Pembrolizumab with ChemoRadiotherapy as treatment for Muscle Invasive Bladder Cancer:

PCR-MIB Study

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TRIAL ONCOLOGY PI	Andrew Weickhardt
Phone	+61 3 9496 5763
Fax	+61 3 9457 6698
Email	andrew.weickhardt@onjcri.org.au
TRIAL RADIATION PI	Farshad Foroudi
Phone	+61 3 9496 2428
Fax	+61 3 9496 9647
Email	Farshad.foroudi@austin.org.au
TRIAL UROLOGY PI	Nathan Lawrentschuk
Phone	+61 3 9455 3363
Fax	+61 3 9457 5829
Email	urologyoncologist@gmail.com
Participating Sites	Olivia Newton-John Cancer Centre, Austin Hospital, Vic Peter MacCallum Cancer Institute, Vic Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, NSW Prince of Wales Hospital, NSW Sir Charles Gairdner Hospital, WA Royal North Shore Hospital, NSW
Clinical Trial Manager	Laura Galletta – Centre for Biostatistics and Clinical Trials (BaCT)

SPONSOR	Australian and New Zealand Urogenital & Prostate (ANZUP) Cancer Trials Group
Address	Level 6, 119-143 Missenden Road, Camperdown. NSW 2050
Phone	02 9562 5033
Fax	02 9562 5008
Email	Margaret@anzup.org.au

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COMPLIANCE STATEMENT

This trial will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) and Good Clinical Practice (GCP). In addition, the trial will be conducted in compliance will all applicable laws and regulatory requirements relevant to the use of new therapeutic agents, Pembrolizumab in Australia and any other participating country. Agreement of the investigator(s) to conduct and administer this trial in accordance with the protocol and associated regulations will be documented in the trial agreements with the Sponsor and other forms required by national authorities in the country where the trial center is located.

The Investigator(s) is responsible for ensuring the privacy, safety and welfare of the participants during and after the trial.

The Principal Investigator at each center has the overall responsibility for the conduct and administration of the trial at their center, and for conduct with the trial center management, the Independent Ethics Committee (IEC) / Human Research Ethics Committee (HREC) and local authorities.

The Protocol and all other trial related documentation including the Patient Informed Consent Form (PICF) and Case Report Form (CRF) must be written in English and under no circumstances be translated into another language without prior written approval from ANZUP.

Variations to the Protocol

No changes from the final approved (signed) protocol will be initiated without the ethics committee's prior written approval of favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the participants or when the change involves only the logistics or administration.

PROTOCOL AUTHORSATION PAGE

PROTOCOL NUMBER:	ANZUP 1502
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TRIAL CHAIR:	Andrew Weickhardt
Signature:	
Date Signed:	9 JAN 2018

SPONSOR:	Australian and New Zealand Urogenital & Prostate (ANZUP) Cancer Trials Group
SPONSOR REPRESENTATIVE:	Ian Davis
Phone:	+61 3 9094 9546
Fax:	+61 3 9899 9137
Email:	ian.davis@monash.edu
Signature:	
Date Signed:	3 JAN 2018

TRIAL SPONSOR AND COORDINATING PRINCIPAL INVESTIGATOR

SPONSOR:	Australian & New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)
SPONSOR REPRESENTATIVE:	Ian Davis
Street Address:	c/- Level 6, 119-143 Missenden Road,
PO Box:	
Suburb:	Camperdown
State:	NSW
Postcode	2050
Phone:	+61 3 9094 9546
Fax:	+61 3 9899 9137
Email:	ian.davis@monash.edu

COORDINATING PRINCIPAL INVESTIGATOR:	A/Prof Andrew Weickhardt
Hospital Street Address:	145 Studley Road
Suburb:	Heidelberg
State:	Victoria
Postcode	3084
Phone:	+61 3 9496 5763
After Hours Contact Number:	+61 3 9496 5000
Fax:	+61 3 9457 6698
Email:	andrew.weickhardt@onjcri.org.au

CONTENTS

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
BaCT	Centre for Biostatistics and Clinical Trials
CIS	Carcinoma in situ
CrCl	Creatinine Clearance
CT C/A/P	CT Chest/abdomen/pelvis
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DICOM	Digital Imaging and Communications in Medicine
DNA	Deoxyribonucleic acid
DMFS	Distant Metastasis Free Survival
DVH	Dose Volume Histograms
ECOG	Eastern Cooperative Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture system
ERC	Ethics Review Committee
FBE	Full Blood Examination
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICRU	International Commission on Radiation Units
IMRT	Intensity Modulated Radiation Therapy
INR	International Normalized Ratio
LFT	Liver function tests
LRPFS	Locoregional Progression Free Survival
OS	Overall Survival
pCR	Pathological Complete Response; equivalent to pT0
PD1	Programmed cell death 1
PSA	Prostate Specific Antigen
PT	Prothrombin time
PTV	Planning Target Volume
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TCC	Transitional cell carcinoma (urothelial bladder cancer)

TIL	Tumor-infiltrating lymphocytes
TMC	Trial management committee
TOE	Trials operations executive
TSH	Thyroid-Stimulating Hormone
TURBT	Transurethral resection of bladder tumour
UECr	Urea, Creatinine and Electrolytes
ULN	Upper limit of normal
UT	Unacceptable Toxicity

1.0 TRIAL SUMMARY

Abbreviated Title	PCR-MIB **P**embrolizumab with **C**hemo**R**adiotherapy for **M**uscle **I**nvasive **B**ladder cancer
Trial Phase	Phase II
Clinical Indication	Patients with nonmetastatic, muscle invasive bladder cancer who either wish to attempt bladder preservation therapy or are ineligible for cystectomy.
Trial Type	Pilot single arm study: Non-randomized cohort of pembrolizumab with chemoradiotherapy
Type of control	No control arm/placebo
Route of administration	**Radiation:** 64Gy of radiation therapy in 32 fractions over 6 weeks and 2 days. **Chemotherapy (concurrent with radiation):** IV concurrent weekly cisplatin 35mg/m^2 (6 weeks) **Pembrolizumab:** IV 200mg 3 weekly commenced concurrently with chemoradiotherapy, and continuing until 12-week cystoscopy
Trial Blinding	Nil
Treatment Groups	30 patients, treated with pembrolizumab and chemoradiotherapy
Number of trial participants	30 patients
Estimated enrolment period	2 years; 5 sites
Estimated duration of trial	2 years of accrual + 3 years follow up
Duration of Participation	19 weeks of study visits; then end of treatment and follow up visits
Objectives	**Primary:** To demonstrate that the addition of pembrolizumab to chemoradiotherapy for muscle invasive bladder cancer is feasible as measured by a satisfactorily low rate of unacceptable toxicity. **Secondary**: 1. To evaluate the efficacy of the addition of pembrolizumab to concurrent chemoradiation regimen using the best response achieved, as assessed by cystoscopy at weeks 19 and 31 of the trial (12 and 24 weeks post completion of chemoradiotherapy). 2. To characterize:

	a. overall survival (OS); b. metastatic disease-free survival (DMFS); and c. locoregional progression free survival (LRPFS). **Exploratory:** To evaluate tumour histopathological, molecular genetics, and immunological parameters and their relationship with response to chemoradiotherapy and pembrolizumab.

2.0 TRIAL DESIGN

This pilot study will enroll patients with maximally resected (via transurethral resection (TURBT) non-metastatic muscle invasive bladder cancer, who either wish to attempt bladder preservation therapy or are ineligible for cystectomy. Patients must have adequate organ function and performance status to receive cisplatin based chemoradiotherapy, and no contraindications to the use of pembrolizumab. The study will enroll 30 patients to be treated with pembrolizumab and chemoradiotherapy.

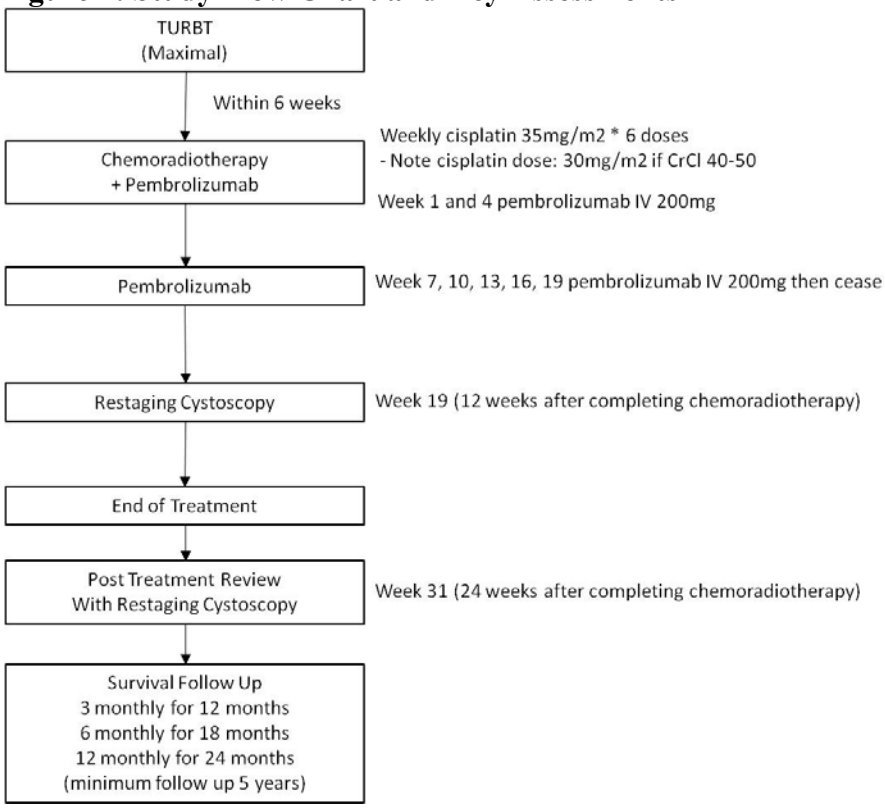
All patients will be planned to be treated with 64Gy of radiation therapy in 32 fractions over 6 weeks and 2 days. All patients will receive cisplatin 35mg/m^2 IV concurrently weekly with radiation therapy for 6 doses total. Pembrolizumab will commence concurrently with radiation and be given 200mg IV every 21 days, continuing until the 12week cystoscopy and assessment.

Surveillance cystoscopy will be performed 12 weeks after the commencement of chemoradiotherapy, and assess the rate of complete response to therapy. End of treatment and post treatment review visits will occur 4 (i.e. week 19) and 12 (i.e. week 31) weeks post cystoscopy. After the week 31 post treatment visit, patients will enter follow up with clinical assessment, cystoscopy and CT staging performed at intervals until close of study.

The objective of the study is to assess the safety and feasibility of combining pembrolizumab with chemoradiotherapy. The primary endpoint assessed will be safety, as defined by a satisfactorily low rate of unacceptable toxicity (G3-4 adverse events or failure of completion of planned chemotherapy and radiotherapy according to defined parameters). The secondary endpoint will be efficacy, as assessed by the proportion of patients achieving a best response of complete response, considering the first two post chemoradiotherapy cystoscopic assessments, at 19 and 31 weeks. Exploratory analysis will include assessment of tumour histopathological, molecular, genetic and immunological parameters.

It is expected that it will take two years to accrue the required 30 patients.

Figure 1: Study Flow Chart and Key Assessments



	Prestudy Assessments	**Chemoradiotherapy**						**Pembrolizumab Adjuvant Period**					**End of Treatment**	**Post Treatment Review**	**Follow Up**
	Week												To be completed 28 days after ceasing treatment at any time and for any reason.	To be completed 12 weeks post ceasing treatment for any reason	
	Within 6 weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**23**	**31**	
Clinical Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cisplatin		X	X	X	X	X	X								
Radiotherapy		X	X	X	X	X	X	X^							
Pembrolizumab		X			X			X	X	X	X	X			
TURBT	X														
Cystoscopy	X											X		X	X
Urine Cytology		X										X		X	X
CT C/A/P	X											X		X	X

*Patients in follow up receive clinical assessment 3 monthly for 12 months, 6 monthly for 18 months, and 12 monthly thereafter for a minimum of 3 years or until death. Cystoscopy and CT C/A/P is performed within 28 days of each of these clinical assessments.

^ Week 7 pembrolizumab dose will occur in same week as last 2 days of radiotherapy.

3.0 OBJECTIVES, HYPOTHESES & ENDPOINTS

3.1 Primary Objective, Hypothesis & Endpoints

Objective: To demonstrate that the addition of pembrolizumab to chemoradiotherapy for muscle invasive bladder cancer is feasible as measured by a satisfactorily low rate of unacceptable toxicity.

Hypothesis: Pembrolizumab in combination with chemoradiotherapy will be safe and well tolerated in patients with previously untreated muscle invasive bladder cancer.

Endpoints: Occurrence of an unacceptable toxicity affecting patients where an unacceptable toxicity is defined by any of the following:

a) Occurrence of a grade 3 or 4 acute toxicity (excluding grade 3 or 4 urinary toxicity), occurring either during treatment or within 12 weeks after scheduled completion of treatment, or

b) Cisplatin being withheld for $\geq$ 2 doses

c) Cisplatin doses being withheld or reduced such that <66% of the intended total cisplatin dose is delivered

d) Radiation treatment being delayed beyond more than 7 weeks

e) Any single pembrolizumab dose being delayed for more than 6 weeks. (Multiple dose delays will not be aggregated).

3.2 Secondary Objectives, Hypothesis & Endpoint

Objectives:

(1) To evaluate the efficacy of the addition of pembrolizumab to concurrent chemoradiation regimen by estimating the complete response rate (see below).

(2) To characterize:

a. overall survival (OS);

b. metastatic disease-free survival (MDFS); and

c. locoregional progression free survival (LRPFS).

Hypothesis: The addition of pembrolizumab will improve the efficacy of chemoradiation in patients with bladder cancer.

Endpoints:

(1) Best response, defined as the better of the responses achieved at either the 1st or 2nd cystoscopic examination after completing therapy. (The 1st and 2nd cystoscopic

examinations take place during weeks 19 and 31 respectively of the trial.) See section 7.1.2.6.2 for definitions of the response levels.

(2) Dates of

i) death,

ii) detection of metastatic disease,

iii) detection of locoregional progression,

iv) any initiation of any new non-protocol anti-cancer therapy

3.3 Exploratory Objective

Objective: To describe tumour histopathological, molecular genetics, and immunological parameters and their relationship with response to chemoradiotherapy and pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Background Chemoradiotherapy

Treatment options for muscle invasive bladder cancer are cystectomy, or chemoradiotherapy, with salvage cystectomy [1]. Chemoradiotherapy is a suitable treatment for patients with muscle invasive bladder cancer who are ineligible for cystectomy, or who wish to preserve their bladder [2]. Cystectomy has a 2-3% procedural mortality rate, higher in smokers, the elderly and patients with medical comorbidities [1]. There are detrimental changes on the quality of life of patients related to the use of an ileal conduit, sexual dysfunction and body image. Five year survival rates are between 30-75%, depending on the stage of the tumour (T2 – 66%, T3 35%, T4 27%) [3] [4]

Five year overall survival rates of 40-60% from both prospective and retrospective series are comparable between patients who undergo cystectomy, and patients who undergo chemoradiotherapy with salvage cystectomy for treatment failure [5] . The only randomized trial comparing chemoradiotherapy to cystectomy was too small to provide estimates of survival effects [6].

Additionally a significant proportion of patients will keep their bladder [2]. Chemotherapy, such as cisplatin, acts a radiosensitising agent when used with radiotherapy [7]. The rationale of chemoradiation is that chemotherapy increases the effectiveness of radiation, acting as a cytoreductive agent and radiation sensitizer. Chemotherapy may also improve outcomes by treating micrometastatic disease. In the BC 2001 trial comparing chemoradiotherapy with 5FU/MMC to radiation alone, 2 year locoregional relapse was reduced to 18% vs 32% in the radiotherapy arm [8].

4.1.2 Pharmaceutical and Therapeutic Background Chemoradiotherapy

Multiple different chemotherapy regimens have been used in combination with radiation for bladder cancer. Reported efficacy and safety are similar between different regimens as summarized in the table[2].

Table 1 Series of trimodality bladder-sparing treatment for muscle-invasive bladder cancer

Investigator (publication year)	No. patients	Clinical stage	Induction therapy		CR rate (%)	Consolidative therapy		5-year OS (%)	5-year BIS (%)
			Neoadjuvant therapy	CRT regimen		CRT regimen	Adjuvant therapy		
Housset (1993)[8]	54	T2-4	–	24 Gy + cisplatin/FU	74	20 Gy + cisplatin/FU	–	59 (3-year)	NA
Given (1995)[16]	93	T2-4	2 or 3 cycles MVAC or MCV	64.8 Gy + cisplatin	63	–	–	39	NA
Tester (1996)[14]	91	T2-4a	2 cycles MCV	39.6 Gy + cisplatin	75	25.2 Gy + cisplatin	–	62 (4-year)	44 (4-year)
Kachnic (1997)[9]	106	T2-4a	2 cycles MCV	39.6 Gy + cisplatin	66	25.2 Gy + cisplatin	–	52	43
Fellin (1997)[17]	56	T2-4	2 cycles MCV	40 Gy + cisplatin	50	24 Gy + cisplatin	–	55	41
Shipley (1998)[13]	123	T2-4a	2 cycles MCV *vs* no chemotherapy	39.6 Gy + cisplatin	61 *vs* 55	25.2 Gy + cisplatin	–	49 *vs* 48	36 *vs* 40
Rodel (2002)[10]	415	T1-4	–	50.4–59.4 Gy + cisplatin or carboplatin(+ FU)	72	–	–	50	42
Danesi (2004)[18]	77	T2-4	2 cycles MCV	69 Gy + cisplatin/FU	90	–	–	58	47
Kragelj (2005)[19]	84	T1-4	–	64 Gy + vinblastine	78	–	–	25 (9-year)	NA
Dunst (2005)[20]	68	T2-4	–	50.4–59 Gy + cisplatin or paclitaxel	87	–	–	45	NA
Weiss (2007)[21]	112	T1-4	–	55.8–59.4 Gy + cisplatin/FU	88.4	–	–	74	61
Perdona (2008)[22]	121	T2-4	2 cycles MCV	65 Gy + no *vs* cisplatin or carboplatin	74.4 *vs* 89.7	–	–	60.4 *vs* 71.8	46.5 *vs* 53.8
Gamal El-Deen (2009)[23]	186	T2-4a	No or 2 cycles MCV/MVAC/GC	55–64.8 Gy + no *vs* cisplatin	58.3 *vs* 81.6	–	–	59.7 *vs* 68.4	NA
Kaufman (2009)[24]	80	T2-4a	–	40.3 Gy + cisplatin/ paclitaxel	81%	24 Gy + cisplatin/ paclitaxel	4 or 6 cycles GC	56	47
Sabaa (2010)[25]	104	T2-3a	3 cycles GC	60–65 Gy + cisplatin	78.8	–	–	54.8	NA

Contemporary chemoradiotherapy series report similar outcomes related to relevant tumour related endpoints including complete response rates, 5-year disease free survival, 5 year overall survival, and rates of distant metastatic disease regardless of chemotherapy regimen. There appears no significant benefit from additional chemotherapy administered before or after the concurrent chemoradiotherapy and this does not form part of usual practice in Australia[2].

Salvage treatment with cystectomy plays an important role in managing patients with chemoradiotherapy and is the gold standard for optimal trimodality therapy should patients relapse. Two approaches here have been reported for patients considered fit for salvage cystectomy. Firstly in the MGH and RTOG protocols, response evaluation is performed after approximately 40Gy of induction therapy [5, 9]. Only complete responders are considered eligible for bladder preservation therapy and proceed with consolidation treatment with the bladder treated up to 64Gy. Conversely, a second alternative is the Erlangen approach [10], where the bladder is evaluated at 4-6 weeks post definitive chemoradiotherapy. The late-response evaluation may theoretically increase the chance of bladder preservation, as some slow responders may still be responding and have not maximally regressed after the 40Gy of treatment. Additionally, split dose radiotherapy is of some concern. However, the two approaches seem equally effective in terms of long term survival and bladder preservation. This study will utilize the latter approach.

An early assessment of efficacy of chemoradiation that is standardly used is the complete response rate, which is determined in most series to be based on first cystoscopic assessment of the bladder cancer 12 weeks after chemoradiotherapy is completed [1, 5]. This involves examination under anesthesia, cystoscopy and biopsy of all previously positive tumor sites that is utilized to evaluate the tumor status (response) following completion chemoradiotherapy. In some patients radiographic or cystoscopic evaluation will reveal abnormalities at the bladder

tumor-site (such as thickening of the wall, ulcerations, or possible nodularities) which contain no identifiable tumor cells histologically. Patients will be considered as having a complete response, or pT0 response, when the bi-manual examination under anesthesia is negative, when all the biopsies are negative for any tumor at the site(s) of the pretreatment tumor(s) and there is an absence of metastatic disease on the most recently performed systemic imaging.

4.1.3 Background Pembrolizumab

Pembrolizumab is a novel antibody to PD1, which has shown activity as an immunomodulating agent in a range of cancers. In preliminary trials of pembrolizumab in metastatic bladder cancer, 26% of patients experienced a radiological response, and at least 60% of patients had tumour shrinkage [11].

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

4.1.4 Pharmaceutical and Therapeutic Background Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular

endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in participants with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Phase 3 trials of pembrolizumab in metastatic bladder cancer are currently underway.

4.1.5 Preclinical and Clinical Trial Data for Pembrolizumab

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale for the combination of pembrolizumab with chemotherapy and radiation

Chemoradiotherapy leads to outcomes similar to cystectomy. However, a significant proportion of patients still fail to achieve a complete response to chemoradiation, require a cystectomy, relapse locally, or develop distant metastatic disease.

Approximately 30% of patients fail to achieve a complete response to therapy, with a relapse rate of 10% with local-regional disease, and 9-20% distant metastatic disease over 2 years [1, 2, 7, 12]. Improvements in these outcomes are desired.

The use of drugs such as pembrolizumab is transforming cancer medicine, and checkpoint inhibitors are resulting in unprecedented disease response rates and longer-term control. However, while a subgroup of bladder cancer demonstrate exquisite responses to these agents, many patients do not derive any benefit. A major challenge therefore is to develop rational strategies by which the activity of these agents can be broadened.

One potential approach is the combination of immunotherapy with radiation therapy. Radiation therapy induced cell killing has the potential to stimulate the release of tumour antigens and trigger antigenic stimulation. Proof of this concept is provided by *in vitro* studies [13], and anecdotally from clinical observations of tumour regressions at unirradiated tumour sites (the abscopal effect). Importantly, the combination of radiotherapy with immune check point inhibitors has been reported to escalate antitumour responses in clinical case reports [14], and shown to be safe when combined with radiation in several trials [15]. The effect of this combination in bladder cancer however has not been extensively investigated.

Predicting the impact of combining chemotherapy with immunotherapy is less straightforward. While chemotherapy may deplete immune effector cells, the cytotoxic effects of chemotherapy may also enhance antigen-release and stimulate immune responses as postulated for radiation therapy. In preclinical mouse models, chemotherapy synergises with anti-PDL1 treatment to

induce durable anti-tumour responses and treatment with chemotherapy increases the number of tumour-infiltrating CD8+ cells [16] In mice chemotherapeutic agents such as 5FU induce greater cytotoxicity towards myeloid-derived suppressor T-cells, and therefore may serve to enhance immune function [17]. Addressing the safety and efficacy of combining immunotherapy with chemotherapy is therefore an important question. To-date, anti-PD1 drugs have been safely combined with chemotherapy in lung cancer with little additional toxicity and with robust responses that support the potential synergy of the combination [16, 18]. Specifically pembrolizumab has been safely combined with chemotherapy [18] with only 1 dose limiting toxicity out of 24 treated patients, however the efficacy results have not yet been published. Large phase 3 trials of pembrolizumab in combination with cisplatin chemotherapy are currently recruiting in gastric (KEYNOTE 062) and head/neck squamous cancers (KEYNOTE 048) amongst others.

4.2.1 Rationale for the Trial and Selected Participant Population

4.2.2 Rationale for Dose Selection/Regimen Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in participants with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.3 Rationale for Dose Selection/Regimen Cisplatin

Cisplatin dosing has not been uniform across the multiple clinical trials in bladder cancer when used as a radiosensitiser. A commonly accepted regimen is cisplatin given weekly at 35mg/m^2 for a total of 6 doses, and this was used in the TROG 99.06 trial [12]. In this study 3/36 patients (8%) required 2 or more doses of cisplatin to be omitted, and 3/36 (8%) had 1 dose omitted.

4.2.4 Rationale for Endpoints

4.2.4.1 Safety and Efficacy Endpoints

Rates of serious adverse events (Grade 3-4) in chemoradiotherapy trials are generally low, and reported between 5-30% [7, 8, 19]. The radiotherapy discontinuation rate has been reported to be between 0-5% [7, 8, 12, 19]. The radiotherapy completion rate in TROG 99.06 was 95%[12]. The grade 3-4 urinary G3 toxicity was 23% and G3 GI toxicity occurred in 2% [12].

The standard early assessment of efficacy from bladder cancer chemoradiotherapy trials is the complete response rate, as assessed by the 6-12 week cystoscopic assessment of the bladder after commencing chemoradiotherapy. Contemporary series for complete response rates are approximately 70-85% [20] [1, 2, 6, 8, 19].

Outcomes regarding complete pathological response rate depends on the extent of the initial TURBT, which is reported in the literature at experienced centers to be 65-87% [5, 9]. Patients with a visually complete TURBT have a pCR rate of 73-79%, compared to patients with an incomplete pCR rate of 50-63%. The 5 year survival rate is also different between these groups 57 vs 43% [5, 9].

Other endpoints of note and contemporary outcomes include 2 year disease free survival of 60-70% [5, 7], 5 year overall survival of 45-72% [5, 9]. The distant metastatic disease rate has been reported between 17-29% [21, 22].

The primary and secondary endpoints for the study will be

Primary

The primary objective is to assess feasibility of pembrolizumab in combination with chemoradiation, as measured by a satisfactorily low rate of unacceptable toxicities in the patient sample.

The primary endpoint is thus unacceptable toxicity, and is defined as either:

a) occurrence of a grade 3 or 4 toxicity (excluding grade 3 or 4 urinary toxicity), occurring either during treatment or within 12 weeks after scheduled completion of treatment, or

b) failure to complete chemoradiation as planned: prescribed dose of radiation delivered within a maximum 7 weeks; administration of full dose cisplatin without dose reduction or omission of more than two doses; and administration of full dose pembrolizumab without delay of more than 6 weeks.

Secondary

The first secondary objective is to test for an initial efficacy signal, as measured by the complete response (CR) rate.

The first secondary endpoint, CR, is defined as achievement of pT0 at either the 1st or 2nd cystoscopic examination.

The additional secondary objectives are to document (over the 3-5 years of follow up for patients)

- overall survival
- metastatic disease-free survival; and
- locoregional progression free survival

The corresponding secondary endpoints are thus the dates of death, detection of metastatic disease, and detection of locoregional progression, where applicable. Date of initiation of non-protocol anti-cancer therapy will also be collected as part of the definition of DMFS and LRPFS.

4.2.4.2 Biomarker Research

Preliminary reports of the activity of PD1 inhibitors in bladder cancer correlate outcomes in relation to response to therapy in the metastatic setting with expression of PDL1 on tumour infiltrating immune cells [11]. Further work is required for biomarker discovery and validation when PD1 inhibitors are used with chemoradiotherapy.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Histologically-confirmed diagnosis of muscle-invasive T2-T4a, Nx or N0 urothelial cell carcinoma of the bladder. Subjects with tumors of mixed transitional/non-transitional cell histology are allowed, but transitional cell carcinoma must be the predominant histology (≥50%). Subjects with predominant or exclusively non-transitional cell histology are not allowed.

5.1.2 Participant Inclusion Criteria

In order to be eligible for participation in this trial, the participant must:

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.

   Have histologically-confirmed diagnosis of muscle-invasive T2-T4a, Nx or N0 urothelial cell carcinoma of the bladder. Subjects with tumors of mixed transitional/non-transitional cell histology are allowed, but transitional cell carcinoma must be the predominant histology (≥50%). Subjects with predominant or exclusively non-transitional cell histology are not allowed.

3. Must have undergone maximal transurethral resection of the bladder tumour, as is judged as safe as possible by the urologist performing the resection, within 42 days of planned treatment commencement. Where patient has only had a biopsy/partial resection and is otherwise eligible for entry into the study, the case should be rediscussed with the referring urologist to see whether further resection would be feasible prior to embarking with the chemo-radiotherapy.

4. Have elected not to undergo radical cystectomy, or are unsuitable for radical cystectomy.

5. Planned for chemoradiotherapy as definitive treatment.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale
7. Demonstrate adequate organ function as defined in **Table** 2. All screening labs should be performed within 10 days of registering the patient on the trial.

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Platelets	≥100 X 10^9/L
Hemoglobin	≥90 g/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Calculated[a] creatinine clearance	≥40 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**

	Direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN
AST and ALT	≤ 2.5 X ULN
Albumin	≥25 g/L
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy (as long as PT or PTT is within therapeutic range of intended use of anticoagulants) ≤1.5 X ULN unless participant is receiving anticoagulant therapy (as long as PT or PTT is within therapeutic range of intended use of anticoagulants)
[a]Creatinine clearance at screening should be calculated using Cockroft-Gault methodology, or measured with either a 24 hour urinary CrCl, or a nuclear medicine DTPA/ETDA scan	

8. Female participants of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to registering the patient. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

9. Female participants of childbearing potential should be willing to use two methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

10. Male participants should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

11. Willing to consent to the use of their collected tumour specimen, blood and urine as detailed in the protocol for future scientific research including but not limited to DNA, RNA and protein based biomarker detection.

5.1.3 Participant Exclusion Criteria

The participant must be excluded from participating in the trial if the participant:

1. Has concurrent extra-vesical (i.e. urethra, ureter or renal pelvis) urothelial cell carcinoma of the urothelium. Patients who have involvement of the prostatic urethra with urothelial cell cancer (TCC) that was visibly completely resected and no evidence of stromal invasion of the prostate remain eligible.

2. Evidence of tumour-related moderate/severe hydronephrosis unless stented or with nephrostomy to preserve renal function.

3. Extensive or multifocal bladder carcinoma in situ (CIS) precluding curative chemoradiotherapy.

4. Bulky T3/T4a tumours unsuitable for curative treatment (i.e. >10 cms in any dimension); node positive disease.

5. Evidence of distant metastatic disease on CT chest/abdomen/pelvis performed within 42 days prior to study entry. Patients with pelvic lymph nodes deemed to be 'positive' are not eligible for the study unless histological confirmation of the largest most suspicious node is negative for malignancy. Patients with known CNS metastatic disease are excluded from the study

6. Prior pelvic radiotherapy

7. Has had prior intravenous chemotherapy, targeted small molecule therapy, or radiation therapy for treatment of bladder cancer. Prior intravesical use of BCG and mitomycin is permissible.

8. Unsuitable for concurrent cisplatin based chemoradiotherapy based on:
    - CTCAE v.4.03, Grade >2 audiometric hearing loss (25dB in two consecutive wave ranges) if previously performed.
    - CTCAE v.4.03, Grade >2 peripheral neuropathy

9. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of treatment.

10. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to registering the patient. Patients with adrenal insufficiency receiving replacement dose steroids are allowed on the trial.

11. Has a known history of active TB (Bacillus Tuberculosis)

12. Hypersensitivity to pembrolizumab or any of its excipients.

13. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
14. Prior or concurrent known additional malignancy of any site unless disease free for 5 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer, Stage T1a well differentiated prostatic carcinoma in men (Gleason = 3+3, PSA <5)

15. Has any history of active autoimmune disease, Stevens-Johnson syndrome or Guillain-Barre. Exceptions to this are:
    - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
    - Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen who are also be eligible for this study

16. Has known history of, or any evidence of active, non-infectious pneumonitis.

17. Has an active infection requiring systemic therapy.

18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

20. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

21. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

22. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

23. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

24. Has received a live vaccine within 30 days of planned start of study therapy.
    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.1.4 Registering a Patient – General Guidelines

Sites will register eligible patients electronically using the online PCR-MIB electronic data capture (EDC) system. Confirmation of registration will also be provided electronically (via email) as well as, a unique 5-digit patient identification number for the patient.

Full training on the PCR-MIB EDC system will be provided to sites prior to site activation.

Prior to patient registration, the investigator should ensure that all of the following requirements are met:

- The patient meets all inclusion criteria and none of the exclusion criteria should apply.
- The patient has signed and dated all applicable consent forms.
- All baseline assessments and investigations have been performed.
- The eligibility checklist has been completed, signed and dated.
- Ensure any support test/investigation reports to be provided to the Trial Centre are de-identified

N.B. You will NOT be able to register a patient if treatment has commenced or if consent has not been given.

Following registration patients should begin protocol treatment within 10 days. Issues that would cause treatment delays should be discussed with the Coordinating Principal Investigator (CPI).

A patient who withdraws consent prior to commencement of pembrolizumab and chemoradiotherapy may be replaced to ensure 30 patients in total are treated with the combination.

For any queries contact the Centre for Biostatistics and Clinical Trials (BaCT) at Peter Mac.

5.2 Study Assessments

5.2.1 Evaluation during screening period

Screening evaluation (within 6 weeks of treatment start date) shall include:

1. Comprehensive medical history
2. Documentation of concomitant medications at time of screening
3. Full physical examination
4. Documentation of ECOG performance status
5. Vital signs
6. Radiological evaluation with a CT Chest/Abdomen and Pelvis must be performed within 6 weeks of treatment starting
7. Laboratory studies no more than 10 days prior to the treatment start include FBE, UECr, LFTs, TSH and coagulation
8. Pregnancy test in female patients with child bearing potential
9. Cystoscopic evaluation by the participating urologist including a thorough as possible transurethral resection of the bladder tumour, bimanual examination under anesthesia, as well as a biopsy of the base of the resected tumour site. Patients referred from outside with incomplete resections will be considered for re-resection if considered feasible by the urologist prior to chemoradiation. Complete description of the location of tumour, size, morphology, extravesical spread, CIS, ureteric involvement will be provided by the urologist performing the cystoscopy.

5.2.2 Evaluation during chemoradiotherapy period

During the chemoradiotherapy period the following assessments are to be performed within 3 days prior to the start of each week of radiotherapy unless otherwise specified below.

1. Adverse events
2. Vital signs
3. Concomitant medications

4. ECOG performance status
5. Directed physical examination
6. Laboratory tests (FBE, UECr, LFTs) within 3 days of the administration of chemotherapy or pembrolizumab. A TSH,T3, T4 is taken every 6 weeks
7. Documentation of new anticancer therapies
8. Collection of blood and urine samples for biomarker studies (Week 1)

If these assessments have taken place during the screening evaluation (5.2.1) within 10 days of treatment commencement, these do not need to be repeated for the first week of therapy.

Note that biomarker blood and urine samples are to be taken on day 1 of therapy with pembrolizumab prior to therapy, please refer to the PCR-MIB Biomarker Laboratory Manual for further blood sampling information.

5.2.3 Evaluation during pembrolizumab treatment period

The following assessment will take place within 3 days of each scheduled pembrolizumab treatment between week 7 and 19:

1. Adverse events
2. Vital signs
3. Concomitant medications
4. ECOG performance status
5. Directed physical examination
6. Laboratory tests (FBE, UECr, LFTs). A TSH, T3, T4 is taken every 6 weeks
7. Radiological evaluation (CT Chest/Abdo/Pelvis) at week 19
8. Cystoscopy assessment at week 19
9. Urine cytology at week 19
10. Collection of blood and urine samples for biomarker studies at Week 7

Note that biomarker blood and urine samples are to be taken on Week 7 of therapy with pembrolizumab prior to therapy, please refer to the PCR-MIB Biomarker Laboratory Manual for further blood sampling information.

5.2.4 Evaluation at end of treatment visit (Week 23 or when patient ceases treatment)

The following assessment will take place at the end of treatment visit, when a patient ceases treatment for progression, unacceptable toxicities or any other reason:

1. Adverse events
2. Vital signs
3. Concomitant medications
4. ECOG performance status

5. Directed physical examination
6. Laboratory tests (FBE, UECr, LFTs). A TSH, T3, T4 is taken every 6 weeks
7. Radiological evaluations (CT Chest/Abdo/Pelvis)*
8. Cystoscopy assessments*
9. Urine cytology*
10. Documentation of new anticancer therapies
11. Documentation of disease status
12. Collection of blood and urine samples for biomarker studies

* CT chest/abdomen/pelvis, cystoscopy and urine cytology only need to be performed at End of Treatment visit if these assessments have not been performed at Week 19, for instance if the patients has come of study for toxicity prior to Week 19.

5.2.5 Evaluations at post treatment review visit (Week 31 or 12 weeks post last treatment)

1. Adverse Events
2. Vital signs
3. ECOG performance status
4. Directed physical examination
5. Laboratory tests (FBE, UECr, LFTs). A TSH, T3, T4 is taken every 6 weeks
6. Radiological evaluation
7. Cystoscopy assessment
8. Urine cytology
9. Documentation of new anticancer therapies
10. Documentation of disease status
11. Survival status

5.2.6 Evaluations during follow-up

After the end of treatment study visit, patients enter into follow up for OS, LRPFS and DMFS. Follow up for these survival endpoints will be 3 monthly for 12 months after the post treatment review visit, then 6 monthly for 18 months, then 12 monthly until 3 years after the registration of the last patient or study closure. The following assessments will take place at each visit:

1. Vital Signs
2. Directed physical exam
3. Urine cytology
4. Post-study anticancer therapy status
5. Disease Status
6. Survival status

7. Radiological evaluation (CT Chest/Abdo/Pelvis)
8. Cystoscopy assessment

Patients with either local or distant progression do not require vital sign, directed physical examination, urine cytology, or cystoscopy assessment at each visit.

Patients with local progression should continue to receive radiological evaluation for assessment of distant metastatic disease. Patients with distant progression should receive radiological evaluation at the discretion of the investigator.

5.3 Chemoradiotherapy Trial Treatments

The treatment to be used in this trial is outlined below:

Table 3: Trial Treatment

Treatment	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period
Cisplatin	35mg/m^2 (30mg/ m^2 if CrCl 40-50)	Weekly, synchronous during radiotherapy	IV infusion	Weekly during radiotherapy for total 6 doses
Radiotherapy	64Gy in 32 fractions	5 daily fractions per week over 6.4 weeks.	3D- Conformal External Beam Radiotherapy	64Gy
Pembrolizumab	200 mg IV	Q3W	IV infusion	Day 1 of each 3 week cycle, until week 12 cystoscopy, for total 7 doses

5.3.1 Trial Treatment Information

5.3.1.1 Cisplatin

5.3.1.2 Description of Cisplatin

Cisplatin is an antineoplastic compound which is a planar inorganic metal salt supplied as a lyophilised powder. It functions as an alkylating agent by producing interstrand and intrastrand crosslinks which modifies DNA structure and prevents DNA synthesis. It also inhibits RNA and protein synthesis.

5.3.1.3 Supply of Cisplatin

Sandoz, Hospira and Pfizer all produce cisplatin. Investigators can nominate to use any brand of Cisplatin that is readily available at their sites. Cisplatin will be provided to study participants according to usual hospital practice, and in Australia will be funded through the Pharmaceutical Benefits Scheme (PBS). Medication labels will be provided by the participating institution's

Pharmacy Department and will comply with requirements of the Australian Therapeutic Goods Administration. Cisplatin will be dispensed as per standard pharmacy practice.

5.3.1.3.1 Administration of cisplatin

Cisplatin chemotherapy will commence on the same day as radiation therapy. After 1000ml sodium chloride 0.9% is administered as prehydration (10mmol MgS04 is allowed to be added as per institutional preference), cisplatin 35mg/m^2 in 1000mL sodium chloride 0.9% will be administered over 60 minutes. Cisplatin is commercially available. Conceivably the co-administration of dexamethasone with the chemotherapy may reduce lymphocyte counts and efficacy of pembrolizumab. Therefore, the dose of dexamethasone administered with chemotherapy will be 4mg IV rather than 8mg unless $\geq$ G2 nausea/vomiting develops. The 5HT3 antagonist palonosetron 0.25mg IV (or equivalent 5HT3 antagonist) will be given prior to cisplatin. Other antiemetic use such as aprepitant and/or olanzapine is permissible. Dexamethasone 4 mg IV premedication given prior to cisplatin is permitted and allowed to continue at dose $\leq$ 4mg orally daily for 2 days after administration. Increase in dexamethasone dose is permitted in discussion with the principal investigator. Urine output measurement is not necessary before cisplatin administration as high urine flow does not appear to be protective.

Cisplatin will be administered weekly during radiotherapy at 7 day intervals

The chemotherapy is to be given preferably at the beginning of each week of treatment and as far as possible on the same day of the week (or within no more than 72 hours) on each occasion throughout the course of treatment.

No more than 6 doses of cisplatin will be administered.

Patients' renal function and myeloid function will be assessed within 72 hours prior to administration of each dose of cisplatin.

The patient should be assessed by the doctor prior to proceeding with each dose of chemotherapy.

Dose modification is described in 5.3.2.1.

5.3.1.4 Pembrolizumab

5.3.1.4.1 Description of pembrolizumab

Pembrolizumab is a novel antibody to PD1, administered intravenously.

5.3.1.4.2 Supply of pembrolizumab

Pembrolizumab will be supplied in the form of 100mg vials. Details of supply, handling and drug accountability are included in the Pharmacy Manual.

5.3.1.4.3 Administration of pembrolizumab

Pembrolizumab 200mg IV, q3 weekly will be given on the same day as the cisplatin, commencing on day 1 (or within no more than 72hrs) of radiotherapy, and given every 3 weeks (weeks 1, 4, 7, 10, 13, 16 and 19).

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion duration to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion duration is 30 minutes: -5 min/+10 min).

Pembrolizumab will continue after chemoradiotherapy has been completed (weeks 7, 10, 13, 16 and 19) for a total of 7 doses for the whole study, culminating with the 7th dose at week 19 of the study (12 weeks post completion of chemoradiotherapy). Pembrolizumab will continue for up to 7 doses total so long as there is

- no evidence of distant metastatic spread before this time
- no intervening administration of new anti-cancer therapy
- no evidence of locoregional progression
- no radiotherapy administered aside from that dictated in the protocol
- no pembrolizumab related AE severe toxicities as detailed in Table 6, Section 5.3.2.2 that require pembrolizumab to be withheld or discontinued.

5.3.1.4.4 Pembrolizumab Adjuvant Treatment

After chemoradiotherapy, patients will receive pembrolizumab in weeks 7, 10, 13, 16 and 19 (radiation will be scheduled for 2 days in week 7, but cisplatin will not be administered).

Pembrolizumab 200mg IV treatment may be administered up to 3 days before or after scheduled the day of each cycle due to administrative reasons but should occur on the same day. Treatment will finish at week 19.

In the event of a treatment delay due to an adverse event outlined in Table 6, patients may resume pembrolizumab within 3 weeks of the due dose. Subsequent dosing of pembrolizumab will continue until week 19, but not beyond this regardless of the total number of doses that the patient has received.

Cystoscopic assessment of tumour response will take place in week 19 and week 31, and is described in Section 7.1.2.6.

5.3.2 Dose Modifications

5.3.2.1 Cisplatin

Modifications of cisplatin for nephrotoxicity during radiotherapy are listed below. CrCl should be calculated using the Cockroft-Gault methodology. During radiation therapy, CrCl is to be recalculated each week, within 3 days of cisplatin administration.

Table 4: Dose modification of cisplatin dosing based on recalculation of the CrCl

Renal Function	Cisplatin Dosing
CrCl ≥50:	35mg/m^2
CrCl ≥40 but <50:	30mg/m^2
CrCl ≥30 but <40	25mg/m^2
CrCl <30	Withhold dose

Dose increases for patients commenced at 30mg/m^2 are permitted should renal function improve (based on weekly recalculation of CrCl) during radiotherapy and after discussion with the study chair.

An FBE is to be performed within 3 days of each cisplatin administration. Modification parameters for cisplatin dose reduction are displayed below.

Table 5: Dose modification cisplatin based on neutrophil/platelet count

ANC	Platelet Count x10^9		
Value	>150	75-149	<75
≥ 1.4	100%	100%	75%
0.8 – 1.4	100%	75%	75%
≤ 0.8	0%	0%	0%

5.3.2.2 Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 6 below. See Section 5.5.1 for supportive care guidelines, including use of corticosteroids.

Table 6: Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule
	Grade 4	Permanently discontinue		

				out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to

AEs	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		confirm etiology and/or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dosing of cisplatin and radiation can proceed despite the development of pembrolizumab related adverse events with the exception of the dose modifications described specifically in the sections related to cisplatin and radiation.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Coordinating Principal Investigator. The reason for interruption should be documented in the patient's study record.

5.3.3 Timing of Dose Administration

Pembrolizumab should be administered on Day 1 of commencement of chemoradiotherapy after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Pembrolizumab 200mg IV will be given in weeks 1, 4, 7, 10, 13, 16 and 19. Treatment may be administered up to 3 days before or after the scheduled day of each cycle due to administrative reasons.

In the event of a treatment delay due to an adverse event outlined in Table 6, patients may resume pembrolizumab within 12 weeks of the due dose so long as the toxicity has resolved to Grade 1 or less and the patient is on a dose of 10mg or less of prednisolone or equivalent. Subsequent dosing of pembrolizumab will continue until week 19, but not beyond this regardless of the total number of doses that the patient has received.

All trial treatments should be administered on an outpatient basis unless discussed with the Principal Investigator/Sponsor.

5.3.4 Radiation Schedule

The information provides detail on the generation of the conventional image guided radiotherapy.

5.3.4.1 Statement of treatment aim and rationale

The aim of this study is to deliver a radical dose of radiotherapy to the entire bladder volume for eligible participants who provide informed consent. A dose of 64Gy in 32 fractions over 6 weeks and 2 treatment days is prescribed.

The radiotherapy plan is used to deliver treatment for fractions 1 to 32 using a standard planning approach with daily image guidance using Cone Beam CT (CBCT).

5.3.4.2 Credentialing

Sites will complete one credentialing case for completion, submission and approval prior to commencement of radiotherapy. Details of the credentialing process are in the Radiation Manual.

5.3.4.3 Treatment Schedule

Radiotherapy will commence according to standard departmental protocols but not more than 42 days after TURBT. If delays of longer than this are anticipated then a second TURBT is permitted to achieve maximum resection of the tumour prior to radiation.

5.3.4.4 Planning Simulation

CT based planning using standard departmental imaging guidelines is required. Scan properties (thickness, width) should enable accurate delineation of all structures and facilitate the construction of high quality transverse, sagittal and coronal plane reconstructions as well as digital reconstructed radiographs (DRRs). Scan thickness and width of equal to or less than 3mm is recommended.

Scan volume should include the entire bladder volume and all relevant organs at risk. It is recommended that scan extents are L4 – ischial tuberosities.

Patient positioning is to be supine using standard departmental guidelines, using appropriate immobilization. Simulation and treatment position must be identical.

An empty bladder is required for all imaging and treatment processes, all participants must void immediately prior to simulation. Where a participant is unable to void or has a residual bladder volume, any further simulation options to ensure a minimum bladder volume are at the prescribing Radiation Oncologist's discretion.

Rectal preparation is not required, however, the rectal cross section at the central CT slice should be <4.0cm in diameter. Where a rectal diameter is >4.0cm, instruct the patient to return to the bathroom and attempt to pass gas or faecal material. Rescan and review the rectal diameter. In cases where the diameter continues to exceed 4.0cm, any further simulation options to reduce the rectal cross-sectional diameter are at the prescribing Radiation Oncologist's discretion.

Surface markers should be placed at a minimum on skin surface to define the CT reference point and marked with a permanent/semi-permanent marker for subsequent identification at the treatment phase. Additional markers along the midline (minimum of two) are required to assist with alignment and markers on the lateral pelvis to assist with correction of rotation are also required. Measurements of all reference and marker points should be recorded.

5.3.4.5 Target volume definitions/Field Borders

5.3.4.5.1 Target Volumes

Target Volumes are defined from the planning CT, these include:

- **Clinical Target Volume (CTV)** - The clinical target volume (CTV) should include the whole bladder, the tumour bed region, the proximal urethra and, in the male patient, if there is involvement of the bladder neck and/or prostatic fossa, the entire prostatic urethra. Patients who have had a previous prostatectomy and bladder neck involvement should have urethra covered for a distance of 2 cm distal to the bladder neck. Any extra-vesical extension (e.g. peri-vesical fat) will be included in the CTV. No attempt will be made to cover nodal groups including first echelon lymph nodes (obturator) in the immediate vicinity of the bladder. Unusual anatomical variations (e.g. cystoceles and diverticula) should be covered. In cases involving the ureteric orifice, the distal ureter should be covered to a distance of 1 cm.

- **Planning Target Volume -** Will be created by a CTV to PTV expansion of
    - Laterally 0.8cm
    - Anteriorly 1.5cm
    - Posteriorly 1.2cm
    - Superiorly 1.5cm
    - Inferiorly 0.8cm

5.3.4.6 Normal tissue contouring

The rectum and right and left femurs must be contoured on the planning simulation CT scan.

Organ at risk delineation and dose constraints include:

Rectum:

- Delineation: Rectal volume to be marked as a solid structure from the upper field border to the lower field border.

Femurs:

- Delineation: Femurs are contoured from acetabulum to a lower extent equal to the most inferior border of the field edge.

5.3.4.7 Dose prescription and Fractionation:

5.3.4.7.1 Total Dose and Dose per Fraction

The total dose prescribed is 64Gy.

Dose fractions of 2.00Gy are required to be delivered once daily for 32 fractions, 5 fractions/week. In the event of a treatment interruption for any reason, the missing dose fraction(s) should be made up according to the instructions provided in 5.3.4.7.2.

The reason for any treatment interruption must be documented.

5.3.4.7.2 Treatment Duration

The total treatment duration is 6 weeks and 2 treatment days. Treatment should be completed from commencement unless severe acute toxicity is observed.

Where an interruption occurs:

- A minor radiation protocol deviation is recorded when the treatment extends from 6.4 up to 7 weeks
- A major radiation protocol deviation is recorded when the treatment extends beyond 7 weeks

Strategies for managing treatment interruptions (planned or unplanned) include

- Treating 6 fractions per week preceding or following a week where 4 fractions are delivered
- Treating twice a day with a 6hr treatment interval where treatment is not possible on a scheduled day
- Substituting a weekend day for a week day where treatment is not possible on a pre-programmed day
- Note: No more than 6 fractions may be given in any one week.
- Note: The reason for any treatment interruption must be documented.

5.3.4.8 Treatment Planning and Dosimetry

5.3.4.8.1 Planning System Requirements

The requirements for planning systems are described in the separate Radiation Manual.

5.3.4.8.2 Beam Arrangements

There is no prescribed beam arrangement; individual departments are free to use established treatment protocols provided 3 or more fields are employed.

Inverse Planned IMRT, volumetric modulated arc therapy and techniques are allowed if sites are credentialed.

5.3.4.8.3 Lipiodol Injection for Target Volume Delineation and Image Guidance

The use of bladder tumour demarcation with lipiodol injection through flexible cystoscopy is permitted if used as standard of care at the treating center to optimize radiation planning and image guidance. Lipiodol may be injected in the bladder wall prior to radiation planning consistent with previous publications highlighting the benefits of injecting small 0.25ml deposits

circumferential pattern around the primary tumour or resection site, with excess lipiodol removed with irrigation [23]. This must be done prior to radiation planning and commencement.

5.3.4.8.4 Treatment Techniques not permitted

- Techniques utilising beam energies less than 6MV are not permitted.
- Techniques delivered using the following equipment is not permitted
  - Gamma Knife
  - Helical Tomotherapy
  - CyberKnife
  - Protons

5.3.4.8.5 Compensation and heterogeneity corrections

The requirements for compensation and heterogeneity corrections are in the Radiation Manual

5.3.4.8.6 Dose distribution/Reporting

The requirements for dose distribution/reporting are in the Radiation Manual

5.3.4.9 Treatment Verification and Delivery

For all fractions, treatment verification is based on soft tissue based placement derived from a pre-treatment cone beam CT. All isocentre offsets identified on CBCT should be corrected daily (i.e. 0cm action threshold – any offset greater than or equal to 1mm should be corrected).

If the bladder size is larger than the PTV size the patient will be requested to void their bladder and another verification CBCT should be performed prior to treatment delivery.

5.3.4.9.1 Treatment Verification

Treatment Verification comprises the following:

- Daily treatment unit based cone beam CT prior to treatment to ensure soft tissue based Isocentre placement (all fractions)
- Repeat treatment unit based cone beam CT prior to treatment where an initial target CT demonstrates a residual bladder volume that does not fit into a conventional 1.5cm plan.

Treatment verification using daily treatment unit based cone beam verification CT should be completed from commencement of treatment without interruption.

Where a treatment unit based cone beam CT cannot be completed, alternative management strategies will require:

- Use of standard departmental imaging protocols (2D planar KV or MV EPI bone based) on-line and with a zero threshold value.

The reasons for interruption to daily treatment unit based verification cone beam CT must be recorded.

5.3.4.9.2 Data Submission:

Details of data submission requirements are found in the PCR-MIB Radiation Manual.

5.3.4.9.3 Treatment Equipment Specifications/Physical factors

All participants must be treated using external beam radiotherapy on a linear accelerator.

The following specifications apply to equipment used:

- Energy: 6MV or greater
- MLC size: 1.0cm or smaller
- Cone Beam Factors include:
  - Minimum 15cm scan length
  - Volumetric with minimum slice spacing of 3mm
  - kVp greater or equal to 120kVp

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Coordinating principal investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

5.4.1 Acceptable Concomitant Medications

During the period of chemoradiotherapy, dexamethasone 4 mg IV premedication given prior to cisplatin is permitted and allowed to continue at dose $\leq$ 4mg orally daily for 2 days after administration is permissible. After completion of chemoradiotherapy corticosteroids equivalent up to 10mg per day of prednisone is permissible upon discussion with study chair.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section7.2.

5.4.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids is allowed. The use of dexamethasone with cisplatin chemotherapy is permitted as described in 5.3.1.3.1

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5 Rescue Medications & Supportive Care for Pembrolizumab

5.5.1 Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. The use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids is permitted if necessary. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines below are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Refer to Section 5.3.2.2 for timing for restarting treatment and discontinuation criteria.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids 1-2mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 -6 weeks.

- For **Grade 3-4 events, or recurrent Grade 2**, immediately treat with systemic intravenous corticosteroids 1-2mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 -6 weeks. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- Cisplatin and radiation can continue despite pneumonitis if judged safe by investigators

- **Diarrhea/Colitis**:
  Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, treat with systemic corticosteroids 1-2mg/kg prednisone or equivalent., then tapering over 4-6 weeks. If Grade 2 diarrhea persists despite steroids for more than 3 days, management should be escalated to treat patient with IV steroids, and pembrolizumab withheld until colitis resolves to Grade 0-1
  - For **Grade 3 or 4 diarrhea/colitis**, treat with systemic intravenous corticosteroids 1-2mg/kg prednisone or equivalent.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required.

- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).and treat with 0.5-1mg systemic prednisone or equivalent.
  - For **Grade 3-4** events, treat with intravenous 1-2mg/kg corticosteroids for 24 to 48 hours then 0.5-1mg systemic prednisone or equivalent.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids. Permanently discontinue pembrolizumab.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 7 shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab.

Table 7: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Participant is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.6.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-

breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Participants should start using birth control from study Visit 1 throughout the study period and continue until 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.6.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will immediately be removed from the study. It is the responsibility of the site investigators or their designees to report all pregnancy exposures within 24 hours of becoming aware to the BaCT Trial Centre and to Merck Global Safety using the trial specific Pregnancy Reporting Form. The site will continue to contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.4.

5.6.4 Use in Lactating Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the lactating infant, participants who are breast-feeding are not eligible for enrolment.

5.7 Participant Withdrawal/Discontinuation Criteria

Participants may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. A patient who withdraws consent prior to commencement of pembrolizumab and chemoradiotherapy may be replaced to ensure 30 patients in total are treated with the combination. In addition, a participant may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4– Other Procedures.

A participant must be discontinued from trial treatment for any of the following reasons:

- Confirmed radiographic locoregional or metastatic disease progression
- Initiation of new anti-cancer therapies
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the participant
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The participant is lost to follow-up
- Administrative reasons
- The participant or legal representative (such as a parent or legal guardian) withdraws consent.
- Patient decision to withdraw

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 5.2.6 (Evaluations during follow-up)

After the end of treatment visit, each participant will be followed as per the follow-up schedule outlined in Section 5.2.6. Participants will be followed until end of study or until withdrawal of consent, for disease status, initiation of new anticancer therapies, and overall survival.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

	Screening	Chemoradiotherapy						Pembrolizumab Treatment Period					End of Treatment (j)	Post Treatment Review	Follow Up (l)
	-42 to -1 days	Week						Week					To be completed 28 days after ceasing treatment at any time and for any reason.	To be completed 12 weeks post ceasing treatment for any reason	
		1	2	3	4	5	6	7	10	13	16	19	23	31	
Informed consent	X														
Clinic Assessment (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab Tests (b) FBE UECr LFTs TSH, T3, T4 Coagulation	 X X X X X	 X X X X	 X X X	 X X X	 X X X	 X X X	 X X X	 X X X X	 X X X	 X X X X	 X X X	 X X X X	 X X X X	 X X X X	
Cisplatin		X	X	X	X	X	X								
Radiotherapy		X	X	X	X	X	X	X (i)							
Pembrolizumab (c)		X			X			X (i)	X	X	X	X			
Imaging CT Ch/Abdo/Pelvis (d)	X											X	X (k)	X	X
Cystoscopy(e)	X											X	X (k)	X	X
Urine Cytology		X										X	X (k)	X	X
Biomarker blood (f)		X						X					X		
Urine for biomarker		X						X					X		
Pregnancy Test (g)	X	X													
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events (h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Post-study anticancer therapy Status													X	X	X
Documentation of Disease Status													X	X	X
Survival Status														X	X

a. Clinical Assessment: Pre-Treatment - Prior medical and therapeutic history (including concomitant medications, histological documentation of malignancy, full physical exam, ECOG performance status, vital signs and prior anticancer therapy. During Treatment and End of Treatment Visits- adverse events, vital signs, concomitant medications, ECOG performance status and directed physical examination. ECOG performance status assessment during screening must take place within 10 days of treatment. During Follow-Up: Vital signs, ECOG performance status and directed physical exam.
b. Laboratory tests need to be performed within 3 days of each treatment related visit, except for the first visit, when these can be performed within 10 days.
c. Pembrolizumab given if no contraindications based on AE assessment
d. CT chest/abdomen/pelvis. *Note*: Both oral and IV contrast is required. In the event of known allergy to contrast, an MRI abdomen/pelvis may be performed as an alternative. Method of tumour assessment should be consistent throughout all visits Additional scans as clinically indicated.
e. Any additional cystoscopic assessmentis at the clinician discretion during this period.
f. Blood – 50ml of blood drawn at each of 3 visits: as per the PCR-MIB Biomarker Laboratory Manual
g. Patients should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication.
h. Adverse Events: To be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.03
i. Week 7 Pembrolizumab dose will occur in same week as last 2 days of radiotherapy
j. End of treatment review occur either at Week 23, or 28 days after last treatment for patients who discontinue for either progression before week 19, or other reason i.e. toxicity
k. CT chest/abdomen/pelvis, cystoscopy and urine cytology only need to be performed at End of Treatment visit if these have not been performed at Week 19, for instance if patients has come of study for toxicity prior to Week 19.
l.Follow Up visits will be 3 monthly for 12 months after the End of Treatment visit, then 6 monthly for 18 months, then 12 monthly thereafter under study closure, with cystoscopic assessment, urine cytology collection and CT C/A/P within 28 days of each follow up visit. Patients with either local or distant progression do not require vital sign, directed physical examination, urine cytology, or cystoscopy assessment at each visit. Patients with local progression should continue to receive radiological evaluation for assessment of distant metastatic disease. Patients with distant progression should receive radiological evaluation at the discretion of the investigator

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7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the HREC/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to HREC/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the bladder

cancer for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior therapy for bladder cancer

The investigator or qualified designee will review and record prior treatment for urothelial cell bladder cancer.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the End of Treatment visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03 (see Section 13.2). AEs will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Directed Physical Exam

For visits that do not require a full physical exam per the Trial Flow Chart (Section 6.0), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, at treatment discontinuation and at follow-up as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG performance status at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Radiological Assessment

Baseline CT Chest/Abdomen/Pelvis will be performed within 42 days of beginning treatment, then at week 19 and 31 prior to the end of treatment visit (+/- 7 days). The scan will be performed with IV contrast unless this is contraindicated due to renal insufficiency.

Imaging before this time point is at the investigators discretion, with the exception of when patients have documented local progression at the time of their first cystoscopy. In this case, patients require a CT scan of chest/abdomen/pelvis within 2 weeks of the cystoscopy.

Patients will have subsequent CT C/A/P restaging at week 19 (+/- 7 days), week 31 (+/- 7 days) and then within 28 days of each scheduled follow up visit.

7.1.2.6.2 Cystoscopic Assessment

Assessment of disease with cystoscopy will take place within 42 days of commencement.

The initial re-evaluation will take place 12 weeks (week 19 of trial) after completing chemoradiotherapy (+/- 7 days) (week 19 of the trial). Evaluation will include urine cytology, rigid cystoscopy, tumour site biopsy if indicated and bimanual examination after TUR.

The second check cystoscopy is mandatory at 24 weeks after completing chemoradiotherapy (+/- 7 days) (week 31 of the trial). Evaluation will include urine cytology, rigid cystoscopy, tumour site biopsy if indicated and bimanual examination after TUR.

In follow up, patients will receive cytoscopic assessment every 3 months for 12 months after week 31, then 6 monthly for 18 months, then 12 monthly until 3 years after the last patient is registered.

Any additional cystoscopic assessment (ie 6 weeks post chemoradiotherapy) is at the clinician discretion.

At the cystoscopic assessments for response (weeks 19 and 31), patients will be determined to have either achieved a Complete Response, Partial Response, Stable Disease or Progressive Disease. The determination will be based upon the results of the urologist assessment of the bladder at cystoscopy, histological parameters and result of most recent systemic imaging, as follows.

Patients will be considered as having a **complete response**, or pT0 response, when: i) the bi-manual examination under anesthesia is negative, ii) all the biopsies are negative for any tumor at the site(s) of the pretreatment tumor(s), and iii) there is an absence of metastatic disease on the most recently performed systemic imaging.

Patients will be considered to have a **partial response**, when patients have a lower T stage (depth of invasion of tumour) on tumour biopsy than pretreatment tumour T stage and there is an absence of metastatic disease on the most recently performed systemic imaging.

Patients will be considered to have **stable disease** when patients have the same T stage (depth of invasion of tumour) on tumour biopsy compared to pretreatment tumour T stage and there is an absence of metastatic disease on the most recently performed systemic imaging.

Patients will be considered to have **progressive disease** where there is a higher T stage (depth of invasion of tumour) on tumour biopsy compared to pretreatment tumour T stage or distant metastatic disease, or locoregional nodal involvement on the most recently performed systemic imaging or there is the requirement for intravesical therapy.

Table 8: Determination of response to chemoradiotherapy

	Cystoscopic appearance	Histological Grade	Distant Metastatic Disease on Systemic Imaging*	Nodal Involvement[(1)]	Initiation of any new anticancer therapies (including Intravesical Therapy)
Complete Response (all conditions satisfied)	Bi-manual examination under anesthesia is negative (required at first and second cystoscopy)	All biopsies negative for active tumour	Absent	Absent	
Partial Response (all conditions satisfied)		Lower T stage	Absent	Absent	
Stable Disease (any condition satisfied)		Same T stage	Absent	Absent	
Progressive Disease (any condition satisfied)		Higher T stage	Present	Present	Administered

[(1)] Single or multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node). All other nodes above the aortic bifurcation are considered distant lymph nodes.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Patients participating in the study will sign for consent for the use of their tissue for correlative biomarker studies. The Biomarker Laboratory Manual gives detailed instructions on specimens required and handling. Biomarker evaluable material includes

Tumour Tissue:	1) Formalin fixed paraffin blocks (or slides where block is not available) from resected tumour prior to treatment commencement 2) Formalin fixed paraffin blocks (or slides where block is not available) from any recurrent or residual tumour

Blood:	Peripheral blood taken prior to treatment commencement, at week 7 and week 23.
Urine:	Mid-stream urine taken prior to treatment commencement, at week 7 and week 23.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial can be found in the PCR-MIB Biomarker Laboratory Manual.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the end of treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Within 42 days prior to treatment commencement, potential subjects will be evaluated to determine that they fulfil the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and evaluation of ECOG performance status are to be performed within 10 days prior to the first dose of trial treatment

- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

7.1.6 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart for both the

1) Chemoradiation
2) Pembrolizumab treatment period

Specific procedure-related details are provided for this period in Section 6.

7.1.6.1 End of Treatment and Post Treatment Review Visits

Visit requirements are outlined in Section 6.0 - Trial Flow Chart for both the

1) End of Treatment visit (week 23)
2) Post Treatment Review visit (week 31)

The end of treatment visit must be completed within 30 days of ceasing treatment. The post treatment review must be completed 12 weeks post ceasing treatment.

Specific procedure-related details are provided for this period in Section 6.

7.1.6.2 Follow-Up Visits

The follow-up period will extend for 3 years from the registration of the last patient enrolled. Visits will include clinical assessment, physical assessment, imaging, cystoscopy, urine cytology, documentation of disease status and new anti-cancer therapies and documentation of survival status.

Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, detection of metastatic disease determined by the investigator/site and radiologist, death or end of study.

Subjects who have completed the post treatment review visit will move into follow-up and will be assessed until 3 years after registration of the last patient. After the post treatment review visit, follow-up visits will occur as follows:

- 3 monthly for 12 months
- 6 monthly for 18 months
- 12 monthly thereafter for a minimum of 3 years or until study close-out.

7.2 Assessing and Recording Adverse Events

All adverse events will be recorded from the time the consent form is signed through to the commencement of follow up visits. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.6.1. The investigator at each trial site is responsible for assessing and reporting AEs as part of patient safety, routine clinical care and data

collection. A subset of AEs will be classified as 'serious' and will require expedited reporting.

All AEs that occur prior to the commencement of the follow-up visits should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within a 12-week period (90 days) post completion of adjuvant pembrolizumab should also be followed and recorded.

7.2.1 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product (or any other protocol specified intervention including Radiation Therapy, surgery or use of a device) and does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator. Laboratory values need reporting as AEs only if abnormal and deemed clinically significant by the investigator.

AEs include: 'Adverse Drug Reactions', i.e. a reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected.

For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least reasonably possible, i.e. the relationship cannot be ruled out.

Regarding marketed medical products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

7.2.2 Unexpected Adverse Events (UAE)

An Unexpected Adverse Event is an AE for which the nature or severity of the event is not consistent with the information in the relevant source documents e.g. the IB, published information, product information (or with the applicable side effect risk profile for radiation therapy, surgery or use of a device).

UAEs include: 'Unexpected Adverse Drug Reactions', i.e.

The nature and severity of the ADR is not consistent with the information in the Investigators Brochure for an unapproved investigational product, or the product information/package insert/summary of product characteristics for an approved product.

7.2.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck and Sponsor

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported as an SAE within 24 hours to the BaCT Trial Centre and to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

7.2.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them), including the pregnancy of a male participant's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. All participants and female partners of male participants who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

It is the responsibility of the site investigators or their designees to report such events within 24 hours to the BaCT Trial Centre and to Merck Global Safety using the trial specific Pregnancy Reporting Form. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.5 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.5.1 Serious Adverse Events

Adverse events and adverse drug reactions are considered 'serious' if they threaten life or function.

SAEs include: 'Serious Adverse Drug Reactions', i.e. during clinical investigations, adverse events may occur, which if suspected to be medicinal product related ('adverse drug reactions') might be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, monitoring, consent). This is particularly true for reactions, which in their most severe form threaten life or function.

Due to the significant information they provide, Serious Adverse Events (including Serious Adverse Drug Reactions) require expedited reporting. SAEs are defined as any adverse event or adverse drug reaction which:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization*;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was immediately at risk of death at the time of event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

*An event that results in hospitalisation or prolongs an existing hospitalisation will not be considered a serious adverse event if the only reason for the hospitalisation or prolongation was:

- Administration of chemotherapy
- Administration of trial procedures
- Placement of a permanent intravenous catheter
- Hospice placement for terminal care
- Pre-trial scheduled elective surgery
- Outpatient hospitalisation for procedures such as:
    - Elective day surgery
    - Convenience purposes (eg. transportation difficulties)
    - Planned admission as part of supportive care for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding (i.e. did not occur

following urgent admission as a result of weight loss or other patient medical events)

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to study treatment that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the BaCT Trial Centre and to Merck.

SAE reports and any other relevant safety information are to be forwarded within 24 hours to:

BaCT Safety: safety_BaCT@petermac.org

Merck Global Safety Fax No: +1-215-993-1220

ANZUP Safety: sae.anzup@anzup.org.au

All participants with serious adverse events must be followed up for outcome.

7.2.5.2 Attribution of Cause of an Adverse Event

Attribution of cause requires at least a reasonable possibility of a causal relationship between the event and the use of a pharmaceutical product (or any other protocol specified intervention including radiation therapy, surgery or use of a device), i.e. the relationship cannot be ruled out. One or more of the following categories should be attributed as the cause of an event:

- Pharmaceutical product (an SAE which is drug related is considered a Serious Adverse Drug Reaction)
- Radiation Therapy
- Medical Device
- Surgery
- Unrelated to trial treatment (i.e. progressive disease, concurrent medication, concurrent disorder or other

All protocol specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

- Unrelated
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

7.2.5.3 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event eCRF and reported within 24 hours to the BaCT Trial Centre, ANZUP and to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until patient registration, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the BaCT Trial Centre to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Pembrolizumab, must be reported within 24 hours to the BaCT and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.6 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. All adverse events regardless of CTCAE grade must also be evaluated for seriousness. Laboratory values need reporting as AEs only if abnormal and deemed clinically significant by the investigator.

7.2.7 Adverse Event Reporting

All adverse events, which occur whilst the participant is enrolled on the trial, must be reported in the patients' medical records and recorded on the relevant CRF. The Common Terminology Criteria for Adverse Events (CTCAE version 4.03) must be used.

7.2.8 SAE Reporting

All serious adverse events (SAEs) that occur from the time a participant signs the consent form to within 30 days **after the patient has stopped study participation** (defined as time of last dose of investigational product taken), are required to be reported to the Peter MacCallum Centre for Biostatistics and Clinical Trials (BACT), the Sponsor (ANZUP) and to Merck Global Safety. Any SAEs experienced after this 30-day period should also be reported to BACT only if the investigator suspects a causal relationship to the study treatment.

The Principal Investigator (PI) (or delegate) must:

- Determine whether an AE is 'Serious' (see Section 7.2.6.1)
- For SAEs, the PI or his/her delegate must assess the relationship to the study drug, then ascertain the suspected cause
- The attribution to the SAE must be recorded in the patients' medical records and reported on the SAE form.
- The PI or his/her delegate must then determine whether the SAE (or Serious Adverse Drug Reaction) is expected or unexpected.
- Both expected and unexpected Serious Adverse Events and Serious Adverse Drug Reactions must be recorded in the patients' medical records and reported to BaCT and to Merck Global Safety. See below for timelines.

SAEs must be reported by completing the Trial SAE form and emailed/faxed to the following:

Send To:	**Contact Details**
Trial Coordinating Centre, BaCT	Email: safety_BaCT@petermac org Fax: +61 3 9656 1420
Merck Global Safety Attn: Worldwide Product Safety;	Fax: +1 215 993-1220
ANZUP Safety	Email: sae.anzup@anzup.org.au

All SAE must be reported within one working day (24 hours) of becoming aware of the event/information (for initial AND for follow-up). Refer to the table below for further details.

Initial Report	Within one working day (24 hours) of discovery or notification of the event. If the reporting of an SAE is delayed, an explanation must be provided in the comments section of the SAE form.
Incomplete Reports*	If all details are not available at the time of the initial report a completed report must be sent within the next 8 days.
Updated/ follow-up Report	If the event is not resolved (or is 'on-going') at the time of the initial report, the SAE updates need to be submitted to BaCT and marked as follow up and provided **within one working day (24 hours)**.
*The Investigator is ultimately responsible for reporting the SAE and must sign the SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24-hour period, a comment to this effect must be written on the form and the form faxed without signature to BaCT and Merck. The investigator must sign the SAE form as soon as possible and re-fax to BACT and Merck. The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and subsequently notifying the HREC of SAEs as required.	

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to BACT as above, using the SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, Merck may urgently require further information from the investigator for Health Authority reporting.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected by BaCT and the Sponsor and reported to the competent authorities and relevant ethics committees in

accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.2.9 Sponsor Responsibility for Reporting Adverse Events and Serious Adverse Events

The Sponsor is responsible for:

- Implementing and maintaining a suitable recording system to record information from all SAEs received from Trial Sites.
- Ensuring that the coordinating principal investigator (CPI) or delegate is notified of each SAE to enable the SAE to be assessed by the CPI and any other appropriate reviewers for nature (expected/unexpected), causality and whether the TGA needs to be notified of the SAE.
- Under the direction of the CPI or delegate, notifying the TGA (Australia) in accordance with the regulatory authority's detailed guidance of any SUSARs that are fatal or life threatening as soon as possible but no later than 7 days after the site gained first knowledge of the event. Incomplete reports must be completed and forwarded as soon as soon as possible within 8 additional calendar days. All other serious, unexpected ADRs should be reported to the TGA within 15 days after the site gained first knowledge of the event.
- Considering information provided by (non-serious) adverse event data.
- Informing each trial site of new information arising from serious and non-serious adverse events and adverse drug reactions that may affect the conduct of the Trial, or the rights, interests, safety or wellbeing of Trial Participants.
- Under the direction of the CPI or delegate, notifying the TGA of any significant issue that has arisen from analysis of overseas reports or action that has been taken by another country's regulatory authority within 72 hours of first knowledge.
- Reporting Serious ADRs to the responsible HREC according to local requirements

The Investigator at each Trial Site is responsible for reporting Serious ADRs to the responsible Research Governance Office (RGO) according to local requirements.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a single arm study. The primary and secondary objectives for the study will be:

Primary

To assess feasibility of pembrolizumab in combination with chemoradiation, as measured by a satisfactorily low rate of unacceptable toxicities (UT's) in the patient sample. A UT is defined as occurrence of any one of the following events:

a) occurrence of a grade 3 or 4 acute AEs (excluding grade 3 or 4 urinary AE), occurring either during treatment or within 12 weeks after completion of treatment, or

b) Cisplatin being withheld for ≥ 2 doses or any cisplatin dose reductions resulting in <66% of the intended total cisplatin dose being delivered, relative to the cisplatin starting dose.

c) Radiation treatment being delayed beyond more than 7 weeks

d) Any pembrolizumab being delayed for more than 6 weeks (Multiple dose delays will not be aggregated).

Patients will be assessed for acute toxicity at each visit throughout treatment and in follow up as outlined in the trial schema. Expected rates of patients experiencing a G3-4 event excluding urinary toxicity having chemoradiotherapy without pembrolizumab are between 5-30% [7, 8, 19]. Grade 3-4 urinary toxicity is a common adverse event experienced during chemoradiotherapy occurring in 20% of patients [12] related to radiation related changes to the bladder resulting in urinary frequency. Rates of urinary toxicity will be collected during the study, but will not contribute to the assessment total of G3-4 events.

The radiotherapy discontinuation rate has been reported to be between 0-5% [7, 8, 19].

The experimental regimen would be worthy of further pursuit if safe and feasible to deliver to patients without excessive toxicity or modification of radiation or dosage of cisplatin.

Secondary

To test for an initial efficacy signal, as measured by the complete response (CR) rate, defined as achieving pT0 at either the 1st or 2nd cystoscopic examination.

Additional secondary objectives are to document (over the 3-5 years of follow up for patients)

- overall survival
- metastatic disease-free survival; and
- locoregional progression free survival

Cystoscopic assessment will be undertaken 12 weeks and 24 weeks after completion of chemoradiotherapy. This involves examination under anesthesia, cystoscopy and biopsy of all previously positive tumor sites that is utilized to evaluate the tumor status (response) following completion of chemoradiotherapy. In some patients radiographic or cystoscopic evaluation will reveal abnormalities at the bladder tumor-site (such as thickening of the wall, ulcerations, or possible nodularities) which contain no identifiable tumor cells histologically.

Patients will be considered to have had a complete response, or pT0 response, when: i) the bi-manual examination under anesthesia is negative; ii) all the biopsies are negative for any tumor at the site(s) of the pretreatment tumor(s) **and** iii) there is an absence of metastatic disease on the most recently performed systemic imaging.

8.2 Sample Size Calculation

In order to justify continuing to explore pembrolizumab in combination with chemoradiation in a larger study, we must establish that the true underlying risk of unacceptable toxicities (UT's) in the population is acceptably low. To this end we need to decide upon values for a number of important parameters. Firstly, we need to decide upon a decision threshold for the maximum number of UT's allowable in the study sample before we conclude that the regimen is unsafe. In the event that the regimen is concluded to be unsafe, it should either be modified upon recommendation of the TMC before being considered further, or abandoned.

Additionally, we need to define two limits on the true underlying UT rate. The first is a "definitely considered safe" limit, defined such that if the true underlying UT rate is at this limit (or below) then we want to be confident that our decision threshold on the sample will yield a high probability that we will continue into a larger study focused on efficacy. The second is a "definitely considered unsafe" limit, defined such that if the true underlying UT rate is at this limit (or above) then we want to be very confident that our decision threshold on the sample will yield a high probability that we will discontinue – i.e. that we will reject the regimen as it currently stands for further consideration, and defer to the TMC for direction on whether and how to modify it.

To further mitigate risk, we would like accrual to proceed in two stages, with an interim analysis after the first stage at which stopping will be considered if the early evidence of a too high rate of UT's is convincing.

Under the proposed design, we desire to constrain the probability of discontinuation if the true underlying UT rate is at the definitely considered safe limit to a maximum of 20%, and at the same time limit the risk of continuing if the true underlying UT rate is at the definitely considered unsafe limit to 10%. We would like to consider the "definitely considered safe" rate of UT's to be 30%, and the "definitely considered unsafe" rate of UT's to be 50%.

These goals can be achieved with a sample size of 30 patients. Consider a Simon's two stage design whereby accrual will be halted if we see greater than 5 UT's amongst the first 10 patients and greater than 11 amongst the first 30 patients. Given these stopping thresholds, if the true underlying UT rate is 0.3 then the cumulative probability of concluding unsafe after stage 2 of accrual will be 17% and if the true underlying rate of UT is 0.5 then the cumulative probability of concluding unsafe after stage 2 of accrual will be 90%. The relationship between the true underlying UT rate and the probability of concluding unsafe is shown in Figure 2.

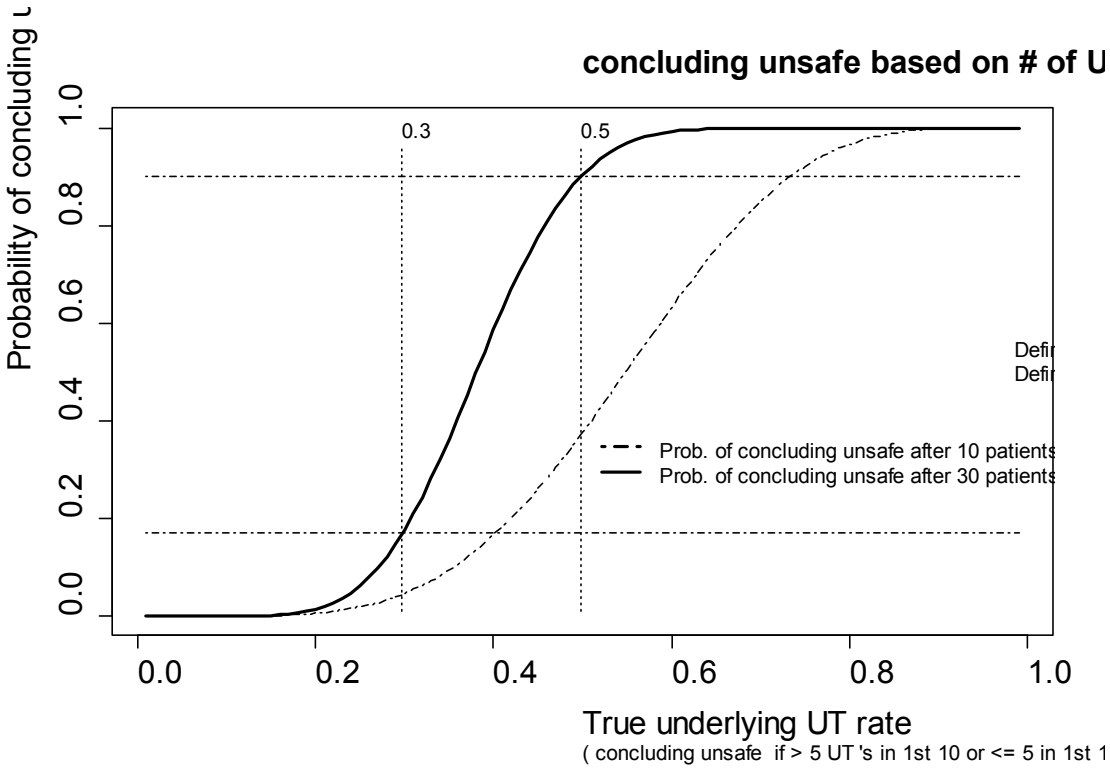

Figure 2: Probability of concluding unsafe as a function of true underlying UT rate

As a secondary objective, we desire to test for an initial signal of efficacy by estimating the proportion of patients achieving a best response of complete response (CR). (See sections 3.2 and 7.1.2.6.2 for the definition of best response.) Similar to the procedure for placing thresholds on the number of UT's we define a threshold for the minimum number of CR's that must be seen in the sample in order to consider the regimen worthy of further investigation on the basis of efficacy. We also define a "maximum uninteresting" true underlying CR rate – the true underlying CR rate at or below which we would not consider the regimen clinically worthy of implementation, and a "minimum interesting" true underlying CR rate – the true underlying CR rate at or above which we would consider the regimen clinically worthy of implementation. We define the maximum uninteresting and the minimum uninteresting rates as being 0.5 and 0.7 respectively. If we place the decision threshold at 18 CR's out of 30, then the probability of judging the regimen worthy of further investigation for efficacy if the true underlying CR rate is 0.5 is 10%, and the probability of judging the regimen worthy of further investigation for efficacy if the true underlying CR rate is 0.7 is 84%. This is illustrated in Figure 3.

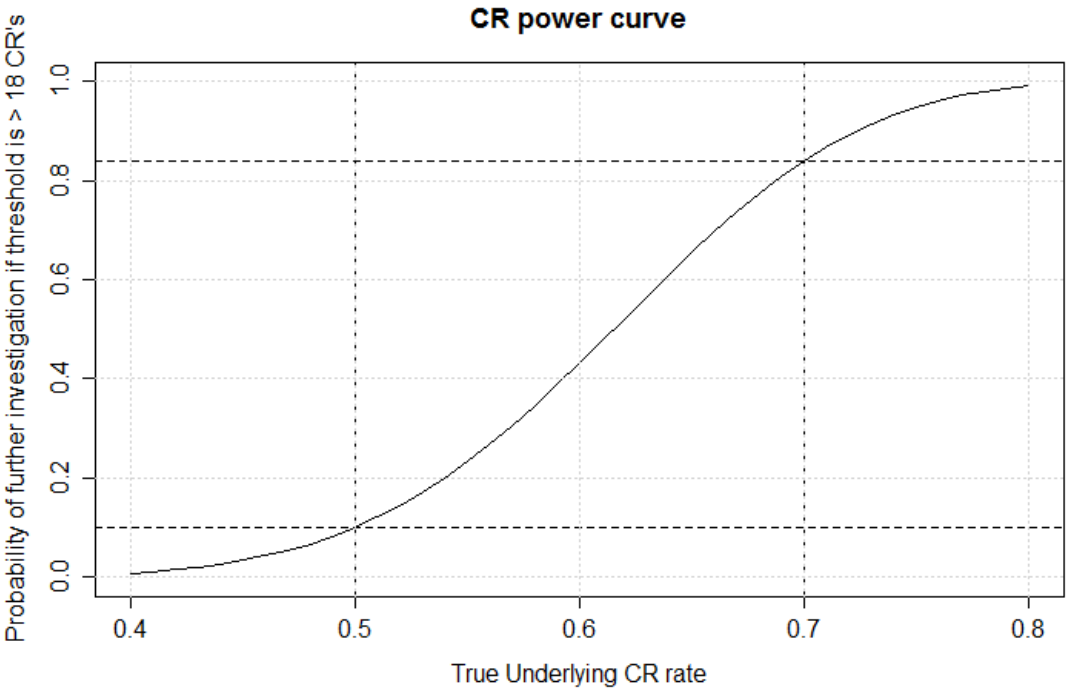

Figure 3: Probability of further investigation as a function of true underlying CR rate.

8.3 Methods of analysis

Binary proportions (UT and CR proportions) and their 95% CI's will be provided using the Clopper-Pearson method. Table 10 provides estimates and 95% CI's for various observed counts from a sample size of 30.

Table 10: Estimated proportions and corresponding 95% CI's for a sample size of 30.

Count	Estimate	95% CI
3	0.1	[0.02, 0.27]
6	0.2	[0.08, 0.39]
9	0.3	[0.15, 0.49]
12	0.4	[0.23, 0.59]
15	0.5	[0.31, 0.69]
18	0.6	[0.41, 0.77]
21	0.7	[0.51, 0.85]
24	0.8	[0.61, 0.92]
27	0.9	[0.73, 0.98]

When estimating the UT rate and its 95% CI, the methods of Jung & Kim (2004) and Koyama & Chen (2008) will be used to adjust for the two stage sampling procedure.

It is expected that it will take two years to accrue the required 30 patients. Accrual will not be suspended pending the results of the interim analysis.

OS, DMFS and LRPFS will be characterized using Kaplan-Meier curves.

Both DMFS and LRPFS will be measured from the date of patient registration. DMFS will be measured until the date of first commencement of any non-protocol anti-cancer therapy, detection of distant metastasis, or death due to any cause. LRPFS will be measured until the date of first commencement of any non-protocol anti-cancer therapy, detection of local or regional progression, or death due to any cause. Occurrence of distant metastasis will be a censoring event for measurement of LRPFS. There are no censoring events for DMFS.

8.4 Exploratory analysis

Tissue, blood and urine will be collected for biomarker analysis as part of the study. Requirements for biomarkers analysis are described in PCR-MIB Biomarker Laboratory Manual.

Resected tumour specimens will be available from the patients enrolled on the trial. These pre-treatment specimens will be comprehensively profiled for the abundance and composition of tumour infiltrating lymphocytes (CD4, CD8, CD3, CD20 and FoxP3 positive cells) by immunohistochemistry using the state-of-the-art Vectra Automated Imaging system recently acquired by the ONJCRI which enables multiplexed immunohistochemical analysis. Descriptive statistics will quantify individual immune parameters and correlation with response.

Blood samples collected prior to treatment, at the end of chemoradiotherapy, and after 24 weeks will be collected from the patients on the trial. PBMCs will be isolated using Ficoll, and changes in specific immune subpopulations (number/ratio) determined by multi-parameter FACS. Changes in the immune regulatory molecules OX-40/LAG3/PD1/ICOS on T cell subsets will be assessed by flow cytometry. Descriptive statistics will quantify individual immune parameters and correlation with response.

Changes in gene expression in CD3+ cells pre and post-treatment will be determined by RNAseq analysis to assess for gene expression changes associated with immune activation [9]. Descriptive statistics will quantify individual immune parameters and correlation with response.

Finally, to independently monitor B cell responses, pre- and post-treatment serum samples from the 30 trial patients will be analysed using CT100 microarrays for changes in titres of 100 cancer-testis auto-antibodies [10]. Descriptive statistics will quantify individual immune parameters and correlation with response.

Other immune endpoints potentially measurable using the biomarker resources from the trial include but not are not limited to circulating DNA, antibody titres, peripheral blood markers of immune change and urine detectable immunological markers.

8.5 Timing of Analyses

A total of three analyses will be performed.

1. The interim analysis for the primary objective (feasibility) will take place after the 10th patient has reached the 31 week assessment time point.

2. Provided that the interim analysis does not result in the trial being closed prematurely due to unacceptable toxicity, the final analysis for the primary objective will take place after the last patient has reached the 31 week assessment time point.

3. Provided that the interim analysis does not result in the trial being closed prematurely due to unacceptable toxicity, the analysis for the secondary efficacy objectives, as well as the analysis of any exploratory objectives, will take place after the last patient has reached 3 years past registration.

9.0 SAFETY PARAMETERS/REVIEW AND MODIFICATIONS TO TRIAL

Given the experimental nature of the addition of pembrolizumab to concurrent chemoradiation, the following safety measures will exist

1) The trial operations executive (TOE) and the trial management committee (TMC) will review safety issues related to the trial through regular teleconferences held throughout the trial.

2) An additional safety review by the TMC will take place 12 weeks after completion of treatment for the 10th patient whereby accrual will be halted if we see greater than 5 UT's amongst the first 10 patients recruited using the Simon's two stage design described above in 8.2. Accrual can continue until the results of the interim analysis are available to the TMC.

3) Modifications to trial

    a. Based on safety discussion the TMC may recommend to either

        i. Omit concurrent pembrolizumab with chemoradiotherapy, and give pembrolizumab 200mg IV q3 weekly at week 7, 10, 13, 16 and 19 alone

        ii. Modify the chemotherapy arm to allow either carboplatin, or 5FU/MMC [8]

        iii. Suspend the study

iv. Any other modification suggested to reduce toxicity made by the TMC

The enrolment to the trial will be monitored by theTMC and if enrolment is reduced due to concerns regarding design of the trial, the TMC will suggest modifications that may include modification of the chemotherapy arm to allow concurrent carboplatin or 5FU/MMC.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Detailed description is in the Pharmacy Manual.

Clinical Supplies will be provided by Merck and distributed by the central pharmacy are summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

10.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the distribution central pharmacy, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11.0 STUDY COMMITTEES

11.1 Trial Management Committee

This study is conducted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) in collaboration with the Centre for Biostatistics and Clinical Trials (BaCT) who will coordinate this study

Study coordination, data acquisition and management and statistical analysis will be performed by the Centre for Biostatistics and Clinical Trials at Peter Mac.

The Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

The TMC will consider whether to continue the study as planned, modify, or stop it, based on reports provided by the BaCT or other information.

12.0 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the participating trial sites and at the Centre for Biostatistics and Clinical Trials at Peter Mac, U and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

12.2 Protocol Amendments

Changes and amendments to the protocol and patient information and consent form (PICF) can only be made by the Sponsor and/or its delegate. Approval of amendments by the

Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

12.3 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded electronically on the Electronic Data Capture e-sytem provided by the Centre of Biostatistics and Clinical Trials. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. Site investigator's will be asked to confirm the accuracy of completed eCRFs by signing key eCRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites and copies provided to BaCT when requested. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

a. Subject's name, contact information and protocol identification.

b. The date that the subject entered the study, and subject number.

c. A statement that informed consent was obtained (including the date).

d. Relevant medical history

e. Dates of all subject visits and results of key trial parameters.

f. Occurrence and status of any adverse events.

g. The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.

All study-related documentation at ANZ sites will be maintained for 25 years following completion of the study.

12.4 Compliance with Trial Registration and Results Posting Requirements

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research

Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no participant will be recruited to the study until all the necessary approvals have been obtained and the participant has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the coordinating center, principal investigator and HREC must be advised immediately.

The sponsor will ensure that information on the trial is listed through the Clinical Trials Data Bank, http://www.clinicaltrials.gov.

12.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

12.6 Audit and Inspection

This study may be subject to audit or inspection by representatives of the collaborative group or the Centre for Biostatistics and Clinical Trials (BaCT) or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA)), US Food and Drug Administration (FDA)).

12.7 Statistical Report

A Statistical Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication. The Statistical Report or summary thereof will be provided to the study investigators, ANZUP and the ethics committees.

12.8 Publication Policy

Authorship recognises the intellectual contributions of investigators and others to a study. It also identifies those who take public responsibility for the study. Authorship is defined as per ICMJE guidelines (www.icmje.org). The Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. The Writing Committee will develop a publication plan, including authorship, target journals, and expected dates of publication. The first publication will be the report of the full trial results based on the main protocol using the study group name with a list of specific contributions at the end. ANZUP will be acknowledged in all publications. All publications must receive prior written approval from the TMC prior to submission

13.0 APPENDICES

13.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

13.2 Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

14.0 REFERENCES

1. Rödel, C., C. Weiss, and R. Sauer, *Trimodality treatment and selective organ preservation for bladder cancer.* Journal of clinical oncology, 2006. **24**(35): p. 5536-5544.
2. Koga, F. and K. Kihara, *Selective bladder preservation with curative intent for muscle-invasive bladder cancer: A contemporary review.* International Journal of Urology, 2012. **19**(5): p. 388-401.
3. Musch, M., et al., *Comparison of early postoperative morbidity after robot-assisted and open radical cystectomy: results of a prospective observational study.* BJU international, 2014. **113**(3): p. 458-467.
4. Nepple, K.G., et al. *Early oncologic outcomes of robotic vs. open radical cystectomy for urothelial cancer*. in *Urologic Oncology: Seminars and Original Investigations*. 2013. Elsevier.
5. Efstathiou, J.A., et al., *Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience.* European urology, 2012. **61**(4): p. 705-711.
6. Coppin, C., et al., *Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group.* Journal of Clinical Oncology, 1996. **14**(11): p. 2901-2907.
7. Sabaa, M.A., et al. *Combined modality treatment with bladder preservation for muscle invasive bladder cancer*. in *Urologic Oncology: Seminars and Original Investigations*. 2010. Elsevier.
8. James, N.D., et al., *Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer.* New England Journal of Medicine, 2012. **366**(16): p. 1477-1488.
9. Mak, R.H., et al., *Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233.* Journal of Clinical Oncology, 2014. **32**(34): p. 3801-3809.
10. Kachnic, L.A., et al., *Bladder preservation by combined modality therapy for invasive bladder cancer.* Journal of clinical oncology, 1997. **15**(3): p. 1022-1029.
11. Powles, T., et al., *MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer.* Nature, 2014. **515**(7528): p. 558-562.
12. Gogna, N.K., et al., *Efficacy and tolerability of concurrent weekly low dose cisplatin during radiation treatment of localised muscle invasive bladder transitional cell carcinoma: a report of two sequential Phase II studies from the Trans Tasman Radiation Oncology Group.* Radiotherapy and oncology, 2006. **81**(1): p. 9-17.
13. Demaria, S., et al., *Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated.* International Journal of Radiation Oncology* Biology* Physics, 2004. **58**(3): p. 862-870.
14. Hiniker, S.M., D.S. Chen, and S.J. Knox, *Abscopal effect in a patient with melanoma.* N Engl J Med, 2012. **366**(21): p. 2035.
15. Apetoh, L., et al., *Combining immunotherapy and anticancer agents: the right path to achieve cancer cure?* Annals of Oncology, 2015: p. mdv209.

16. Giaccone, G., et al., *Safety, activity and biomarkers of atezolizumab (MPDL3280A) with platinum-based chemotherapy (chemo) in non-small cell lung cancer (NSCLC): A Phase Ib study.* ESMO, 2015. **P247**.
17. Vincent, J., et al., *5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell–dependent antitumor immunity.* Cancer research, 2010. **70**(8): p. 3052-3061.
18. Papadimitrakopoulou, V., et al., *Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 Cohorts A and C.* J Clin Oncol (Meeting Abstracts), 2015. **33**(15_suppl): p. 8031-.
19. Birkenhake, S., et al., *Concomitant radiochemotherapy with 5-FU and cisplatin for invasive bladder cancer.* Strahlentherapie und Onkologie, 1999. **175**(3): p. 97-101.
20. George, L., et al., *Clinical outcome in patients with locally advanced bladder carcinoma treated with conservative multimodality therapy.* Urology, 2004. **64**(3): p. 488-493.
21. Rödel, C., C. Weiss, and R. Sauer. *Organ preservation by combined modality treatment in bladder cancer: the European perspective*. in *Seminars in radiation oncology*. 2005. Elsevier.
22. Housset, M., et al., *Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study.* Journal of clinical oncology, 1993. **11**(11): p. 2150-2157.
23. Pos, F., et al., *Lipiodol injection for target volume delineation and image guidance during radiotherapy for bladder cancer.* Radiotherapy and Oncology, 2009. **93**(2): p. 364-367.
24. Hussain, S., et al., *A phase I—II study of synchronous chemoradiotherapy for poor prognosis locally advanced bladder cancer.* Annals of oncology, 2001. **12**(7): p. 929-935.