A parallel group phase I/II marker lesion study to assess the safety, tolerability and efficacy of intravenous or intravesical Pembrolizumab in intermediate risk recurrent non-muscle invasive bladder cancer

Statistical Analysis Plan

Version 2.0 – 03Nov2017

Based on Protocol version 2.0 – 28Jul2017

Name	Title	Role (Author/Reviewer/Approver)
Peter Dutton	Medical Statistician	Author, Approver
Joanna Moschandreas	Senior Medical Statistician	Author, Approver
Lucy Griffiths	Trial Manager	Reviewer
Andrew Protheroe	Chief Investigator	Reviewer & Approver

Oncology Clinical Trials Office (OCTO)
Oxford Clinical Trials Research Unit (OCTRU)
Centre for Statistics in Medicine (CSM)

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1. Introduction

This document details the proposed presentation and analysis for the main paper(s) reporting results from the parallel group phase I/II marker lesion study to assess the safety, tolerability and efficacy of intravenous or intravesical pembrolizumab in intermediate risk recurrent non-muscle invasive bladder cancer (PemBla), funded by the Oxford NIHR Biomedical Research Centre, CRUK Oxford Centre and Merck Sharp & Dohme. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Key personnel

List of key people involved in the drafting and reviewing this SAP, together with their role in the trial and their contact details.

Trial statisticians

Mr Peter Dutton
Medical Statistician
Centre for Statistics in Medicine
University of Oxford
Botnar Research Centre
Windmill Road
Oxford. OX3 7LD
Email: peter.dutton@csm.ox.ac.uk

Dr Joanna Moschandreas
Senior Medical Statistician
Centre for Statistics in Medicine
University of Oxford
Botnar Research Centre
Windmill Road
Oxford. OX3 7LD
Email: joanna.moschandreas@csm.ox.ac.uk

Trial Manager
Mrs Lucy Griffiths

Oncology Clinical Trials Office (OCTO)
Department of Oncology, The University of Oxford
Old Road Campus Research Building
Oxford OX3 7DQ, UK
Tel: +44 (0)1865 227190 or 617013
Email: octo-pembla@oncology.ox.ac.uk

Chief Investigator
Dr Andrew Protheroe
Department of Oncology
Oxford Cancer and Haematology Centre
Churchill Hospital
Oxford University Hospitals NHS Trust
Old Road, Oxford. OX3 7LJ
Tel: +44 (0)1865 572300
Email: andrew.protheroe@oncology.ox.ac.uk

2. Background Information

This trial will evaluate the safety and efficacy of intravenous and intravesical administration of Pembrolizumab, a PD-1 inhibitor, in the setting of recurrent intermediate risk bladder cancer.

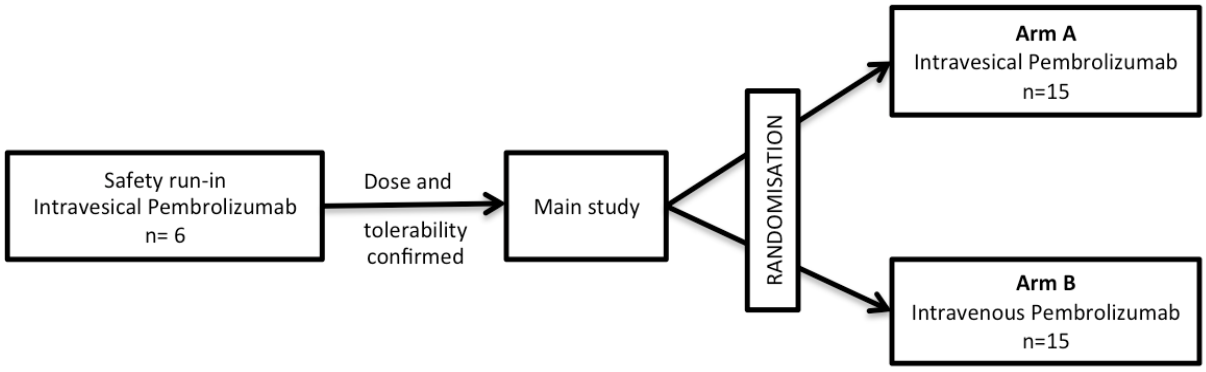
2.1 Research Hypotheses and Study Objectives

Primary Objective	**Endpoints/ Outcome measures**
• To assess the safety, tolerability and toxicities of intravesical and intravenous pembrolizumab after TURBT in patients with intermediate risk NMBIC	• Incidence and severity of adverse events (NCI CTCAE v4.03)
Secondary Objectives	**Endpoints**
• To provide a preliminary assessment of efficacy of treatment with intravesical pembrolizumab in patients with intermediate risk NMIBC	• Complete response rate of marker-lesion as assessed clinically at TURBT and confirmed on biopsy of tumour bed • Recurrence and progression free interval
• To provide a preliminary assessment of efficacy of treatment with intravenous pembrolizumab in patients with intermediate risk NMIBC	• Complete response rate of marker-lesion as assessed clinically at TURBT and confirmed on biopsy of tumour bed • Recurrence and progression free interval
Tertiary/Exploratory Objectives	**Endpoints**
• Determine correlation between expression of PD-L1, PD-L2 and PD-1+ infiltrating lymphocytes and efficacy of pembrolizumab therapy after TURBT in intermediate risk NMIBC patients	• Tumour/stromal cell PD-L1 and PD-L2 expression and presence of PD-1+ infiltrating lymphocytes in pre and post treatment tumour samples measured by immunohistochemistry and FACS analysis

• Definition of gene expression signatures and genetic profiles capable of predicting efficacy of pembrolizumab treatment in NMIBC patients.	• Gene expression profiling and DNA sequencing on pre-treatment blood and tumour samples
• To evaluate the effects of pembrolizumab treatment on the immunological profile and tumour specific immune responses in patients with intermediate risk NMIBC • Identification of myeloid or T cell responses in the tumour microenvironment associated with response to treatment	• Analysis of TCR repertoire and clonality of infiltrating T cells in resected tumour specimens, urine and normal bladder tissue • Analysis of TCR repertoire and clonality of PBMC before, during and after treatment • Analysis of cytokines in blood and urine
• To investigate the pharmacokinetics of intravesical pembrolizumab	• Analysis of blood levels of pembrolizumab during treatment

2.2 Study Design and trial expected time-points

The PemBla trial is a parallel group, open label, multi-centre, phase I/II marker-lesion study in recurrent intermediate risk NMIBC. Thirty patients (fifteen in each of two arms) will be randomised 1:1 to treatment with either intravesical pembrolizumab (Arm A) or intravenous pembrolizumab (Arm B). The main study will be preceded by a single institution safety run-in phase involving intra-patient dose escalation in six patients to confirm the safety and tolerability of intravesical pembrolizumab and the dose to be used in the randomised phase. The primary outcomes are safety, tolerability and toxicity.



Date of grant activation:	21Apr2017 (date contract between UOxford and Merck fully executed)
Date of start of recruitment:	Expected 01Aug2017
Date expected end of recruitment:	15Mar2019
Date expected end follow-up:	15Mar2021
Date expected start of analysis:	Final analysis expected spring/summer 2021
Date end of grant:	Grant is not date bound but paid in milestones, final payment will be upon verification of Final study results posted on Clinicaltrials.gov
Target number of subjects:	36 (6* + 15 per arm)

Participating Centres: 3 - Churchill, Royal Surrey and Southampton General

*For phase I six evaluable patients are required so more patients may be recruited to fulfil this criteria.

2.3 Eligibility

2.3.1 Inclusion criteria

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

1. Be willing and able to provide written informed consent for the trial and comply with the protocol scheduled follow-up visits and examinations for the duration of the study
2. Be ≥ 18 years of age on day of signing informed consent
3. Have recurrent NMIBC for which adjuvant treatment post TURBT would be a reasonable treatment option
4. Main study only:
    a. Have recurrent, multiple (minimum 2) tumours consistent with NMIBC
    b. Have at least one lesion of between 5-10mm in size clinically that can be left un-resected at TURBT as the marker lesion
    c. Have histologically confirmed low grade transitional cell NMIBC at original and any subsequent diagnosis
5. Have a normal upper urinary tract (as evidenced by ultrasound or CT urography within 2 years prior to randomisation) and no evidence of tumour in prostatic urethra at flexible cystoscopy
6. Have a performance status of 0 or 1 on the ECOG Performance Scale
7. Have adequate organ function as defined in the table below:

Lab Test	Value required
Haemoglobin (Hb)	≥ 9 g/dL without transfusion or EPO dependency
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Total bilirubin	≤ 1.5 times the upper limit of normal (ULN) or direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST)	≤ 2.5 x ULN
Serum creatinine OR Measured or calculated creatinine clearance[a]	≤ 1.5 x ULN OR ≥ 60ml/min for subject with creatinine levels > 1.5 x institutional ULN
Albumin	≥ 25g/L
International Normalized Ratio (INR) or Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or APTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated as per institutional standard	

8. Female subjects of childbearing potential should have a negative urine or serum pregnancy test at screening and within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
9. Both male and female subjects of childbearing potential (Section 5.1) must be willing to use an adequate method of contraception as outlined in section 5.1 for the course of the study and until 120 days after the last dose of the study medication

2.3.2 Exclusion criteria

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

1. Has received prior radiotherapy to the pelvis
2. Has significant urinary incontinence or known bladder instability
3. Main study only:
    a. Has more than 2 out of 3 of the following present at the current time:
        i. ≥ 8 tumours
        ii. Tumour ≥ 3cm in size
        iii. Frequent recurrence (> 1/year)
    b. Has a previous history of any of the following: T1 tumour, high grade/G3 tumour, carcinoma in situ, multiple recurrent large (> 3cm) Ta, G1 or G2 tumours.
    c. Had a primary tumour of unknown pathological stage or grade
    d. Has disease for which resection of all visible tumours is not possible
4. 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 28 days of the first dose of trial treatment
5. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Subjects requiring use of inhaled or intranasal corticosteroids or local steroid injections would not be excluded
6. Has a known history of active TB
7. Has received intravesical BCG treatment within 30 days prior to the first dose of trial treatment
8. Has hypersensitivity to pembrolizumab or any of its excipients
9. Has had treatment with any other anti-cancer monoclonal antibody within 28 days prior to enrolment or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier
10. Has had treatment with prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of administration of study drug or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
11. Has a known additional malignancy that is progressing or requires active treatment. 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
12. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurological symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for a t least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability
13. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin or physiologic corticosteroids replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment
14. Has a known history of, or any evidence of active, non-infectious pneumonitis
15. Has an active or intractable infection requiring systemic therapy
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator
17. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial

18. 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 to 120 days after the last dose of trial treatment
19. Has received prior therapy with an anti-PD-1, anti PD-L1, or anti-PD-L2 agent
20. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)
21. Has known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected)
22. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

2.4 Treatment Interventions

Both experimental treatments arms will give Pembrolizumab. Arm A will be given by intravesical administration at a dose and schedule to be determined by the TMG following analysis of the safety run-in. Arm B will be by intravenous infusion at a dose of 200mg. See Figure 2.1 for details.

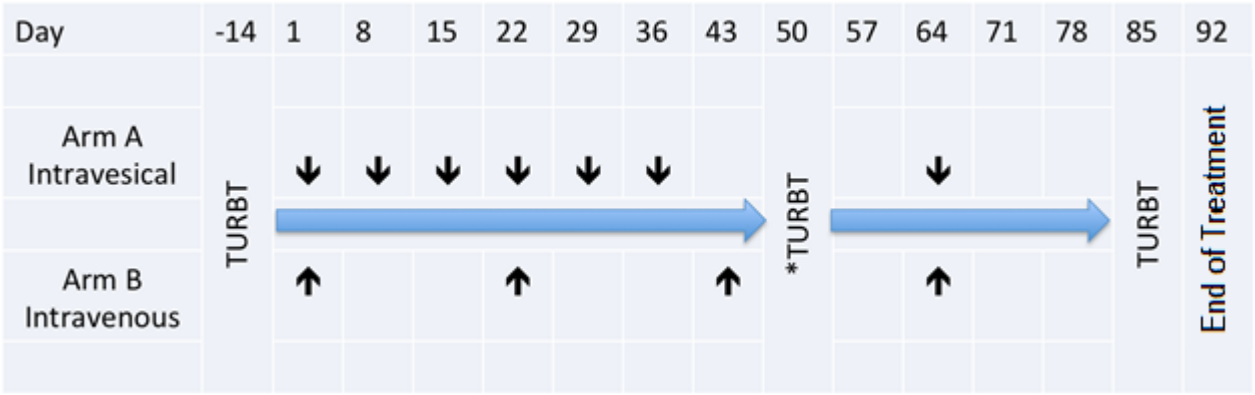


Figure 2.1 Schedule of treatment administration for main study. *TURBT for resection of second non-marker lesion in at least 5 patients in each arm. Black arrows denote treatment administration

2.5 Sample Size

The primary aim of this study is safety, tolerability and toxicity and therefore the sample size has been chosen to give reasonable information on these endpoints. In considering the secondary endpoint of response, using A'Hern's single stage phase II design with significance level 0.05 (one sided), power 0.8, we have set 20% as the highest level of efficacy at which we would not continue to another trial (A'Hern, 2001). Based upon existing intravesical therapies a complete response rate of 55% may be achievable. The 20% threshold requires a minimum of 13 patients in each arm of the trial, and if there are 6 successes in an arm then a 55% complete response rate is plausible. Thirty patients will be randomised in total, to allow for drop out - No adjustment will be made for the multiple testing caused by having two arms.

2.6 Randomisation

Randomisation will be 1:1 by minimisation, using site as a stratification variable. Patients will be assigned with a probability of 0.8 to the treatment that minimises the imbalance (Brown et al, 2005).

Full details on the randomisation schedule are available in the Randomisation and Blinding Plan, stored in the confidential statistical section of the TMF.

2.7 Outcomes Assessment Schedule

Visit Description	Screening	TURBT	Pre-treatment	On treatment									TURBT	End of treatment visit	Follow-up
Day	**-44 to -15**	**-14**	**-13 to 1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64**	**85 +/-7**	**92§ +7**	
Informed consent	X														
Demographics & History	X														
Concomitant medication	X			X	X	X	X	X	X	X		X		X	
Physical examination	X			X	X	X	X	X	X	X		X		X	
Height and weight	X														
ECOG PS	X			X	X	X	X	X	X	X		X		X	
Vital signs[a]	X			X	X	X	X	X	X	X		X		X	
Blood for haem and biochem[b]	X			X	X	X	X	X	X	X		X		X	
Blood for TFTs[c]	X						X			X		X		X	
Urinalysis[d]	X			X	X	X	X	X	X	X		X		X	
Pregnancy test	X			X				X		X		X		X	
Blood for germline DNA[e]				X											
Blood for immunoprofiling[f]		X		X	X	X	X	X	X	X	X[+]	X	X		
Inclusion/exclusion criteria	X														
Resection of bladder tumour(s) TURBT		X									X[+]		X*		
Tumour assessment		X											X*		
Bladder barbotage		X									X[+]		X*		
Bladder biopsy[g]		X									X[+]		X*		
Registration	X														
Randomisation			X*												
AEs		X		X	X	X	X	X	X	X		X		X	
Urine for cytokines[h]				X	X	X	X	X	X	X	X	X	X		
Research Blood **[i]				X					X						
Administration of intravesical Pembrolizumab (Safety run-in and Arm A) [j]				X	X +/-1	X +/-1	X +/-1	X +/-1	X +/-1			X* +/-1			
Administration of intravenous Pembrolizumab (Arm B) [j]				X			X +/-3			X +/-3		X +/-3			
Recurrence data (RFS and PFS)															X
Optional tumour sample at recurrence or progression															X

Visits shaded in grey are only applicable to patients who are due for drug administration on that day

* For patients in the main study only (not patients in safety-run in)

** For patients receiving intravesical treatment only

[+] For patients who have consented to having second non-marker lesions resected only

[§] The end of study visit for patients in the safety run-in will be performed on day 64

[a] Vital signs to include systolic / diastolic blood pressure, pulse rate, respiratory rate, oxygen saturations and temperature. To be performed according to the vital signs scheduling details in section 8.3.

[b] To include FBC, clotting screen, sodium, potassium, urea, creatinine, calcium, phosphate, total protein, albumin, bilirubin, ALP, AST and/or ALT

[c] To include TSH, T3 and T4

[d] To include Blood, White Cells, Protein, Nitrites, pH, culture and sensitivity

[e] 10ml of blood in EDTA tube, taken pre-treatment

[f] 50ml of blood in Na-Heparin tubes

[g] Biopsy of normal bladder epithelium ± tumour bed if complete response of marker lesion

[h] For patients receiving intravesical treatment, urine for cytokines will be collected pre-dose and post-dose (first post-treatment urine sample after the drug has been voided from the bladder) on day 1 and thereafter post-dose only. For patients receiving intravenous treatment, urine for cytokines will be collected pre-dose only.

[i] Blood for research will be taken pre-dose and 2 hours post dose (counted from the completion of syringe/catheter administration of suspension into the bladder) for patients receiving intravesical treatments on day 1, and pre-dose only at cycle 6 (d36).

[j] Trial treatment should begin 14 days after TURBT or as close as possible to this date.

3. Quality Control and Data Validation

The PemBla Trial Office will monitor the compliance of study sites taking part in the trial on an ongoing basis. Where non-compliance with the protocol or the standard procedures set out in the Investigator Agreement is suspected, the Chief Investigator for the study will contact the study site to resolve any problems. If appropriate, the matter will be referred to the PemBla Trial Management Group at their next meeting or by correspondence with members if urgent.

OCTO staff will be responsible for checking forms for compliance with the protocol, data consistency, missing data, timing and maintaining regular contact with site personnel to check on progress and deal with queries as they arise.

Duplicate analysis of the response endpoint will be undertaken by a second statistician and this will be documented in the final statistical report. Any deviation in these analyses will be accounted for and corrections made.

The primary outcome and key secondary outcomes will be analysed, following the analyses detailed in this SAP, by a second statistician independently using different statistical software (if possible). Any discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report).

4. Interim Analysis and Data Review

There is no Data and Safety Monitoring Committee (DSMC). SAEs upon receipt are reviewed by an independent nominated clinician as part of the trial office SAE Standard Operating Procedure. Cumulative reports of all AEs & SAEs are reviewed by the TMG and an Independent Trial Steering Committee (IEPTOC) will be in place to monitor the safety of the trial on an ongoing basis (IEPTOC meets, on average, 6-monthly).

Section 5 details the monitoring and decision process which will oversee the safety run-in portion of the study. The TMG will be responsible for the day to day monitoring and steering the dosing of patients during this time.

5. Safety run-in decision process

The TMG will be responsible for oversight, monitoring and decision making during the safety run-in portion of the study. This section details the triggers for a TMG meeting as well as the decisions available to the TMG.

5.1 The planned safety run-in (Protocol Section 5.2)

The safety and tolerability of intravesical Pembrolizumab will be evaluated in six evaluable patients following TURBT for NMIBC prior to the main (phase 2) study commencing. Treatment will be administered once weekly according to the following schedule. Intra-patient dose escalation of intravesical Pembrolizumab will be performed in paired patient cohorts with the anticipated doses as shown below.

Table 5-1 Planned dose escalation

Cohort	Patient	Dose of Intravesical Pembrolizumab (mg)					
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
1	1	50	50	100	100	200	200
	2	50	50	100	100	200	200
2	3	100	100	200	200	200	200
	4	100	100	200	200	200	200
3	5	200	200	200	200	200	200
	6	200	200	200	200	200	200

Patients will be assessed for dose limiting toxicities (DLT) as well as for overall tolerability of the treatment. A DLT is defined as a clinically significant, drug related, grade 4 haematological or $\geq$ grade 3 non-haematological toxicity occurring within 7 days of administration of the first treatment at a given dose for that patient. Treatment start dates will be staggered by at least one week between patients. In addition, treatment of patients in cohort 2 and 3 will not commence until both patients in the preceding cohort have cleared the DLT period for the D15 dose.

If more than 1 patient experiences a DLT at a certain dose, this dose will be declared non-tolerated and further escalation will cease. Patients who have already commenced treatment at the same dose and are tolerating treatment may continue at this dose. If a DLT occurs in either patient at the first dose of cohort 1, or in more than 1 patient at subsequent doses, the TMG will meet to consider the available safety data and determine how to proceed. Recruitment of further patients to a cohort or investigation of intermediate doses or treatment intervals may be considered.

Patients who do not receive at least 5 out of the 6 scheduled treatments, except for reasons of drug-related toxicity, will be replaced such that there are 6 patients evaluable for tolerability. Patients who are replaced in this manner are not evaluable.

When considering the dose to take forward to the randomised part of the study the TMG will also consider the overall tolerability of the treatment. Patients must be able to receive at least 5 out of the 6 treatments for the regime to be defined as tolerable.

5.2 Replacement of patients

Six evaluable patients are required for the TMG to confirm the tolerated intravesical dose for the main study. Should a patient become unevaluable and need to be replaced, the patient should be replaced into the same cohort unless the next cohort has already been opened[1] . For example, if patient 2 in cohort 1 does not receive the last two doses and Cohort 2 has already been decided by the TMG to be opened to recruitment, the

[1] Treatment of patients in cohorts 2 & 3 can start once both patients in the preceding cohort have cleared the DLT period for the D15 dose.

replacement patient can be assigned to start as one of the two patients in Cohort 2. To ensure 6 evaluable patients complete the safety period, a third patient would be recruited into Cohort 3.

Cohorts will be considered complete when two patients have successfully received at least 5 doses. Patients who miss more than one dose, except for reasons of drug-related toxicity, will be replaced.

Patients missing more than one dose due to drug-related toxicity will not be replaced[2].

5.3 TMG monitoring and monitoring triggers

Provided that a patient does not experience a DLT the treating investigator will be responsible for the day to day care of the patient including within patient dose escalations. i.e. Intra-patient dose escalation will be overseen and managed by site. No TMG safety review nor OCTO input will be required. Within patient dose escalation will not exceed the doses laid out in

[2] Protocol 6.1 (page 26): "During the safety run in phase patients who do not receive at least 5 out of the 6 scheduled treatments, except for reasons of drug-related toxicity, will be replaced such that there are 6 patients evaluable for tolerability".

Table 5-1.

Planned triggers:

1. In the event of a DLT
2. If it is not clear if a patient is evaluable
3. To review safety data once 2 patients in a cohort have cleared the DLT period for the D15 dose (to make a decision regarding opening the next cohort)
4. The TMG may also decide to review events that would meet DLT criteria except for not occurring within 7 days of administration of the first treatment at a given dose for that patient
5. Upon completion of the run in, to review all safety data prior to opening the main (phase II) study

The TMG will meet if one of the planned triggers occurs. There may be cause for the TMG to meet to review the safety data for some other (unplanned) reason.

5.4 TMG meeting

Upon a monitoring trigger occurring the following procedure will be followed:

1. The Trial Manager (TM) will inform the TMG that a meeting is required following a triggered event, detailing the trigger for the meeting. A date for the meeting will be fixed. The meeting may take place in person, via T/C or via email discussion.
2. The TM may arrange for a datalock to be sent to the statistical team prior to the meeting.
3. The decisions made by the TMG at the meeting will be recorded in the minutes and will be circulated to all parties.

5.5 Data considered by the TMG

The TMG will be provided with available safety data. The TMG may request further data to help make their decisions as informed as possible.

5.6 TMG decisions

The TMG will review all the available data and will be responsible for making informed decisions aimed at finding a safe and tolerable dose while protecting the trial patients from toxic dose levels.
The TMG may make the following decisions during the safety run-in phase:

1. Declare one or more doses toxic, preventing further patients receiving doses at or above this dose. Within patient dose escalation will cease at the highest dose not declared toxic.
2. Determine the patient evaluability and replacement
3. Recruit further patients to a cohort and/or investigate intermediate doses or treatment intervals.

At the end of the safety run-in phase the TMG will meet to decide on the dose which will be taken forward to the randomised phase of the study for the intravesical arm.

6. Specification of Statistical Packages

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS or R statistical software. The relevant package and version number will be recorded in the Statistical report.

7. Descriptive Analyses

7.1 Representativeness of Study Sample and Patient Throughput

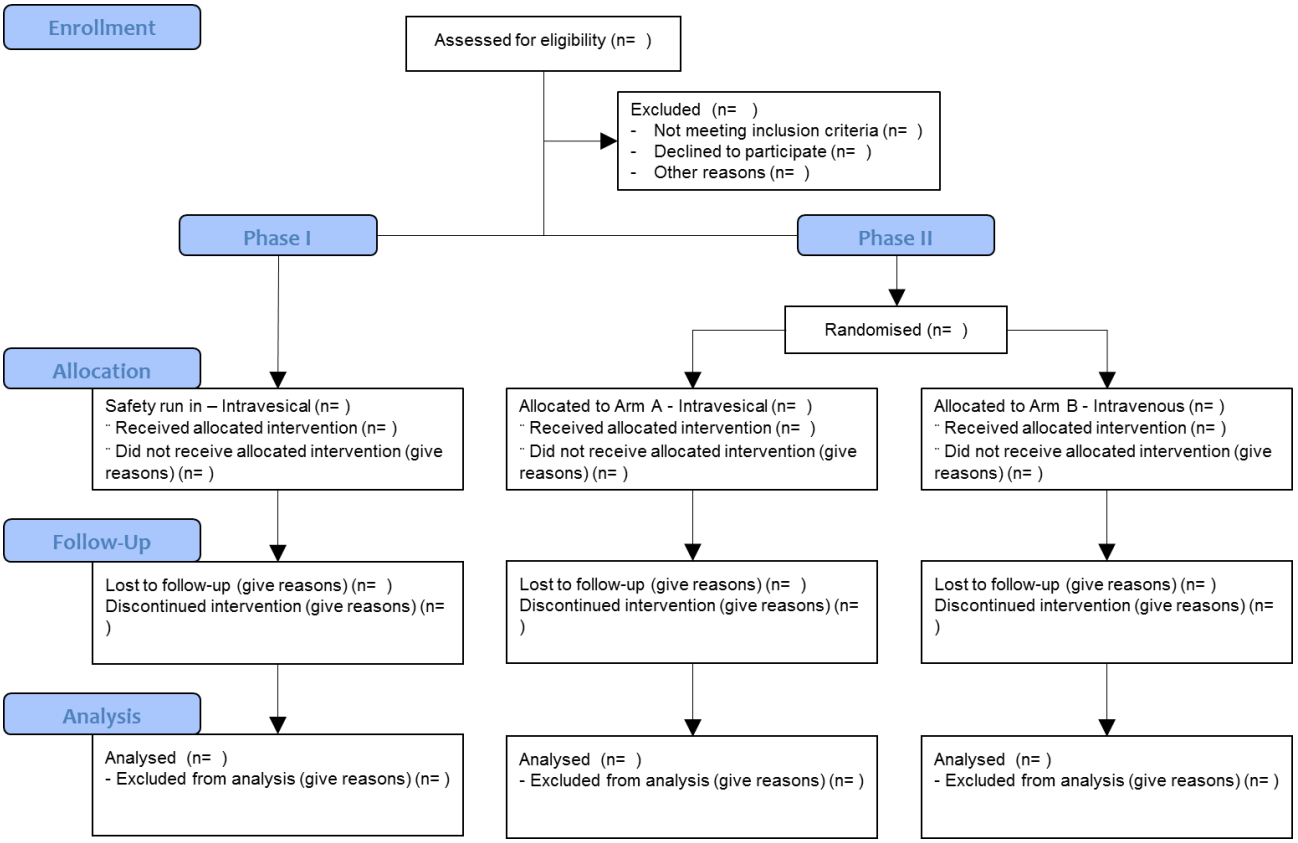


Figure 7.1 Consort flow diagram

A flow diagram of the safety run in will also be provided.

7.2 Baseline Characteristics

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (minimum, maximum) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variables.

Table 7-1 Baseline characteristics

		Safety Cohort 1 (n=)	Safety Cohort 2 (n=)	Safety Cohort 3 (n=)	Arm A (n=)	Arm B (n =)
Age	Mean (SD)[1]					
Gender	Male					
Ethnicity	…					
Smoking status	Current					
	Ex-smoker					
	Never smoked					
Site of primary Tumour	…					
Histology	…					

Prior Surgery	Yes					
Prior Chemo and/or intravesical treatment	Yes					
Treating Centre	Churchill					
	Royal Surrey (Guildford)					
	Southampton General					

[1]Or median (min, max) if not normally distributed.

7.3 Comparison of Losses to Follow-up

Loss to follow-up together with reasons will be reported for each separate cohort in the intravesical safety run-in and by intervention arm in the randomised stage of the study. There will be no statistical comparison between arms.

7.4 Description of Available Data

Missing data will be investigated and supplemented where possible. The completeness and correctness of the data will be monitored as per the monitoring plan.

The number of patients with missing data will be presented by each dose level. The reason for missing data will be indicated e.g. loss to follow-up, consent withdrawn, removed from study due to serious adverse events, death.

7.5 Description of Compliance with Intervention

The compliance with treatment will be reported by treatment group in a graphical and tabular format. Dose delays, omissions and reduction will be reported with reasons where available.

7.6 Unblinding of Randomised Treatments

The study is unblinded and there is no direct comparison between treatment arms. For this reason all analysis will be unblinded.

7.7 Reliability

Data derivation/manipulation will be checked to ensure validity of the derived data, where appropriate.
Calculations performed by the computer may be checked by hand for 10 observations within the dataset, where appropriate.
Analysis of the primary and secondary endpoints may be checked independently.

8. Definition of populations for Analysis

Populations for analysis are defined as follows:

Population for (DLT and tolerability) safety run-in analysis: patients receiving at least 5 out of 6 scheduled treatments, or withdrawing early due to drug-related toxicity, will contribute to the DLT and tolerability analysis. Patients who do not receive at least 5 out of the 6 scheduled treatments, except for reasons of drug-related toxicity, will be excluded and replaced, such that there are 6 patients evaluable for tolerability.

Safety population: all participants who receive at least part of one dose of trial treatment will be evaluable for the safety analyses. In the safety run-in part of the study, all safety population patients will be evaluable

for AEs. In the main study, safety analysis of patient data will be undertaken according to the treatment actually received (not as randomised).

Population for efficacy analysis: all analyses in the main trial will be on a modified intention-to-treat basis. This means that patients will be analysed as they are randomised irrespective of the treatment actually received. The intention-to-treat population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomisation number. This will be modified by omitting patients without the endpoint/outcome measure.

9. Analyses to address primary aims

The primary aim is to assess the safety, tolerability and toxicities of intravesical and intravenous pembrolizumab.

9.1 Intravesical safety run-in

The number of patients experiencing a dose limiting toxicity (DLT) per cohort will be reported. Full details of all dose limiting toxicities will be listed. No formal comparison will occur between dose levels.

A DLT is defined as a clinically significant, drug related, grade 4 haematological or $\geq$ grade 3 non-haematological toxicity occurring within 7 days of administration of the first treatment at a given dose for that patient.

A summary of worst reported AEs will tabulated by cohort and graphs of worst adverse events over time will be produced and presented according to whether they are considered treatment-related or not. A summary of drug-related toxicities (as stated in the Protocol, table in Section 8.5) will also be given.

A sensitivity analysis will be carried using the safety population treating patients who withdraw for toxicity without experiencing a DLT as having had a DLT. Patients who withdraw, prior to observing a DLT, for any other reasons will be excluded.

9.2 Main study (Phase II trial)

The number and proportion of patients experiencing a grade 3-5 adverse event will be reported for each treatment group with 95% confidence intervals. The same analysis will be repeated for SAEs. Numbers and proportions with grade 1+ adverse events will also be reported.

A summary of worst reported AEs will tabulated by treatment arm and graphs of adverse events over time will be produced.

9.3 Pre-specified Subgroup Analysis

There are no pre planned subgroup analyses.

9.4 Treatment by Centre Interaction

No analysis of within centre effects will be done. The trial will not recruit a sufficient number of patients to explore this.

10. Analysis to address secondary aims

10.1 Efficacy

Complete response of marker lesion (CR) occurs:

1. when the marker lesion is not visible (at surgery on day 85) and there is a negative tumour bed biopsy (pathological CR) or
2. when the marker lesion is not visible (at surgery on day 85) but there is no negative tumour biopsy i.e. microscopic evidence of tumour or no biopsy done/biopsy NE (clinical CR)

The number and proportion of patients with a CR (and 90% CI) at TURBT on day 85 (± 7) will be reported for each treatment arm. A p-value comparing the data to the null hypothesis of p=0.2 will be computed (as per the A'Hern design). Patients who do not have TURBT will be treated as non-responders for the efficacy endpoint.

There are no planned subgroup or sensitivity analyses.

10.2 Recurrence and progression free interval

Recurrence is defined as the appearance of at least one new lesion (in the bladder).

Progression is defined as development of any of the following[3]:

- T1 disease (lamina propria invasion)
- > T2 disease (muscle invasive)
- Lymph node (N1+) or distant metastases (M1)
- High grade (G3) disease or CIS

Since in this setting the definition of progression requires a worsening of disease staging patients may have a recurrence without progression. These events may also occur at the same time.

Patient follow-up is for 2 years or until disease recurrence, progression or death whichever is sooner (Protocol V1.0 17Feb2017). Therefore, if there is progression (with or without recurrence, or vice versa), the patient will be withdrawn from the study.

Recurrence free interval (RFI): Assessed from time of TURBT on day 85 (± 7) to recurrence or progression. Patients in whom there is no recurrence (within the bladder) will be censored at the last-known recurrence free follow-up or at time death. The patients included in the RFI analysis will be those remain on study at day 85 (ie have not had recurrence, progression or died by day 85) , undergo TURBT and are not found to have had a recurrence at that time.

Progression free interval (PFI): Assessed from time of randomisation to progression. Patients who do not progress will be censored at the time of recurrence or death or the last-known progression free follow-up.

Kaplan-Meier curves for RFI and for PFI will be presented for each treatment group, with RFI and PFI estimates given at 6 months, 1 year and 2 years along with 90% CI.

There are no planned subgroup or sensitivity analyses.

11. Additional Analyses

The analysis of the Tertiary / Exploratory endpoints will be detailed in a separate analysis plan being led by the WIMM (Weatherall Institute of Molecular Medicine, University of Oxford). All translational sample

[3] Progression could theoretically occur without recurrence (dramatic progression of the marker lesion or nodal/metastatic disease without a new bladder tumour) but is very unlikely in this population.

analysis will be performed between the WIMM and Qualtek (a 3rd party lab which has been contracted to do the PD-L1 analysis. CSM is not responsible for these analyses.

12. Appendix: Glossary of abbreviations

AE	Adverse events
DLT	Dose limiting toxicities
SAE	Serious adverse events
CI	Chief Investigator
NMIBC	Non-muscle invasive bladder cancer
PFI	Progression free interval
RFI	Recurrence free interval
SAP	Statistical Analysis Plan
TM	Trial Manager
TMG	Trial Management Group
TURBT	Transurethral Resection of Bladder Tumour

13. Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_02Nov2017	Peter Dutton Joanna Moschandreas	Protocol version 1.0 17Feb2017	Not applicable as this is the 1st issue
V2.0_03Nov2017	Peter Dutton	Protocol version 2.0 28Jul2017	Updated to reflect ammendments to protocol

14. References

A'Hern RP (2001) Sample size tables for exact single-stage phase II designs. Stat Med 20(6):859-66

Brown S, Thorpe H, Hawkins K and Brown J (2005) Minimization – reducing predictability for multi-centre trials whilst maintaining balance within centre. Stat Med 24:3715-3727