TRIAL SUMMARY

PROTOCOL TITLE	Phase II Trial of the Immune Checkpoint Inhibitor Pembrolizumab for Patients Suffering from Metastatic Prostate Cancer.
TARGET DISEASE	Metastatic castration resistant prostate cancer (mCRPC).
STUDY OBJECTIVES	Primary objectives: To determine the efficacy of Pembrolizumab 200 mg IV 3-weekly in patients with mCRPC with putative phenotypes associated with immunotherapy sensitivity after progression on standard treatments. Secondary objectives: In patients with mCRPC with putative phenotypes associated with immunotherapy sensitivity: 1. To determine radiological antitumour activity of pembrolizumab 200mg IV 3-weekly after disease progression on standard treatments. 2. To estimate the biochemical antitumour activity of pembrolizumab 200mg 3-weekly after disease progression on standard treatments. 3. To evaluate the duration of survival benefit in patients who receive pembrolizumab 200mg IV 3-weekly after progression on standard treatments. 4. To report the safety of pembrolizumab 200mg IV 3-weekly after progression on standard treatments. Exploratory objectives: 1. To explore the association of high mutational load (HIMUT), Microsatellite Instability (MSI), DNA repair defects including MMR-, PD-1, PD-L1 and PD-L2 positivity and tumour infiltrating lymphocytes with response. 2. To assess tumour tissue for other molecular determinants of response, progression and disease stability using next generation sequencing technology. 3. To assess the baseline clinical characteristics of the subjects enrolled and to correlate these with the acquired molecular and pathological criteria. 4. To collect peripheral blood lymphocytes to explore the association of HIMUT, MSI and MMR- with PD-1 positivity and lymphocyte activation markers.

	5. To analyse whole blood RNA expression signatures from whole blood samples (PAXgene) by expression array (Olmos *et al*, Lancet Oncology 2012).
STUDY DESIGN	The trial involves two parts; Part A and Part B. **Part A:** This is an open-label, single arm, phase II trial initially pursuing a two stage Simon Minimax design [Simon 1989]. **Part A Stage 1:** mCRPC patients will continue their LHRH analogue therapy. This cohort will include 24 patients as the first stage of a two-stage Phase II trial. If more than 5 responses in these first 24 patients are reported the trial will proceed to stage 2. Anti-tumour activity will be assessed (measured by response rates) by PSA, imaging assessments (CT and bone scan, and when indicated whole body MRI) and CTC count measures **Part A Stage 2:** A further 21 patients will be enrolled to this stage, increasing the total number of patients enrolled to 45 patients. Futility will be concluded if ≤5 responses occur in stage 1 or ≤13 responses occur in patients recruited to stage 1 and stage 2. The null hypothesis will be rejected and activity worthy of further research claimed, if >13 responses are reported from the first 45 patients. **Part B:** Biomarker enrichment stage**:** If the null hypothesis from part A is rejected the study may continue, after discussion with the sponsor, with stratified recruitment into biomarker defined cohorts in order to increase the precision with which the response rate can be estimated within mCRPC molecular subgroups of interest. It is anticipated that approximately 55 participants will be enrolled in Part B of the study, to make a total of 100 mCRPC participants in parts A and B, including ≥9 patients for each of the biomarker subgroups: A. MMR defective disease by immunohistochemistry; B. Tumours with evidence of bi-allelic CDK12 loss; C. Tumours with high MSI-NGS with either: • deleterious MMR gene mutation OR; • high CD3 (≥70th centile) OR; • HIMUT (≥11); D. Tumours with HIMUT with either high CD3 or a deleterious mutation in a DNA repair gene; E. The presence of DNA repair defects (HR, NHEJ, NER) with high CD3 count; Each biomarker subgroup (A-E) will follow a Gehan design, with the aim of estimating the response rate within each biomarker subgroup, while discarding cohorts that do not show enough anti-tumour activity (30%). Nine patients per subtype will be initially assessed. The probability of observing no responses

	among 9 patients is less than 0.05 if the true response probability is greater than 30%. If no responses in 9 patients are observed, further investigation in the biomarker-specific cohort will be discarded. If ≥1 responses are seen in 9 patients in a subtype, recruitment would continue to 20-25 patients such that the final estimate of the response rate has a standard error of approximately 10%. Response rates with confidence intervals will be reported for each subtype.
TRIAL POPULATION	mCRPC patients with high mutational load/microsatellite instability (MSI)/other DNA repair defects including mismatch repair (MMR) /high CD3 count, progressing on standard treatments.
RECRUITMENT TARGET	In Part A, initially 24 participants will be entered into this trial in Stage 1; a further 21 participants can be enrolled in Stage 2. If more than 13 responses are observed, a further 55 participants may be enrolled in Part B, to a total of 100 study participants. It is expected that the duration of recruitment will be approximately 24-months. Multiple sites will enrol patients to this trial.
TREATMENT REGIMEN	All patients, who have progressed on standard treatment, will receive pembrolizumab 200mg intravenously on day 1 of a 21-day cycle. Patients may continue with pembrolizumab treatment as long as they remain free from intolerable toxicity for a maximum of two years, if in the Investigator's opinion they are receiving clinical benefit, and/or they do not meet any discontinuation criteria.
PRIMARY ENDPOINT	**Composite response rate by 24 weeks**, defined as the best response observed within 24 weeks of treatment, and on the basis of the following outcomes; if any of these occur, patients will be considered to have responded: • Objective response by iRECIST [1] and modified Prostate Cancer Working Group 3 (modified PCWG3) criteria [2] • CTC count conversion from ≥5 to <5 cells/7.5ml [3] in patients with baseline CTC count ≥5 • PSA decline of ≥50% (PCWG3 criteria [2]). Radiological response has to be confirmed by a second scan four or more weeks after the first scan showing response. PSA and CTC responses will need confirmation by a second consecutive value obtained three or more weeks after the first value indicated a response. Response by PSA or CTC count conversion needs to occur without evidence of radiological progression at the time of the response assessment.

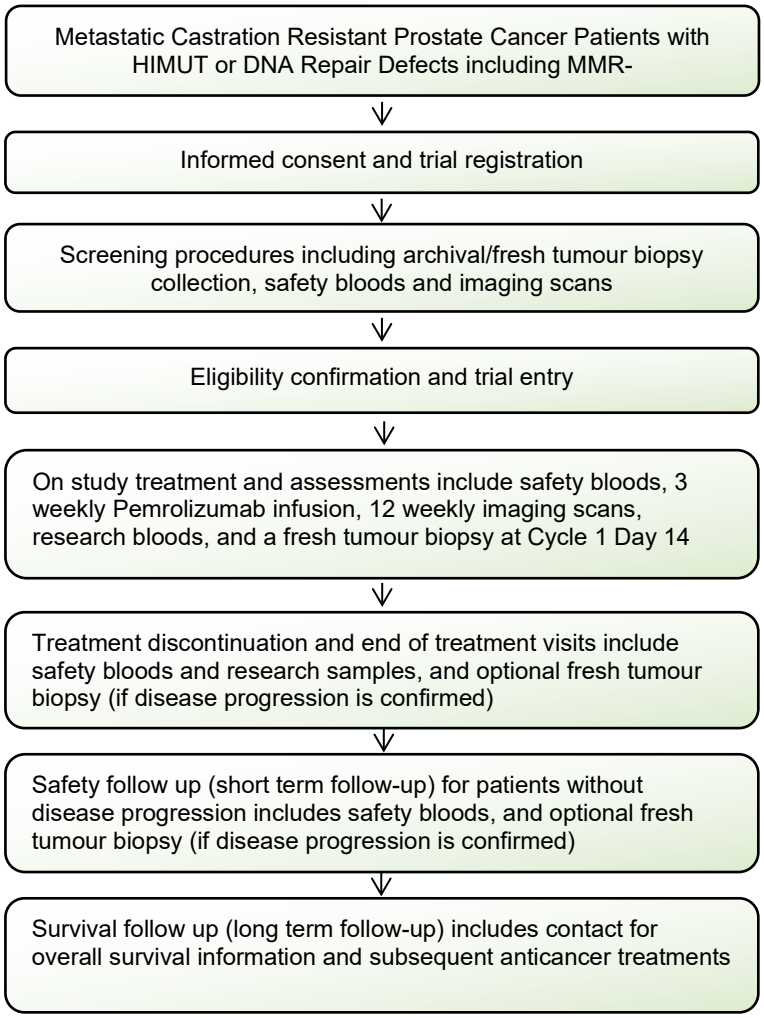
SECONDARY ENDPOINTS	• **Composite response rate while on treatment**, defined as the best response while patient is on treatment and on the basis of objective response by iRECIST, and/or CTC count conversion and/or PSA decline of ≥50%, as defined above for the primary endpoint.
	• **Radiological endpoints:**
	  ○ Radiological progression-free survival (rPFS);
	  ○ Time to radiological progression;
	  ○ Progression free survival (PFS);
	  ○ Bone disease objective response by WBMRI criteria (see Appendix A2).
	• **Biochemical endpoints**:
	  ○ Time to PSA progression;
	  ○ Duration of PSA response (decline of ≥50%);
	  ○ Maximum PSA decline at any time during the trial treatment and PSA decline at 12 weeks.
	• **Overall survival (OS)**
	• **Safety and tolerability as defined by CTCAE v4.0 criteria**

EXPLORATORY ENDPOINTS	• **Molecular endpoints:**
	  ○ Immune checkpoint expression including PD-1, PDL-1 and PDL-2 expression
	  ○ Mutational load (number of mutations per MB of DNA sequenced)
	  ○ Presence of mismatch repair defects as determined by immunohistochemistry, MSI-NGS or microsatellite instability (MSI).
	  ○ CD3, CD8, lymphocyte infiltration
	  ○ T-Reg infiltration (CD4+ CD25+ FoxP3+)
	
	Both diagnostic archival FFPE tumour tissue (when available)
	and fresh mCRPC tumour tissue will be analysed.
	• Next Generation Sequencing (NGS) data from tumour/blood including analyses of neoepitopes by targeted panel NGS (DNA and RNA) and exome/transcriptome analyses when feasible as well as from immune cells (eg T-cell receptor).
	• Immunophenotyping endpoint:
	  ○ WBC immunophenotyping
	• Whole blood mRNA expression profiling

FOLLOW UP	Patients will have an 'off study' visit at the time of treatment discontinuation, and an End of Treatment visit 30-days post last dose of IMP. Patients who discontinued treatment without showing disease progression on imaging scans will enter in the safety follow-up (short term follow up period) and will be followed up for radiological disease progression every 12 weeks

	or until they start the next treatment. Patients with disease progression will be followed up for survival status (long term follow-up).

TRIAL SCHEMA



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