fitness for treatment
- Presence of prostate adenocarcinoma on prostate biopsy*
- Confirm availability of surplus tissue from diagnostic biopsy

*Standard of care imaging assessments need not be completed in the 7 day screening period.

4.8 Evaluations during the study

Evaluations on day 1

On the day the first dose of xentuzumab is given:

- Current symptoms, assessment for adverse events
- Concomitant medications
- Physical examination as detailed in 5.2.
- Vital signs: BP, pulse, temperature
- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Blood PSA, insulin, HbA1c, IGF-1
- Research blood samples
- Xentuzumab infusion: to commence after blood has been taken for the above assessments. Xentuzumab infusion can then be started without waiting for the day 1 blood results, provided the screening blood tests were taken within the 7 days pre-cycle 1. The infusion is to be administered over 1 hour (with up to 15 minutes extra if needed for staff time to end infusion). Record time of starting and completing infusion. Patient to be monitored during the infusion and for one hour after the end of infusion. Grade 1 to 2 infusion reactions will be managed by reducing the infusion rate to 2 hours. For symptomatic treatment of infusion reactions hydrocortisone, antihistamines such as chlorphenamine, an antipyretic/analgesic, and/or a bronchodilator may be administered. Severe reactions require immediate and permanent discontinuation of xentuzumab infusion.

Evaluations on day 8 (+/- 1 days)

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature
- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Xentuzumab infusion: administered over 1 hour (may be slowed to 2 hours if required due to infusion reaction, with up to 15 minutes extra if needed for staff time to end infusion). Monitor patient during infusion and for at least 15 minutes after end of infusion as is standard practice. Record time of starting and completing infusion. At clinical discretion patient may then leave if there are no symptoms of infusion reaction, or continue to monitor as appropriate.

Evaluations on day 15 (+/- 1 days)

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature
- Weight

- Physical examination as detailed in 5.2.
- ECOG performance status
- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Blood PSA, insulin, HbA1c, IGF-1
- ECG
- Xentuzumab infusion: administered over 1 hour (may be slowed to 2 hours if required due to infusion reaction, with up to 15 minutes extra if needed for staff time to end infusion). Monitor patient during infusion and for at least 15 minutes after end of infusion as is standard practice. Record time of starting and completing infusion. At clinical discretion patient may then leave if there are no symptoms of infusion reaction, or continue to monitor as appropriate.

Evaluations on day 22 (+/- 1 days) It is acceptable for this visit to be missed for participants whos surgery takes place within 6 days of the 3rd dose

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature
- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Xentuzumab infusion: administered over 1 hour (may be slowed to 2 hours if required due to infusion reaction, with up to 15 minutes extra if needed for staff time to end infusion). Monitor patient during infusion and for at least 15 minutes after end of infusion. Record time of starting and completing infusion. At clinical discretion patient may then leave if there are no symptoms of infusion reaction, or continue to monitor as appropriate.

Evaluations on day 29 (+/- 1 days, **participants whose surgery is taking place after day 29 only)**

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature
- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Xentuzumab infusion: administered over 1 hour (may be slowed to 2 hours if required due to infusion reaction, with up to 15 minutes extra if needed for staff time to end infusion). Monitor patient during infusion and for at least 15 minutes after end of infusion. Record time of starting and completing infusion. At clinical discretion patient may then leave if there are no symptoms of infusion reaction, or continue to monitor as appropriate.

Evaluations on day 36 (+/- 1 days, **participants whose surgery is taking place after day 36 only) - Where prostatectomy is unexpectedly delayed beyond day 36, patients will continue to be dosed with weekly xentuzumab to within 6 days of surgery, up to a maximum of 10 doses in total**

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature

- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH and glucose
- Xentuzumab infusion: administered over 1 hour (may be slowed to 2 hours if required due to infusion reaction, with up to 15 minutes extra if needed for staff time to end infusion). Monitor patient during infusion and for at least 15 minutes after end of infusion. Record time of starting and completing infusion. At clinical discretion patient may then leave if there are no symptoms of infusion reaction, or continue to monitor as appropriate.

Evaluations 1-3 days before surgery (Day 23 - Day 41), non-fasting

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature
- Weight
- ECOG performance status
- Physical examination as detailed in 5.2.
- ECG to confirm fitness for surgery
- Haematology: Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH, glucose.
- Blood PSA, insulin, HbA1c & IGF-1
- Research blood samples, NB take blood same time of day (±3 hr) as Day 1 sample.

Day of surgery (day 24 – 42 unless surgery has been delayed)

Standard of care radical prostatectomy with collection of research tissue samples:

- Core biopsies (2-3) taken in theatre from radical prostatectomy for immediate fixation.
- Fresh frozen punch biopsy from index tumourprocessed fresh or stored as listed in section 6.1 for later analysis.

4.9 End of Study (EoS) evaluations at 6 weeks after surgery (± 7 days)

- Assessment for adverse events
- Concomitant medications
- Vital signs: BP, pulse, temperature
- ECOG performance status
- Physical examination as detailed in 5.2
- Haematology: Hb, WBC with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and ALT, LDH, glucose.
- Blood PSA, insulin, HbA1c and IGF-1

Follow-up evaluations

There is no long-term follow-up as part of the trial. Further follow-up for trial purposes will only be completed if a participant has an ongoing drug-related AE that is related to trial participation at the end of study visit, or if participant's female partner has become pregnant. Participants will otherwise be followed-up post the end of study visit as per standard care post-prostatectomy.

4.10 Evaluations on early withdrawal

Patients who withdraw before starting treatment will have no further trial evaluations. Where possible, patients who have had at least one xentuzumab infusion and withdraw early will complete all evaluations listed for the day before surgery visit. The evaluations listed in the day before surgery visit should be completed as soon as possible from the point of withdrawal, unless the day before surgery visit has already been performed. This is irrespective of whether the participant is due to receive surgery or not. This is not applicable for those who withdraw consent.

5 EARLY PATIENT WITHDRAWAL

Treatment Withdrawal
During the course of the trial, a patient may withdraw early from treatment. This may happen for a number of reasons, including:

- Unacceptable toxicity e.g. severe infusion reaction
- AE/SAEs requiring discontinuation
- Loss to follow-up
- Significant protocol deviation or inability to comply with trial procedures
- Clinical decision
- Patient decision

When the patient stops treatment early, the 'End of Treatment' Form needs to be completed, and any other relevant CRFs (example SAE Form). The reason for withdrawing from treatment early should be clearly documented in the medical records.

Participants who are withdrawn from treatment should complete the same evaluations that are listed in the 'day before surgery' visit. This includes collection of research samples if the patient agrees.

Consent Withdrawal
Consent withdrawal means that a patient wishes to withdraw from the study altogether. Under these circumstances, the site needs to document all relevant discussions in the patient notes and notify the Trial Office, which will allow the office to mark all future CRFs as not applicable. Under these conditions, investigators are still responsible to follow up any SAEs till resolution.

5.1 Patient evaluability and replacement

The trial will be assessed on a modified intention-to-treat basis. Patients who are not evaluable for the primary endpoint may be replaced at the TMGs discretion, this includes:

- Patients who receive fewer than 3 doses of xentuzumab e.g. due to early withdrawal
- Patients who for any reason do not have their planned standard of care prostatectomy
- Patients whose prostatectomy reveals predominantly neuroendocrine/small cell cancer
- Patients from whom diagnostic biopsy or surgical specimens were not taken or were of insufficient quantity or quality for analysis.
- Patients who do not receive their planned standard of care prostatectomy within 6 days of their final dose of xentuzumab.

If patients miss a dose(s) for unavoidable reasons (e.g. participants with covid infection or unable to attend for treatment in the scheduled visit window) they can remain on the trial provided they resume weekly dosing with the final dose of xentuzumab within 6 days of surgery.
All participants who receive one or more doses of xentuzumab will be evaluable for safety analysis.

As noted above, patients withdrawing early after one or more doses of xentuzumab, irrespective of their stage in the trial, will undergo evaluations on the day before surgery.

6 SAMPLES FOR LABORATORY ANALYSIS

6.1 Samples to be analysed

Diagnostic Laboratories
Samples for haematology and biochemistry analysis including analysis of PSA, HbA1c, insulin and IGF-1 will be labelled with standard patient identifiers and sent to the local hospital diagnostic laboratory. Results will be processed in the standard way and entered into the routine hospital reporting system. Samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice.

Pathology
The routine diagnostic biopsies and routine prostatectomy tissue will be labelled, processed for routine haematoxylin and eosin (H&E staining) and reported according to local hospital protocols. Cores from the diagnostic biopsy that are surplus to diagnostic need and research samples from the prostatectomy will be sent for analysis in a central laboratory as per guidance in the following section.

Sample handling
Please refer to the sample handling manual for assay/sample handling and storage.

Blood samples
Blood samples will be obtained from trial subjects by suitably delegated site staff (as detailed in section 5).
•Samples for analysis in the clinical Haematology and Biochemistry Laboratories will be sent as routine samples.
•Blood (25ml) for research analysis will be taken into EDTA or heparin tubes to obtain plasma and PBMCs, serum collection tubes for serum, and into blood collection tubes (BCT) to collect ctDNA and PBMCs. Blood will be processed to plasma, serum PBMCs,circulating tumour DNA (ctDNA) and genomic DNA (gDNA) as detailed in the Sample Handling manual.

Tissue samples
Research cores will be taken in theatre from the prostatectomy for rapid fixation to ensure comparability between the biopsy and prostatectomy and avoid artefacts due to slow fixation of large prostatectomy sample (risk of degradation of phospho-signals), this material is used forIHC. The main prostatectomy sample will be transported fresh to cut-up at the John Radcliffe Hospital. Fresh punch research biopsies will be taken from the tumour and benign area(s) in the radical prostatectomy specimen. These samples may be processed fresh or stored for example by cryopreservation in CS10 medium or snap frozen in liquid nitrogen or dry ice/ethanol. Similarly stored and processed punch biopsies from non-WINGMEN trial radical prostatectomies (e.g. other biobanked samples where appropriate consent has been provided) will serve as controls.

This will be carried out by suitably delegated staff, further detail on sample handling and storage can be found in the WINGMEN sample handing manual.

Formalin-fixed paraffin-embedded (FFPE) tissue blocks from diagnostic prostate biopsies, in-theatre cores and radical prostatectomies will be selected for tumour content by Professor Clare Verrill or other Pathologist, using H&E stained sections (section 7.1 above) as a guide. Blocks will be selected to enable comparison of tumour present in the biopsy with the index tumour in the prostatectomy. Tissue samples will be analysed as per detailed in the WINGMEN sample handling manual.

Samples for biobanking

Participants in this trial will be invited to permit the collection and long term retention of the study samples for use in possible other future research linked to trial data. Consent to participate in the Biobank is optional and not a requirement of participation in the main study.

6.2 Labelling and confidentiality of samples sent

All research samples sent to analytical Laboratories will be labelled with the trial code, trial patient number and date taken. Should a laboratory receive any samples carrying unique patient identifiers the recipient must immediately obliterate this information and re-label.

6.3 Clinical reporting of exploratory research assay results

The results of the WINGMEN trial research assays are exploratory and are not intended to influence the individual patients' medical care. Findings will not be reported routinely to the responsible clinician except in the event that the result might be beneficial to the patient's clinical management e.g. if tumour mutation profiling reveals a clinically relevant actionable mutation.

6.4 Trial sample retention at end of study

The Chief Investigator has overall responsibility for custodianship of the trial samples. Laboratories are instructed to retain any surplus samples pending instruction from the Chief Investigator on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research study any surplus samples may be retained for use in other projects that have received ethical approval or transferred to a licensed tissue bank, in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

6.5 Withdrawal of consent for sample collection and/or retention

A patient may withdraw consent to provide samples for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in the medical record and will inform the Trial Office accordingly. The investigator should discuss with patients the valuable use of samples that have already been provided and under circumstances where these samples have already been processed and anonymised, it would not be possible to destroy such samples.

7 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

7.1 Name of IMP

The unlicensed IMP used in the trial is xentuzumab. Trial specific stock of xentuzumab is provided by Boehringer Ingelheim Ltd.

7.2 Treatment dose

Treatment doses will be given weekly and will consist of 1000 mg of xentuzumab delivered intravenously over 1 hour (+15 minutes optional).

7.3 Duration of treatment

Patients should receive 4 weekly doses of xentuzumab on days 1, 8, 15 and 22, prior to prostatectomy. In the event that surgery takes place later than day 29 a 5th dose should be administered on day 29. If surgery is further delayed up to 10 doses in total can be administered. In the event that surgery takes place prior to day 22, it is acceptable for patients to have only 3 doses. The final dose of xentuzumab should be within 6 days of the scheduled prostatectomy. A maximum of 10 doses of xentuzumab can be given.

7.4 Management of drug administration

Xentuzumab is administered as an intravenous infusion over 1 hour (+15 minutes optional) after dilution in isotonic sodium chloride solution (0.9%).

Patients should be monitored during and after the infusion for any sign of an infusion-related reaction, such as chest tightness, shortness of breath, flushing, tremor or rash. Patients must be monitored for 1 hour after the first infusion but at the clinician's discretion may be monitored for less than an hour after subsequent infusions as is standard practice, provided no symptoms of an infusion reaction have been observed.

In the event of an infusion reaction appropriate therapy should be initiated (e.g. corticosteroids/antihistamines) as per standard local policy. For mild to moderate infusion reactions a slower infusion rate and prophylactic antihistamines may be indicated for future infusions, refer to further guidance in section 7.6. Severe infusion reactions require immediate and permanent discontinuation of infusion.

If patients miss a dose(s) for unavoidable reasons (e.g. participants with covid infection or unable to attend for treatment in the scheduled visit window) they can remain on the trial provided they resume weekly dosing with the final dose of xentuzumab within 6 days of surgery.

7.5 Special precautions

In common with other monoclonal antibodies xentuzumab may cause an infusion reaction in a minority of patients and this may be severe. Xentuzumab should be given under close supervision of medically qualified staff and with availability of resuscitation facilities.

7.6 Dose modification

All doses of xentuzumab will be 1000mg with no dose reduction. In the event that a patient experiences unacceptable toxicity at this dose, the patient should be withdrawn from further treatment.

Infusion reactions

In the event of mild to moderate infusion reaction a slower infusion rate may be used, the infusion duration doubled from 1 to 2 hours. Treatment with an antihistamine/corticosteroid may also be given, per standard local policy. Severe infusion reactions require immediate and permanent discontinuation of infusion.

Management of other toxicities

Patients with advanced cancer treated with xentuzumab in previous trials have experienced drug-related adverse events including decreased appetite, nausea, diarrhoea, constipation, fatigue, reduced weight, infusion-related reaction, reduced WBC and hyperglycaemia. The majority of drug-related AEs have been of grade 1-2 (Xentuzumab Investigator Brochure). Refer to the current xentuzumab IB for guidance on management and give symptomatic treatment as appropriate. In the event of unacceptable toxicity, the patient should be withdrawn from further treatment.

7.7 Compliance

All doses of xentuzumab will be delivered intravenously at the research site. Site staff will document compliance with the protocol specified treatment schedule.

7.8 Management of overdose

In the case of xentuzumab overdose the patient should be monitored for evidence of toxicity and standard supportive treatment provided based on any signs or symptoms experienced.

Administration of a dose of study drug exceeding that permitted by the trial protocol should be notified to the trial office. Any toxicity resulting from administration of an overdose of study drug should also be reported as an adverse event/ serious adverse event (as appropriate) as per reporting processes detailed in section 10.

8 OTHER TREATMENTS (NON-IMPs)

8.1 Support medication

Local policy may be followed for anti-emetics and for antihistamines/corticosteroids in the event of an infusion reaction.

8.2 Concomitant medication and non-drug therapies

Concomitant medication may be given as medically indicated. All patients will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to the first treatment visit. They must also inform the Investigator about any new medication started while on the trial.

Details must be recorded in the medical record and the appropriate CRF including indication, doses, frequency and start/stop dates) of concomitant medication taken during the trial until the completion of the off-study visit.

8.3 Prohibited therapies

Patients should not be prescribed any other anti-cancer or investigational therapies while participating in this study. In addition, the following are prohibited:

- Systemic corticosteroids (unless required for treatment of an infusion reaction)
- Insulin, metformin or other oral hypoglycemic agents (unless indicated to manage an adverse reaction of altered glucose metabolism)
- Anti-androgens

8.4 Drug Interactions/ Potential Drug Interactions

There are currently no known clinically significant drug interactions for xentuzumab. However, as the IMP is relatively new interactions may exist that are as yet unknown. Investigators should refer to the current Investigator Brochure for the latest information on drug interactions.

8.5 Post-Trial Treatment

There will be no provision of the IMP beyond the trial treatment period.

9 DRUG MANAGEMENT

9.1 Drug supplies

Xentuzumab is supplied as liquid formulation containing xentuzumab 10 mg/mL in 20 ml in individually boxed vials (200 mg xentuzumab/vial). The excipients are L-Histidine/L-Histidine hydrochloride monohydrate, mannitol, sucrose, polysorbate 20, and water for injection.

Xentuzumab will be supplied free of charge by Boehringer Ingelheim KG and QP released to Almac who will do a second QP release to site pharmacy.

Any required supportive medication is to be sourced and funded locally.

9.2 Drug ordering

The initial supply of xentuzumab will be supplied direct to site via temperature-controlled shipment by Almac, once Boehringer Ingelheim are informed by the Trial Office that all required approvals are in place. Subsequent supplies will be ordered by the Trial Office in batches. The ordering process will be described in detail in the WINGMEN pharmacy manual.

OCTO will closely monitor the use of supplies and ensure that adequate supplies are in place prior to each patient being recruited. Close communication will be maintained between Trial team and the pharmacy to ensure that recruitment and treatment are managed appropriately.

9.3 IMP Receipt

A copy of each delivery note and temperature monitoring form should be scanned and emailed as a PDF attachment to Boehringer Ingelheim Clinical Trials Supply Unit (CTSU) & the OCTO Trials Office (octo-wingmen@oncology.ox.ac.uk). The original should be kept in the Pharmacy File. If supplies are damaged on arrival contact the Trial Office. Damaged supplies should be destroyed on site and a Drug Destruction Log completed.

9.4 Handling and storage

Xentuzumab is supplied as a liquid formulation at 10 mg/mL in 20 mL single use vials, which contain 200 mg of xentuzumab per vial. Unopened vials of xentuzumab should be kept in the original outer carton and refrigerated at 2-8^{o}C in a safe, secure refrigerator. Do not freeze.

The investigator or an authorised designee will ensure that xentuzumab is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

9.5 Labelling

The supplied xentuzumab vials will have been labelled by Boehringer Ingelheim KG for clinical trial use as per the requirements of Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP).

Site pharmacies are permitted to add additional labels to the IMP at site as per standard local procedures (e.g. addition of patient identifiers) providing the original label is not obscured.

9.6 Dosing dispensing

Xentuzumab should be prepared in site pharmacy for administration using aseptic technique, by dilution in 0.9% sodium chloride in an infusion bag. Diluted solutions can be stored at room temperature (≤25ºC) for up to 6 hours before administration. Infusion bags containing xentuzumab diluted solutions may also be stored up to 24 hours at 2-8ºC, provided that the solution was prepared under controlled, aseptic conditions, followed by a maximum of 6 hours at room temperature (≤25ºC) before administration. Prior to use and after dilution, the vials and infusion bag should be inspected for particulate matter or discolouration. If either of these changes is detected, xentuzumab solutions should not be used

9.7 Drug accountability

Drug accountability is the responsibility of the site pharmacist listed on the trial delegation log. Full drug accountability records must be maintained for xentuzumab. The site pharmacy may amend the Drug Accountability Logs provided by the trial office or use their own documentation if it captures all the information requested on the Drug Accountability Logs and has been approved by the Trial Office in advance.

Copies of completed accountability logs must be supplied to the trial office on request.

9.8 Drug returns from patients

There is no requirement to collect patient returns (this is not applicable as all treatment doses will be delivered at the trial site).

9.9 Drug destruction

Disposal of xentuzumab will be according to the table below.

The original Drug Destruction logs should be placed in the Pharmacy File and a copy scanned and emailed to octo-wingmen@oncology.ox.ac.uk.

Used / partially used vials	Disposal at site according to local hospital policy.
Expired drug	Disposal at site according to local hospital policy. Documented on Drug Destruction Log.
Drug left unused	Once authorised to do so, any unused drug should be disposed of at site according to local hospital policy. A Drug Destruction Log should be completed.

9.10 Occupational safety

The product is not expected to pose an occupational safety risk to site staff under normal conditions of use and administration.

10 SAFETY REPORTING

The Investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Should an Investigator become aware of any study drug related SAEs following this period these must also be reported as stated below. Adverse event monitoring starts from the time the patient consents to the study until they complete the trial. All reportable AEs will be followed to a satisfactory conclusion. Any reportable drug-related AEs that are unresolved at the end of treatment visit are to be followed up by the Investigator until resolution or stabilisation.

All AEs reported to the trial office will be processed according to internal SOPs. The trial office may request additional information for any AE as judged necessary. De-identified safety data will be made available to Boehringer Ingelheim to facilitate pharmacovigiliance monitoring of xentuzumab.

10.1 Adverse Event Definitions

An Adverse Event or experience (AE) is any untoward medical occurrence in a study subject temporally associated with the administration of an investigational medicinal product (IMP) or a comparator product, whether or not considered related to the IMP or a comparator product. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and /or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

A Serious Adverse Event (SAE) is any AE, regardless of dose, causality or expectedness, that:

• **Results in death**	
• **Is life-threatening**	This refers to an event in which the subject 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.
• **Requires in-patient hospitalisation or prolongs existing inpatient hospitalisation**	In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
• **Results in persistent or significant incapacity or disability**	This means a substantial disruption of a person's ability to conduct normal life functions. It does not include

	experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which do not constitute a substantial disruption.
• **Is a congenital anomaly or birth defect**	
• **Is any other medically important event**	Defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any new primary cancer must be reported as an SAE regardless of the discontinuation of study medication up until the end of study visit.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified by Boehringer Ingelheim at the WINGMEN project level as being of particular concern for prospective safety monitoring and safety assessment within this trial AESI need to be reported to the OCTO safety team via the same method and within the same timeframe that applies to SAE reporting.

The following are considered as AESIs in the WINGMEN study :

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

> **For patients with normal ALT and AST levels at baseline:**
> An elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or ALT and/or AST elevations ≥10 fold ULN.

Patients with abnormal liver function tests must have their abnormalities and the etiology documented in detail as baseline conditions. Every effort should be made to explain possible deteriorations of baseline conditions. These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test.

An Adverse Drug Reaction (ADR) is an AE which is considered to be causally related to any dose of the IMP. This means that a causal relationship between the IMP and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

An Unexpected Drug Reaction is an adverse drug reaction, the nature or severity of which, is not consistent with applicable product information (referring to information in SPC or IB).

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information

(e.g. Investigator's Brochure for an unapproved investigational product or SPC for an approved product).

10.2 Clinical laboratory abnormalities and other abnormal assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays and scans) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above. By definition, **all Grade 3 or 4 laboratory abnormalities should usually be reported as SAEs**. However, if a lab result is categorised as CTCAE grade 3 or 4 but did not fulfil the safety reporting criteria for an SAE (e.g. asymptomatic, not life threatening, no intervention required) it is the clinician's decision whether to report the event. If the event is not reported the reason why should be documented in the patient notes.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.3 Determining adverse event causality

A Serious Adverse Reaction (SAR) is a SAE that may be related to trial treatment. The assessment of "relatedness" must be determined by a medically qualified individual and is primarily the responsibility of the PI at site or agreed designee. SAEs that will be considered related will include any SAE that is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using the Table below.

The Investigator must endeavour to obtain sufficient information to confirm the causality of the adverse event (i.e. relation to surgery, study drug, background treatment, other illness, progressive malignancy etc) and give their opinion of the causal relationship between each AE and study drug. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further specialist opinion.

Classification	Relationship	Definition
Drug-related	**Definitely related**	• Starts within a time related to the study drug administration *and* • No obvious alternative medical explanation.
	Probably related	• Starts within a time related to the study drug administration *and* • Cannot be reasonably explained by known characteristics of the patient's clinical state.
	Possibly related	• Starts within a time related to the study drug administration *and*

		• A causal relationship between the study drug and the adverse event is at least a reasonable possibility.
Not drug related	**Probably not related**	• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.
	Definitely not related	• The AE is definitely not associated with the study drug administered.

10.4 Reference safety information (RSI) for assessment of expectedness

The reference safety information (RSI) for the trial is section 7.6.2 of the xentuzumab IB and lists all the expected side effects associated with the use of xentuzumab. The assessment of expectedness of reported SAEs will be made by the PI or an appropriately trained member of the site staff. A copy of the current OCTO, CI and MHRA approved version of the RSI document must be held in the Site File for reference. Any change or update to the RSI during the trial will be made via substantial amendment.

At the time of writing the only expected SAR for xentuzumab is infusion related reaction. Serious infusion reactions have been experienced by 3 out of 368 patients receiving xentuzumab in blinded clinical trials. A further 11 patients experienced non-serious infusion reactions.

10.5 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

All SUSARS must be reported to the responsible Authority and main REC by the Trial Office within the required timelines:

- Fatal or life threatening SUSARs will be reported within 7 days of the Trial Office receiving the initial report. Any additional information will be reported within 8 days of sending the first report.
- All other SUSARs will be reported within 15 days of the Trial Office receiving the initial report

In addition, other safety issues qualify for expedited reporting where they might materially alter the current risk assessment of an IMP or be sufficient to change IMP administration or the overall conduct of the trial.

10.6 Expedited reporting of SAEs

The following SAE reporting requirements apply regardless of the Investigator's assessment of the causality or expectedness of the SAE. All SAEs should be reported on the trial SAE report form (see SAE report form and completion guidelines).

If a Serious Adverse Event occurs that requires reporting, a Serious Adverse Event reporting form should be completed and scanned and emailed as a PDF attachment within 24 hours of becoming aware of the event to:

Pharmacovigilance Office, OCTO
Email: octo-safety@oncology.ox.ac.uk

If the SAE has not been reported within the specified timeframe, a reason for lateness must be provided when sending the SAE Report Form. Investigators should also adhere to their local Trust policy for incident and SAE reporting in research.

10.7 Follow-up of Serious Adverse Events

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE is a suspected SUSAR then follow up information must be provided as requested by the trial office.

If new or amended information on a reported SAE becomes available, the Investigator should report this on a new SAE form using the completion guidelines. If using the original form to notify further information, you must initial and date all new or amended information so that all changes are clearly identified.
SAEs that are considered to be definitely unrelated to the trial intervention will not be followed up and monitored, unless Boehringer Ingelheim KG assess the de-identified SAE differently based on previous company experience with the drug. In this unusual scenario Boehringer Ingelheim KG may request some further information in order to make their assessment.

OCTO will collaborate with the reporting site in order to obtain additional information. However, Boehringer Ingelheim KG may not override the assessment of causality given by the reporting investigator or the nominated clinician who reviews each event. Boehringer Ingelheim KG's assessment will not be included in the TMF.

10.8 Reporting Adverse Events on the CRF

All AEs, including Serious AEs must be recorded on the case report forms (CRF) for that patient (unless otherwise specified in section 10.9). The information provided will include date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome and relationship of the AE to study drug. Any concomitant medications or other any therapy used to treat the event must be listed. The Investigator will provide an "other" cause for serious AEs considered to be unrelated to the study drug. Sites should ensure data entered into the CRF is consistent with the SAE report information where applicable.

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

AEs which are serious must be reported to OCTO from the time of consent up to and including the Day of the End of Study visit. Any SAE that occurs at any time after completion of medication treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator consider to be related to any study drug must be reported to OCTO.

Terms and Grading of Events
All adverse events and toxicities must be graded according to the NCI Common Terminology Criteria for adverse events (NCI-CTCAE) Version 5.0.

10.9 Events exempt from being reported as AE/SAEs

Progression of underlying disease
As this is a short duration window of opportunity study in a population with localised disease suitable for radical prostatectomy, patients are unlikely to experience disease progression while on study. However, in the event of disease progression and resultant death this will be captured on the CRF. Adverse events including hospitalisation that are clearly consistent with disease progression will not be reported as individual AE/SAEs. Clinical symptoms of progression will only be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms, but is not supported by tumour measurements, or disease progression is so evident that the investigator may elect not to perform further disease assessments.

Death on study
Death due to disease under study is to be recorded on the Death CRF form providing the death is not unexpected or if a causal relationship suspected. The investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to the study IMP or other protocol treatment intervention is suspected.

Elective admissions and supportive care
Elective admissions to hospital for patient convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting. Hospital admission for prostatectomy is considered standard for this patient group and should not be reported as an SAE. However, if an elective admission is prolonged due to an event that meets the criteria for a serious adverse event this should be reported as an SAE.

10.10 Informing Investigators of new safety information

The Trial Office or the Chief Investigator will ensure that all investigators are kept informed in a timely manner, as new safety profile information becomes available. Investigators are responsible for briefing their study team and onward transmission to their R&D office as appropriate.

10.11 Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

For assessment of SARs in the DSUR, the RSI that was approved at the start of the safety reporting period will be used. When there has been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

11 PREGNANCY

All participants in this trial will be male. In the event that the partner of a participant becomes pregnant during trial participation this will require expedited reporting. A pregnancy form should be completed and scanned and emailed to the trial office within the same timelines as an SAE. All reported pregnancies should be followed and the outcome reported using the same form. If the outcome of the pregnancy meets any of the criteria for seriousness, it must also be reported as an SAE. Examples of pregnancy outcomes that are SAEs include reports of:

- congenital anomalies or developmental delay, in the foetus or the child.
- foetal death and spontaneous abortion.
- suspected adverse reactions in the neonate that are classified as serious

12 DEFINING THE END OF TRIAL

For this study the end of the trial is defined as "The last visit of the last patient undergoing the trial (LPLV)". The study will be stopped when the stated number of patients to be recruited is reached and all participants have reached their final study visit.

The sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

13 STATISTICAL CONSIDERATIONS

13.1 Sample size and power

In a preclinical prostate cancer model, xentuzumab suppressed IGF-1R phosphorylation (pIGF-1R) with an effect size of 0.68 (G*Power v3.1). Using Wilcoxon signed rank test, matched pairs, 2-tailed), recruitment of 20 patients (20 matched pre/post-treatment pairs) will be significant with 80% power, alpha = 0.05. Using a one-tailed test based on the hypothesis that xentuzumab will reduce pIGF-1R, we will need 16 patients, 16 matched pairs of tissue. We will recruit 20-30 patients in case some prostate biopsies are inadequate or unsuitable for translational studies.

14 STATISTICAL ANALYSIS PLAN

Change in phospho-AKT (or downstream target) and phospho-IGF-1R immunoreactive score before and after treatment will be assessed using the Wilcoxon matched pairs signed rank test. Changes in PSA and other IHC markers including Ki67 index, IGF-1R, RRM2, CD31 and immune markers CD4, CD8, PD-L1, FoxP3 will be assessed using a paired samples t-test or a Wilcoxon matched pairs signed rank test if normality assumptions are not satisfied.

The severity of adverse events (AE) will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Adverse events will be summarised; highest grade per patient AE summaries will be presented, according to whether the AEs are considered treatment-related or not, and over time.

A detailed statistical analysis plan will be written and will be finalised before any analysis is undertaken. The analysis plan will be written in accordance with current Standard Operating Procedures.

14.1 Inclusion in analysis

Patients with both pre- and post-treatment data will be included in the analysis, regardless of whether or not they completed xentuzumab treatment. All patients will be included in the safety analysis.

14.2 Subgroup analysis

The Phase II trial of xentuzumab with enzalutamide in men with metastatic prostate cancer suggested benefit from xentuzumab in patients whose tumours contained high *IGF1* mRNA (31), with a trend to benefit in patients whose tumours contained moderate/high PTEN by immunohistochemistry (Hussain, de Bono, unpublished). It has also been reported that relatively high serum IGF-1 associates with benefit from IGF axis inhibition (reviewed in (16). Therefore, we will analyse changes in tumour and circulating markers in:

- Men whose tumours contain moderate/high PTEN vs low/negative PTEN by IHC;
- Men with baseline serum IGF-1 values above the median vs below the median;
- Men whose tumours contain *IGF1* mRNA above the median vs below the median, if we are able to perform transcriptomic profiling on baseline prostate biopsy material (section 7.2).

14.3 Interim Analyses

There will be no interim analysis or early stopping rules.

14.4 Procedures for reporting any deviation(s) from the original statistical plan

Any deviation(s) from the original statistical plan will be documented and described and justified in the final study report.

14.5 Final analysis

Based upon projected accrual rates, this trial is expected to complete recruitment within 24 months of opening to recruitment. Final analysis will begin after all patients have reached the end of study (or prematurely withdrawn) and when central laboratory assay results required for primary, secondary and tertiary/exploratory objectives are available for analysis.

15 TRIAL COMMITTEES

15.1 Trial Management Group (TMG)

The Chief Investigator will chair a TMG responsible for overseeing the successful conduct and publication of the trial. The TMG will include the Chief Investigator, Co- Investigators, Trial Manager, Trial Statistician and others as required. TMG membership and decision making procedures will be documented in the TMG charter.

15.2 Data and Safety Monitoring

There is no Data and Safety Monitoring Committee (DSMC). An independent Trial Steering Committee (IEPTOC) will be in place to monitor the safety and progress of the trial.

15.3 Trial Steering Committee

The Independent Early Phase Trials Oversight Committee (IEPTOC) will fulfil the role of Trial Steering Committee. IEPTOC is an existing committee which provides oversight of several trials managed by the Oncology Clinical Trials Office and includes independent external committee members. IEPTOC will provide overall supervision of the safe and effective conduct of the trial according to its charter.

At least annually it will review trial progress against agreed milestones, adherence to protocol, patient safety and consider new information.

16 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan. See section on patient confidentiality for information on management of personal data.

16.1 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 which could be electronic or paper (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographsand correspondence.

Primary Objective	Endpoint	Data required	CRF data	Non-CRF	Source data	Source data location
Assess the amount of IGF pathway blockade induced by xentuzumab	Phospho-IGF-1R and phospho-AKT (or downstream target) immunohistochemistry	IHC Sample analysis Results	No	Yes	Central laboratory records/ data files/ meta data	Central Laboratory- Oxford University
Secondary Objectives	**Endpoints**	**Data required**	**CRF data[1]**	**Non-CRF[2]**	**Source data**	**Source data location**
Assess feasibility of treatment in the pre-prostatectomy setting	Number of patients whose radical prostatectomy is performed on schedule after 3 doses of xentuzumab.	Metrics from treatment data	Yes	No	Patient notes	Patient notes
Assess safety and tolerability of xentuzumab administered in the pre-prostatectomy setting	Treatment-related adverse events scored using CTCAE v5.0	Adverse events	Yes	No	Patient notes	Patient notes
Tertiary/ Exploratory Objectives	**Endpoints**	**Data required**	**CRF data[1]**	**Non-CRF[2]**	**Source data**	**Source data location**
Assess change in PSA following administration of xentuzumab in the pre-prostatectomy setting	Change in serum PSA	Sample analysis results	No	Yes- Results from sample analysis	Central laboratory records/ data files/ meta data	Central Laboratory- Oxford University
Assess changes in tissue markers following administration of xentuzumab in the pre-prostatectomy setting	Changes by IHC and/or immunofluorescence on FFPE tissues in tissue markers e.g. Ki67 index, IGF-1R, RRM2, CD31, immune markers PD-L1, CD4, CD8, FoxP3.	IHC Results Multiplex immunofluorescence (mIF)	No	Yes- Results from IHC and mIF analysis	Central laboratory records/ data files/ meta data	Central Laboratory- Oxford University

Assess changes in circulating markers following administration of xentuzumab in the pre-prostatectomy setting	Changes in circulating markers of response to IGF blockade e.g. IGF-1, insulin, IGFBPs, serum IGF bioactivity, metabolomic profile, PBMC immunoprofiling	Sample analysis results	No	Yes	Central laboratory records/ data files/ meta data	Central Laboratory- Oxford University
Correlate changes in IGF-1R expression, IGF axis activity with baseline and post-treatment cancer profile, which may include PTEN status by IHC, tumour mutation status, transcriptional, immune and phospho-proteomic profile	Tumour profiling eg by gene mutation panel, IHC for PTEN, FISH for TMPRSS2-ERG, transcriptional and phospho-proteomic profile, quantification of immune cell infiltration.	Sample analysis results	No	Yes	Central laboratory records/ data files/ meta data	Central Laboratory- Oxford University

CRF data: captured in OpenClinica eCRF. Database held on server hosted by Oxford University; **Non-CRF Data**: For data that are not being collected in OpenClinica CRFs, it is necessary to have quality control at every step: database validated, restricted access, version control, audit trail, evidence of training and qualification or supervision by trained and qualified person.

16.2 Database considerations

Data management will be performed via a web-based, bespoke trial database (OpenClinica). OpenClinica is a dedicated and validated clinical trials database designed for electronic data capture. See: http://www.openclinica.org. The trial office will provide sites with instructions and a video link for training purposes.

The participants will be identified by a unique trial specific number which will be provided once the patient has been registered on the study, and year of birth. The name and any other identifying detail will NOT be included in any trial data electronic file.

16.3 Case reports forms (CRFs)

The Investigator and study site staff will ensure that data collected on each subject is recorded in the CRF as accurately and completely as possible. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s). CRFs entries will not contain any source data (unless otherwise specified in the completion instructions provided by the trial office). It is important to ensure that:

- the relevant CRFs are completed.
- all CRF data are verifiable in the source documentation or the discrepancies must be explained.
- CRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible.
- Data queries are resolved and documented by authorised study staff in a timely fashion. The reason for the change or correction should be given where appropriate.
- As much data as possible is entered and cleaned in preparation for each study database lock point.

Note: 'in a timely fashion' means within no more than 10 working days of the initial event and within 28 days of receipt of a data query unless otherwise specified.

The above considerations also apply to patients who are withdrawn early. If a patient withdraws from the study, the reason must be noted on the appropriate form and the patient must be followed-up as per protocol.

16.4 Accounting for missing, unused, or spurious data.

The statistical analysis plan will describe the procedure for accounting for missing, unused or spurious data.

17 CLINICAL STUDY REPORT

All clinical data will be presented at the end of the study as data listings. These will be checked to confirm the lists accurately represents the data collected during the course of the study. The trial data will then be locked and a final data listing produced. The clinical study report will be based on the final data listings. The locked trial data may then be used for analysis and publication.

18 STUDY SITE MANAGEMENT

18.1 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete the delegation log provided prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

18.2 Study site set up and activation

The Principal Investigator leading the investigational study site is responsible for providing all required core documentation. Mandatory Site Training organised by the trial office must be completed before the site can be activated. The Trial Office will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the trial database and able to enter patients.

18.3 Study documentation

The trial office will provide an Investigator File and Pharmacy File to each investigational site containing the documents needed to initiate and conduct the study. The trial office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

19 REGULATORY AND ETHICAL CONSIDERATIONS

The Sponsor and Investigators will ensure that this protocol will be conducted in compliance with the UK Clinical Trials Regulations[1] and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

19.1 Ethical conduct of the trial and ethics approval

The protocol, patient information sheet, consent form and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC). Principal Investigators will be approved by the REC and HRA.

19.2 Regulatory Authority approval

This study will be conducted under a UK Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Authorisation (CTA). Approval to conduct the study will be obtained from the Responsible Authority prior to initiating the study.

19.3 NHS Research Governance

Investigators are responsible for ensuring they obtain local Trust management agreement to conduct the trial in accordance with local arrangements and policies.

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

19.4 Protocol amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the Responsible Authority application (if applicable), the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product(s) used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study.

All amendments will be generated and managed according to the trial office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC, HRA, regulatory and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients (see below).

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

19.5 Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the trial office IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the trial office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The Trial office will follow written procedures to implement the changes accordingly.

19.6 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined a formal decision to:

- interrupt the treatment of subjects already in the trial for safety reasons;
- stop recruitment on safety grounds; or

- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The trial office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

19.7 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial”

Investigators must notify the Trials Office immediately if any serious breach is suspected. In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

19.8 Trial Reports

This protocol will comply with all current applicable Regulatory Authority, Research Ethics Committee and Sponsor reporting requirements.

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

For assessment of SARs in the DSUR, the RSI that was approved at **the start of the safety reporting period** will be used. Where changes to the RSI have been approved by substantial amendment during the reporting period, the RSI used for the next DSUR will differ from the RSI used to assess expectedness for SARs on or after the date the amendment is approved.

The trial office will determine which reports need to be circulated to Principal Investigators and other interested parties. Study sites are responsible for forwarding trial reports they receive to their local Trust as required.

20 EXPENSES AND BENEFITS

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate.

21 QUALITY ASSURANCE

21.1 Risk assessment

A risk assessment and a monitoring plan will be prepared before the study opens and will be reviewed throughout the study if necessary in the light of significant changes while the study is ongoing or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

21.2 Monitoring

Regular monitoring will be performed according to the monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution. For other non-critical data items, OCTO staff may resolve data queries centrally providing the correct answer is clear. Such changes will be clearly identified in the CRF and the study site informed.

Study sites will also be monitored remotely and/or by site visit as necessary to ensure their proper conduct of the trial. OCTO staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Monitoring reports will be sent to the site in a timely fashion. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance.

Sites will provide copies of the participant screening log to the trial office on request for remote monitoring purposes. This must not include patient personal identifiers.

21.3 Audit and Regulatory Inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the Trial Office without delay.

22 RECORDS RETENTION & ARCHIVING

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated

and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects must be retained in accordance with applicable national legislation and the host institution policy.

Retention and storage of laboratory records for clinical trial samples must also follow these guidelines. Retention and storage of central laboratory records supporting PK or PD endpoints and the disposition of samples donated via the trial must also comply with applicable legislation and Sponsor requirements.

It is the University of Oxford's policy to store data for a minimum of 5 years. Investigators may not archive or destroy study essential documents or samples without written instruction from the trial office. If there is a possibility that the research results will be used to apply for marketing authorisation, the research data will be archived for 15 years minimum. Copies of research data held by sites will be stored at site according to local policies. Data held at the University of Oxford will be stored electronically on a secure backed-up database, according to the policies of OCTO and the University of Oxford.

23 PATIENT CONFIDENTIALITY

The study will comply with the UK General Data Protection Regulation (UK-GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. Personal data recorded on all documents will be regarded as confidential.

The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s) with the exception of the CRF and consent form, where participant's year or birth will be recorded. During participant registration, participant initials may be transferred from site to the randomisation system as a validation check in this process. Participant initials do not form part of the trial dataset. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.
Patients consent forms will be retained for the life of the sample when patients have consented for study samples to be used beyond this study, to meet HTA traceability requirements.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

24 STUDY FUNDING

The WINGMEN trial is funded by Prostate Cancer UK (Reference RIA16-ST2-024). The Oncology Clinical Trials Office is also supported by Cancer Research UK core funding. Boehringer Ingelheim Ltd are providing xentuzumab free of charge to support the study. This study is further supported via the University of Oxford core clinical and research infrastructure.

This trial is on the NIHR portfolio. Local research network support should be available to support entry of participants into this trial.

25 SPONSORSHIP AND INDEMNITY

25.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship and authorise the trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator and Sponsor will be put in place between the parties.

25.2 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

25.3 Contracts/Agreements

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate. A Clinical Trial Agreement (CTA) will be placed between the Sponsor and participating organisations prior to site activation. The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

26 PUBLICATION POLICY

The sponsor will retain ownership of all data arising from the trial. The intention is to publish this research in a specialist peer reviewed scientific journal on completion of the study. The results may also be presented at scientific meetings and/or used for a thesis. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. Authors will acknowledge that the study was Sponsored by and performed with the support of the Sponsor and other funding bodies as appropriate.

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

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APPENDIX 1: ECOG PERFORMANCE SCALE

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

APPENDIX 2: COCKROFT & GAULT FORMULA

$$\text{GFR for males} = \frac{1.23 \times [140\text{-age}] \times \text{weight (kg)}}{\text{Serum creatinine (µmol/l)}}$$

APPENDIX 3: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Initial	1.0	30Apr2021		
002	2.0	TBC	Valentine Macaulay, Simon Lord, Tim Coutts	• Improved consistency of wording for tertiary objectives and endpoints throughout the document • Added new power calculation • Added that participants will be evaluable for the primary endpoint after receiving 3 cycles of xentuzumab, to allow recruitment of participants with a shorter window between diagnosis/treatment decision and surgery. • Added allowance for dose delay/omission • +15 minute window added to dose duration. • Added explanation that Day 1 treatment can be based on blood results from during the screening period (within 7 days prior to day 1). • Punch biopsies taken from the prostatectomy will be processed fresh or stored in a biobank where patients have consented to this • Additional Research Blood samples added • Exclusion criteria #1 changed to specify that systemic corticosteroids are excluded, also changed under prohibited therapies • Protocol now consistently refers to CTCAE v5.0 as the criteria for grading adverse events • Minor changes to tertiary endpoint wording, tertiary

				endpoints now read consistently throughout protocol • Addition of recruitment flyer for potential participants. • Minor changes to protocol layout and formatting, OCTO contact details, CI contact detail. • Removed planned recruitment period from protocol synopsis. • Removed SAE reporting telephone number. • Wording added to COVID risk/benefit (end of section 1) to give the correct number of additional visits (in line with the rest of protocol and PIS) • Clarified timeframe for screening bloods in Day 1 evaluations description on page 24. • All references to CTRG/Clinical Trials, Research & Governance changed to RGEA/Research Governance, Ethics & Assurance in line with sponsor office name change