Clinical Trial Protocol

Trial Title:	A phase II study combining pembrolizumab with olaparib in metastatic pancreatic adenocarcinoma patients with mismatch repair deficiency or tumour mutation burden ≥ 4 mutations/Mb
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1 Protocol Signatures:

I give my approval for the attached protocol entitled "A phase II study combining pembrolizumab with olaparib in metastatic pancreatic adenocarcinoma patients with mismatch repair deficiency or tumour mutation burden ≥ 4 mutations/Mb" dated 05 December 2023

Chief Investigator

Name:

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled "A phase II study combining pembrolizumab with olaparib in metastatic pancreatic adenocarcinoma patients with mismatch repair deficiency or tumour mutation burden ≥ 4 mutations/Mb" dated 05 December 2023 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles Articles 2 to 5 of the Good Clinical Practice as outlined in the European Clinical Trials Directives 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, The Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of The Sponsor

Principal Investigator

Name:

Signature: _____

Date: _____

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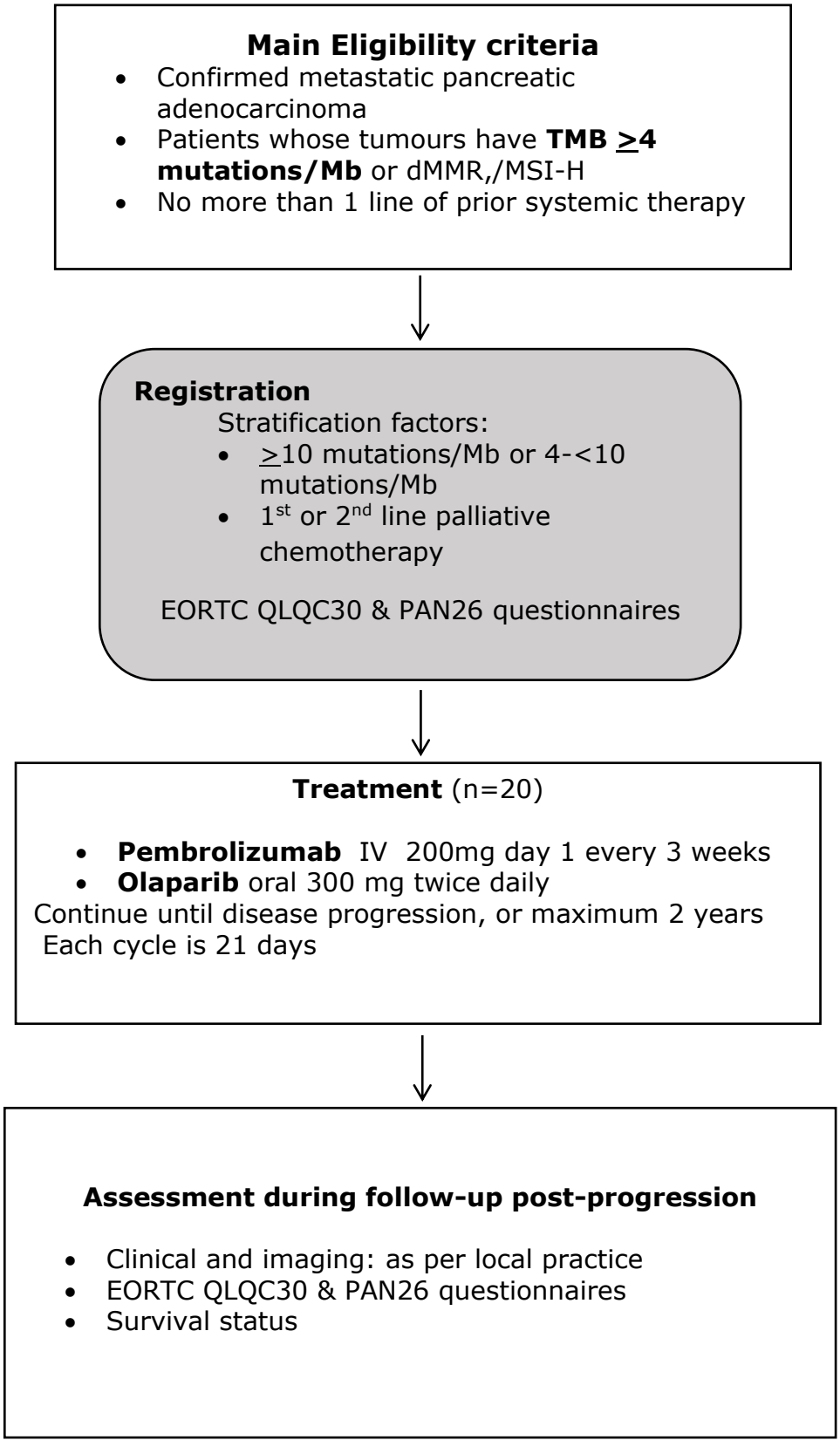
3. Abbreviations

AE/AR	Adverse event/Adverse Reaction
ADR(s)	Adverse drug reaction(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APTT	activated partial thromboplastin time
AST	Aspartate aminotransferase
BCR	B cell receptor
CA 19-9	Cancer antigen 19-9
CCTU-CT	Cambridge Clinical Trials Unit – Cancer Theme
CI	Chief investigator
COPD	Chronic Obstructive Pulmonary Disease
CPI(s)	Checkpoint inhibitor(s)
CRC	Colorectal cancer
CTA	Clinical Trial Authorisation
CTCAE/ NCI CTCAE	National Cancer Institute Common terminology criteria for adverse events
CT scan	computerised tomography scan
CYP3A4	Cytochrome P450 3A4
DCR	Disease Control Rate
DDR	DNA Damage Repair
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF/CRF	electronic Case Report Form/Case Report Form
EOTRC QLQ	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire
Free T3/T4	Free triiodothyronine/ Thyroxine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
Hb	Haemoglobin
HRA	Health Research Authority
HDR	Homologous Recombination Deficiency
IB	Investigators brochure
ICF	Informed Consent Form
ICH	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International normalised ratio
ISF	Investigator site file
IrAE(s)	Immune-related adverse event(s)
IUD	Intrauterine Device
IUS	Intrauterine System

IV	Intravenous
KPS	Karnofsky performance status
LH	Luteinizing Hormone
MDT	multidisciplinary team
Mb	Megabase
MDS	Myelodysplastic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MMR/ dMMR	Mismatch Repair/ Mismatch Repair Deficiency
mPDA	metastatic Pancreatic Adenocarcinoma
MSD	Merck Sharp Dohme Ltd
MSI high (MSI-H)	microsatellite instability high
NIHR	National Institute of Health Research
NHSE GLH	NHS England Genomic Laboratory Hubs
NYHA	New York heart Association
PARPi	poly-ADP ribose polymerase inhibitor
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PDA	Pancreatic Adenocarcinoma
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1
PFS	Progression Free Survival
PI	Principle Investigator
PK	Pharmacokinetics
PPI	Patient and public involvement
PSA	Prostate Specific Antigen
PSF	Pharmacy Site File
R&D	Research and Development
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RSI	Reference safety information
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	T cell receptor
TEN	Toxic epidermal necrolysis
TIL	Tumour Infiltrating Lymphocyte
TMB	Tumour Mutation Burden
TMF	Trial Master File
TMG	Trial Management Group
TNM	tumour, nodes, and metastases classification
TSC	Trial Steering Committee
TSH	thyroid-stimulating hormone
ORR	Objective Response Rate
OS	Overall Survival
QoL	Quality of Life
ULN	Upper Limit of Normal range
WOCBP	Women of childbearing potential

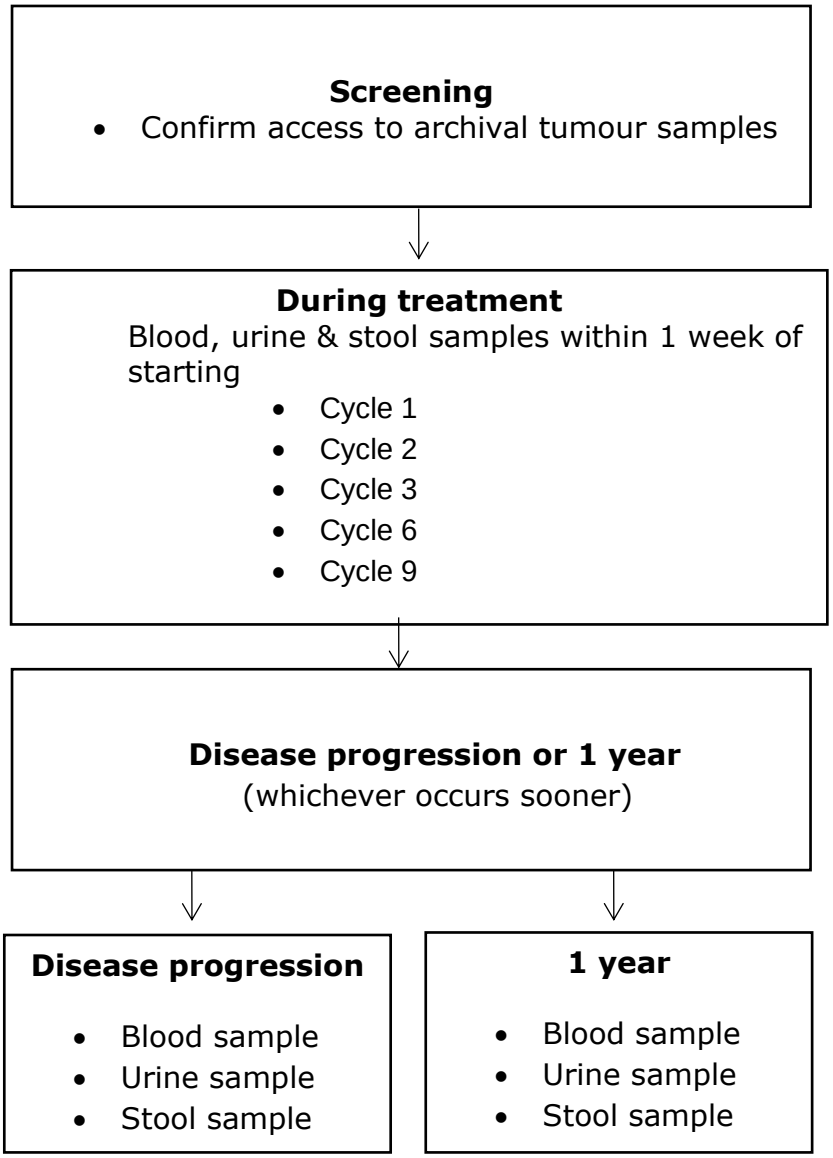
4 Trial Flow Chart

4.1 Trial schema



4.2 Translational schema

Please refer to the PemOla Laboratory Manual for full details of research sample collection and processing. The sample collection schedule is summarised below.



No translational samples will be collected after the 1 year visit, even if patients remain on the trial past that visit.

5 Introduction

5.1 Background

Pancreatic adenocarcinoma (PDA) is one of the 10 most common cancer types: over 8,500 UK patients are diagnosed with this disease each year[1]. Despite modern interventions, outcomes have changed little in the last 50 years and PDA is projected to be the second most common cause of cancer death by 2030[2]. Up to 80% patients are diagnosed with disease too late for surgery and median survival with metastatic pancreatic adenocarcinoma (mPDA) is under 1 year even with optimal chemotherapy. Developing more effective treatments for mPDA is a global unmet need[3].

Immunotherapy drugs called checkpoint inhibitors (CPIs) are radically improving outcomes for many cancer types considered hitherto to be difficult to treat, but benefits have not yet been realised in PDA[4]. Tumour mutational burden (TMB), defined as the total number of somatic mutations per coding area of a tumour genome, is an emerging clinical biomarker associated with response to CPI therapy[5]. TMB has been shown to vary markedly among tumour types. Higher TMB is commonly observed in cancers associated with mutagens, such as ultraviolet light exposure in melanoma and smoking in non–small cell lung cancer (NSCLC)[6], with prevalence of high TMB (TMB-H; defined here as 10 mutations per megabase (mut/Mb) of DNA in approximately 50% of patients with melanoma and 40% of patients with NSCLC. By comparison, the prevalence of TMB-H in mPDA is <2% and the benefits of immune checkpoint inhibition in this very small patient subgroup is not clear cut[7-11]).

CPI monoclonal antibodies targeting the PD-1 receptor (e.g. pembrolizumab and nivolumab), or its ligand, PD-L1(e.g. durvalumab and atezolizumab), are the most CPIs in current clinical practice, with good toxicity profiles and roughly equivalent efficacy. Despite the improvements in survival achieved even in the most responsive tumour types, only the minority of patients treated with these agents will respond. Rational drug combination strategies focusing particularly on enhancing tumour immunogenicity are needed and indeed are being employed with the aim of increasing response to CPIs[12].

5.1.1 Role of immune checkpoint inhibitors in mPDA

Response to anti-PD-1 and PD-L1 antibodies have proved disappointing in unselected PDA populations[4]. On the other hand, limited clinical data points to potential for immune responsiveness in the 2% mPDA patients whose tumours harbour mismatch repair deficiency (dMMR) phenotypes[7-10].

In 2017, the CPI, pembrolizumab, was licensed in the USA for patients with dMMR cancers, determined either by DNA sequencing of the tumour MMR genes, or immunohistochemistry (IHC) testing for the resulting microsatellite instability proteins ('MSI-H' tumours). Licensing was based on an objective response rate (ORR) of 28% in a cohort of 61 colorectal cancer (CRC) patients and 38% in 77 non-CRC patients[14], of whom 7 had mPDA. All patients were heavily pretreated. Detailed outcomes by cancer type for the non-CRC cohort were not provided, but the ORR ranged from 27-49%. More recently, the results of the Keynote-158 study evaluating efficacy of pembrolizumab in a separate cohort of previously treated patients with non-CRC dMMR/MSI-H cancers was published and has provided breakdown by tumour type[15]. The single arm study of 233 advanced cancer patients included 22 patients with mPDA. Their ORR was 18% (95%CI 5-40%), with median progression free survival (PFS) 2.1 (95%CI 1.9-3.4) months and median overall survival (OS) 4 (95%CI 2.1-9.8) months. However,

medians can be deceptive: duration of benefit in responding patients was 13.4 (95%CI 8.1-16+) and the shape of the survival curve plateauing around 20%[16] is highly reminiscent of the survival curves reported in the first randomised trials testing CPIs in metastatic melanoma patients[17,18]. Testing a combination immunotherapy strategy in a mPDA subpopulation selected for dMMR /MSI-H is warranted.

dMMR/MSI-H tumours are generally associated with the highest TMB, exceeding 10 (mut/Mb), while PDAs generally have low TMB (average 1 mut/Mb). A subgroup of PDAs have higher than average TMB in the range of 4–10 mutations/Mb, but no evidence of dMMR[19]. These tumours are enriched for a variety of other surrogates of DNA damage repair (DDR) deficiency, such as high *BRCA* COSMIC mutation signature, genomic instability and specific defects in key DDR genes including *BRCA1* and *2*[20]. For patients with hypermutated, dMMR/MSI-H tumours, there is a strong rationale for CPIs[13-15,21], but there is no access for mPDA patients currently, because (a) mutation status is not routinely tested for and (b) anti-PD-1 antibodies are not licensed for this indication in Europe, since the European Medicines Agency does not have a mechanism to license a drug across multiple tumour types based on a molecular signature. Potential gains at least for those mPDA patients with dMMR tumours appear promising, albeit based on very limited data in the public domain, while the benefits for patients with high TMB independent of dMMR are not yet defined. Since the defects associated with high TMB frequently reflect DDR deficiency, we hypothesise that combining pembrolizumab with a Poly ADP-ribose polymerase inhibitor (PARPi) will offer best chance of response and survival in this PDA subgroup, and this is supported by recent data showing PARP inhibition enhances checkpoint blockade by activating the cGAS/STING pathway[22-25].

5.1.1.1 Rationale for combining anti-PD1 and PARP inhibition

Genomic instability is a hallmark of cancer; DNA is continually exposed to endogenous and exogenous sources of damage and multiple DNA repair pathways work to maintain genomic integrity under normal conditions. Failure to repair DNA damage results in a variety of genomic aberrations including gene mutations that impact on carcinogenesis as well as response to anti-cancer therapy. PARPis are a class of drugs that exert their therapeutic effects through preventing single-strand DDR, which leads to the accumulation of toxic DNA double-strand breaks specifically in cancer cells with DDR deficiency, including those harbouring *BRCA1/2* gene mutations[26]. An international programme of trials is underway focusing on the role of PARPi in *BRCA1/2* mutant cancers, including PDA. As an early indicator of potential clinical application, the POLO trial recently reported that the PARPi, olaparib, was able to maintain response after platinum-based chemotherapy in a proportion of mPDA patients with germline BRCA mutations [28] , which led to olaparib being approved by the FDA for this patient group.

PARPis such as olaparib have now been shown to exert their anti-cancer effects through other mechanisms and there is growing evidence that they can boost cancer immunity[29]. Early preclinical and clinical studies suggest combining checkpoint blockade with PARP inhibition is a promising new therapeutic strategy, but which has not yet been tested in patients with PDA. DNA damage caused by PARPi may increase tumour antigen release, attract tumour infiltrating lymphocytes (TILs) and upregulate PD-L1 expression, working to prime response to CPIs. Of note, when testing this combination in advanced prostate cancer patients, the subgroup of patients with higher TMB appeared to benefit most[30] and high TMB generally correlates with response to CPIs across most cancer types[31-33]. Modern molecular profiling now enables identification of subgroups of patients with high TMB as a potential biomarker of

response to CPIs[34], but as yet few trials have prospectively selected patients for an intervention on this basis.

5.2 Data from pre-clinical studies

There is mounting evidence that PARPis have wide therapeutic potential[26]. Recent studies have demonstrated that PARPis synergise with CPIs, modulating the immune response independently of *BRCA1/2* mutations[22,23]. PD-1 is a protein receptor expressed on T cells that prevents them recognizing and attacking inflamed tissues and cancer cells and PD-(L)1 antibodies reverse so-called T cell exhaustion, enabling T cells to invade and potentially destroy cancer cells anywhere in the body. Pembrolizumab is one of the most well-established and effective CPIs in clinical practice. The PD-1 receptor ligand, PD-L1, is found on both tumour and T cells. In a breast cancer model, PARPi upregulated PD-L1 expression and activated T cell killing[24]. This was achieved by triggering the cGAS-STING pathway[22],[24] - a component of the innate immune system that functions to detect cytosolic DNA and cause inflammation - leading to activation of interferon gamma generating cytotoxicity. The combination of PARPi and CPI was associated with the highest anti-tumour efficacy compared with either agent alone in treated mice. In normal pancreatic tissue, PARP is present in the nucleus, while in PDA, PARP is present both in the nucleus and cytoplasm[35], where STING activation occurs, so there is a good rationale for this combination in PDA.

5.3 Clinical Data

Based on accumulating evidence suggesting a synergistic interaction between CPIs and PARPis, a potential overlap for PD-1- and PARP-sensitive patient populations, as well as the non-overlapping safety and metabolic profiles of the 2 drug classes, a series of clinical studies have been undertaken to assess the safety and efficacy of combining anti-PD-(L)1 antibodies and PARPis. The number of trials and indications is growing, with some phase III trials now recruiting[26]. The published data is summarised below.

A first phase 1 trial of durvalumab (a PD-L1 antibody) and olaparib in advanced ovarian and breast cancer patients reported a high disease control rate (DCR) of 83% and no dose-limiting toxicities[36] .

The TOPACIO Phase 1/2 study was designed to evaluate efficacy and safety of pembrolizumab plus niraparib (a PARPi) in patients with recurrent, platinum-refractory/resistant ovarian cancer and triple-negative breast cancer. In the ovarian cancer cohort of 60 patients, response was not dependent on biomarker or platinum status. In BRCA mutant (n=16) and BRCA non-mutated patients (n=44), the ORR was 25% and 24%. ORR was 27% in a homologous recombination deficiency (HRD) biomarker subgroup[37]. In the breast cancer cohort of 46 patients, BRCA mutation (n=15) or HRD mutation (n=5) status was associated with 55% ORR compared to 28% in the overall patient population[38].

The MEDIOLA Phase 1/2 study was designed to evaluate efficacy and safety of durvalumab plus olaparib in 32 patients with relapsed, platinum-sensitive ovarian cancer harbouring a germline BRCA mutation and 30 patients with triple-negative breast cancer. An ORR of 63% was reported[39]. Responses were seen even in heavily pre-treated patients. There was no statistically significant association observed between baseline PD-L1 status or TILs and best objective response, but a trend was noted where higher PD-L1 and TIL densities were observed in archival samples in patients who had stable disease (SD)/PR/CR. In breast cancer patients, the combination was similarly effective with an ORR of 63%. Median duration of response (DOR) was 9.2 months and median PFS was 8.2 months. The median DOR compares

favorably to the median of 6.4 months reported in the OlympiAD study of olaparib monotherapy in BRCAm patients with metastatic breast cancer[40].

A Phase 2 study combining durvalumab and olaparib in metastatic castration-resistant prostate cancer patients (NCT02484404) 9 of 17 prostate specific antigen (PSA) responses of greater than 50%; 4 out of 9 responders had radiographic ORR Median radiographic progression-free survival (rPFS) for all patients was 16.1 months (95% CI: 4.5–16.1 months) with a 12-month rPFS of 51.5% (95% CI: 25.7–72.3%). Two-thirds of the responders had mutations in *DDR* genes and the median rPFS in those patients was 16.1 months (95% CI: 7.8–18.1 months) with a 12-month PFS probability of 83.3% versus 36.4% in patients without mutations[41].

KEYNOTE-365 (NCT02861573) was a phase Ib/II umbrella study of pembrolizumab combination therapies in metastatic castration-resistant prostate cancer. Cohort A evaluated pembrolizumab plus olaparib in 41 docetaxel-pre-treated patients who progressed. PSA response for patients with elevated PSA at baseline was 13%, ORR for patients with measurable disease was 7% and disease control rate was 32%. The authors concluded that the combination has some albeit limited activity in this difficult to treat population[42].

All studies have reported that the observed safety profile for the combination was consistent with individual profiles of anti-PD(L)1 antibodies and PARPi.

In conclusion, a series of studies combining PARPi with anti-PD-(L)1 antibodies have all shown efficacy in preclinical models and early clinical trials in heavily pre-treated cancer patients. PARPis can be safely combined with standard doses of anti-PD-(L)1 antibodies. Application of this combination regimen is exemplified by a unique case report of a patient with mPDA whose molecular profile included a germline *BRCA1* mutation as well as very high TMB, but no microsatellite instability. Following platinum-based chemotherapy, the patient achieved a complete response with pembrolizumab and olaparib.[54]

5.4 Biomarker identification and prevalence

Comprehensive genomic profiling has confirmed that PDA is a molecularly diverse disease [16,43] and small subsets of patients may have actionable mutations that could potentially be used to select an intervention. Molecular profiling of cancers including PDA is evolving and TMB is expected to be routinely assessed as part of NHS England Genomic Laboratory Hub (NHSE GLH) gene testing panels, which were established in 2021. Until such time as an NHS service is routinely available, the *Precision-Panc* pan-UK research platform provides this capability. Funded by Cancer Research UK, *Precision-Panc* encompasses discovery, preclinical and clinical research developments in PDA (https://www.precisionpanc.org/). The *Precision-Panc* Master Protocol enables molecular profiling of tumour biopsies embedded within the standard diagnostic pathway, to facilitate subsequent enrolment in Pancreatic Cancer Individualised Multi-Arm Umbrella Study (PRIMUS) clinical trials asking specific biomarker-associated questions. PemOla is now established as the PRIMUS 008 trial.

Evaluation of 324 PDAs tested via the *Precision-Panc* platform has shown that 1.2% of tumours had high TMB (defined as $\geq$10 mut/Mb), mainly characterized by dMMR/MSI-H. Just over 9% had TMB $\geq$ 4 mut/Mb. The predictive value of TMB is by no means clear-cut, with evidence of variability of response to checkpoint blockade across cancer types and unclear associated with survival outcomes. A retrospective review of nearly 1,700 patients treated with immune checkpoint inhibitors reported that none of 2 PDA patients with TMB >10 mut/Mb

responded, while 3 of 34 PDA patients with TMB <10 mut/Mb did[44]. Setting a TMB threshold of 10 mut/Mb would both make recruitment challenging but also potentially exclude patients who might benefit from receiving immunotherapy. The PemOla study TMB threshold of ≥4 mut/Mb was chosen to widen treatment access and maximise opportunities for response.

In addition to established UK molecular profiling pathways, patients with mPDA gaining genomic profiling information via other validated molecular platforms such as Foundation Medicine which confirms TMB ≥4 mutations/Mb, or presence of other dMMR gene mutations, or whose tumours are found to be MSI-high by IHC, will also be eligible for this trial.

5.5 Biological correlates with response and toxicity

This study will evaluate a relatively novel immunotherapy combination regimen. By collecting and analysing biological samples from patients prior to and during treatment, we plan to study how TMB interplays with other immune markers and their correlation with both treatment response and toxicity.

Response to immune checkpoint therapy has been associated with microbiota composition. In addition, gut bacteria have been demonstrated to bioaccumulate and modify drugs with implications for pharmacokinetics (PK), pharmacodynamics (PD) and toxicity. Therefore, we will use stool and urine samples to assess microbiome composition, and drug and drug metabolite concentrations.

6 Rationale for Trial

We hypothesise that TMB will be an effective biomarker to select a subgroup of patients with mPDA most likely to benefit from treatment with CPIs and that pembrolizumab combined with olaparib will offer superior outcomes compared with standard chemotherapy options currently available.

7 Trial Design

7.1 Statement of Design

This is a phase II single arm, open label, prospective trial investigating the efficacy of pembrolizumab plus olaparib in mPDA patients exhibiting TMB ≥4 mutations/Mb, including tumours with dMMR/MSI-H.

7.2 Number of Centres

We plan to open this study in approximately 20 centres currently conducting *Precision-Panc* and PRIMUS trials across the UK. In addition, this trial is part of the NIHR CRN 'Just in Time' Pilot Scheme. This scheme aims to facilitate recruitment of rare patients at UK sites not initially listed as the main trial recruitment centres, since their local recruitment rate is likely to be very low (<3 patients per annum). Once a patient has been identified locally, the trial aims to be rapidly set up at the local site so the patient can be recruited within around 2 weeks of identification.

7.2.1 Justification for Just-in-Time site activation

- Uncommon patients. PemOla is recruiting an uncommon subgroup of patients with metastatic PDA: tumours with high TMB represent approximately 5% of tumours.
- Familiar treatment. Pembrolizumab and olaparib are licensed drugs, being used in an unlicensed indication in the PemOla trial. Participating centres will be familiar with prescribing these drugs and managing patients receiving them.

- Multiple sites required. Together, points 1 and 2 mean that PemOla needs to be available to patients at any of the >150 NHS sites that regularly treat pancreatic cancer patients. Prospective set-up of all those sites which may recruit only one patient per year at most is not feasible, and onward referral of patients to a small number of specialist sites is neither realistic, nor appropriate.
- Rapid set up is necessary. It is clinically necessary to minimise the interval from the diagnosis of metastatic cancer to the start of treatment. For PemOla, it is highly desirable for the oncologist to be able to discuss the study and obtain consent for planning treatment at the first clinic appointment. Trial treatment will typically aim to be started within 2-3 weeks of that first approach, if possible.

7.3 Selection of Participating sites

Criteria for the selection of sites will be determined by the Trial Management Group (TMG) and will be described in a separate Cambridge Clinical Trials Unit (CCTU) document 'Registration of Interest/Feasibility Assessment Template' maintained in the Trial Master File (TMF).

Only sites fulfilling the trial-specific criteria will be selected to recruit for the trial. Initiation of sites will be undertaken in accordance with CCTU internal processes. Conditions and documentation required for site activation will be detailed on the trial specific Participating Site Initiation Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

7.3.1 Principal Investigator Responsibilities

Once the site has been activated, the local site Principal Investigator (PI) is responsible for ensuring the following:

- Attendance at the site initiation meeting
- Adherence to the most recent version of the protocol
- All relevant staff are trained in protocol requirements
- Delegation of activities to appropriately trained staff (this must be documented on the delegation of responsibility and signature log)
- Appropriate recruitment and medical care of patients in the trial
- Timely completion of electronic case report forms (eCRFs) and resolution of data queries
- Accurate maintenance of the Investigator Site File (ISF)
- Dissemination of all trial related information, when applicable
- Ensuring appropriate attendance at the TMG teleconferences if required and ensure appropriate safety information is made available to the CCTU-CT in advance of the meeting.
- Dissemination of important safety or trial related information to all stakeholders at the participating site
- Safety reporting within the timelines and assessment of causality and expectedness of all serious adverse events (SAEs)
- Timely completion of any remote monitoring activities
- Assistance with any on-site monitoring activities
- Archiving of the ISF upon confirmation of CCTU-CT end of trial

7.4 Number of Participants

20 evaluable patients will be recruited to assess the primary endpoint, ORR.

7.5 Participants Trial Duration

The trial duration for an individual patient consists of a 28-day screening period, treatment period until disease progression or up to 2 years, followed by an end of treatment assessment and follow-up until death, loss to follow-up, or trial closure.

7.6 Trial Objectives

7.6.1 Primary objective

- To determine the objective response rate (ORR, by RECIST 1.1) associated with pembrolizumab plus olaparib in patients with mPDA and TMB $\geq$ 4 mut/Mb or dMMR/MSI-H

7.6.2 Secondary objective

- To assess safety, duration of response (DOR), progression-free survival, overall survival and quality-of-life (QoL) associated with treatment

7.6.3 Exploratory objective(s)

- To determine the prevalence of high TMB in UK mPDA patients
- To ascertain whether MMR protein IHC ('MSI-H') correlates with molecular hyper mutation status determined by genomic sequencing
- To assess molecular and immune biomarkers, which may correlate with treatment response and provide further mechanistic insight into the mode of action of the combination regimen.
- Response rate using iRECIST
- To assess the role of microbiome composition on a) immunotherapy response rate, b) drug PK/PD
- To determine stool, urine, and serum drug / drug metabolite concentrations to assess differences in PK/PD across individuals.

7.7 Trial Outcome Measures

7.7.1 Primary outcome measure

- ORR assessed by RECIST version 1.1 and CT scanning every 9 weeks for the first 9 cycles (27 weeks), then 12 weekly.

7.7.2 Secondary outcome measure

- **Safety and toxicity** using NCI CTCAE version 5.0
- **DOR**: the time (in days) from the first documentation of objective response (CR or PR, confirmed or unconfirmed, whichever status was recorded first, using RECIST criteria) until the first documented disease progression, or death (if before progression).
- **PFS:** the time from registration to disease progression, or death, whichever occurs first, assessed by the treating investigators. Patients who remained alive without disease progression at the time of data analyses are censored at their last date of clinical follow-up for progression. Median, 1 year and 2-year PFS rates will be measured.
- **OS:** the time from registration to death. Patients who remain alive are censored at their last contact date for OS. Median, 1 year and 2-year OS rates will be measured.
- **QoL**: using the EORTC QLQC30 and PAN26 QoL questionnaires.

7.7.3 Exploratory outcome measure

- Retrospective analysis of TMB on a single validated molecular profiling platform
- Rate of TMB ≥10 and ≥4 mut/Mb in mPDA
- Correlation of MSI-H IHC with DNA hypermutation status
- Predictive biomarker and mechanistic studies
- iRECIST response rate
- Microbiome composition
- Drug and drug metabolite levels in stool, urine, and plasma

8 Selection and withdrawal of participants

The following eligibility criteria are to be assessed.

8.1 Inclusion Criteria

To be included in the trial the participant must meet the following criteria:

- Have given written informed consent to participate.
- Aged ≥ 18 years old
- Histologically or cytologically confirmed PDA
- Confirmation that the PDA has TMB ≥4 mutations/Mb, or dMMR gene mutation, or MSI-H by IHC
- Radiologically confirmed stage 4 mPDA, with measurable disease
- Received no more than 1 prior systemic therapy regimen for unresectable (stage 3 or 4) PDA
- Received no more than 1 prior systemic therapy for metastatic disease
- Measurable disease which has not been irradiated in prior radiotherapy
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Life expectancy >12 weeks from the date of screening assessment
- Adequate bone marrow function
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9 /L
    - Haemoglobin (Hb) ≥ 90 g/L
    - Platelets ≥100 x 10^9 /L
- Adequate liver function
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 x upper limit of normal range (ULN), or <5 x ULN in the presence of liver metastases
    - Total bilirubin <1.5 x ULN
- Adequate renal function defined as a calculated creatinine clearance by Cockcroft-Gault of ≥50 mL/min

8.2 Exclusion Criteria

The presence of any of the following will exclude participant inclusion:

- Patients with resectable or locally advanced PDA
- Other invasive malignancies diagnosed within the last 2 years which have not been treated with curative intent
- Prior CPIs or PARP inhibitors. This includes any prior therapy with an anti-PD-1, or anti-PD-L1, or anti PD-L2 agent, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g, CTLA-4, OX 40, CD137)
- Requirement for non-physiological dose of daily oral steroids, or regular use of any other immunosuppressive agents; prednisolone dose of ≤ 10mg (or equivalent steroid dose) is allowed. Use of inhaled or topical steroids is allowed.

- Significant acute or chronic medical or psychiatric condition, disease or laboratory abnormality, which in the judgment of the investigator would place the patient at undue risk or interfere with the trial. Examples include, but are not limited to:
    - A history of COPD, interstitial lung disease, sarcoidosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, cystic fibrosis or bronchiectasis affecting pulmonary function, causing breathlessness at rest
    - Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease
    - Uncontrolled ischaemic heart or other cardiovascular event (myocardial infarction, new angina, stroke transient ischaemic attack, or new congestive cardiac failure) within the last 2 months
    - Stable but significant cardiovascular disease defined by heart failure (New York Heart Association (NYHA) Functional Classification III or IV) or frequent angina
    - Presence of active infection
    - Cirrhotic liver disease, known HIV, chronic active or acute hepatitis B, or hepatitis C
    - History of severe allergy or hypersensitivity reactions
    - Autoimmune disease requiring chronic use of immunosuppressive agents.
    - Replacement therapy using physiological doses for adrenal or pituitary insufficiency is allowed.
    - Known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.
    - Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention
    - Has myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML.
- Women who are pregnant, or plan to become pregnant, or are lactating.
- Women of child-bearing potential and male patients who are unwilling to adhere to the contraception requirement from informed consent until the last dose of the trial treatment and for either 150 days (for women) or 270 days (for men) after the last dose of trial treatment (see section 10.11.1).
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the trial medication.
- Concomitant use of known potent CYP3A4 inhibitors and inducers. Restrictions relating to concomitant medications are described in section 10.9. Please consider wash-out periods.
- Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to screening.
- Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients
- Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

- Has received a live vaccine or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
- Participant received colony-stimulating factors (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 28 days prior to the first dose of study intervention.
- Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
- Participant has persistent toxicities (>CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.
- Has had an allogenic tissue/solid organ transplant
- Judgment by the Investigator that the patient should not participate in the trial.

8.3 Participant Withdrawal Criteria

Patients may withdraw from the trial treatment, or from the trial completely, at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator.

A patient may be withdrawn from the trial in the case of:

- Patient choice
- Intercurrent illness which prevents further continuation in the trial
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion, including new, alternative treatment options.
- Pregnancy
- Bone marrow findings consistent with MDS or AML
- Administration of both study interventions is interrupted for more than 6 consecutive weeks.
- Any other safety, behavioural, or administrative reasons.

If the patient explicitly states they no longer wish to contribute further data to the trial, the investigator should inform the co-ordinating centre in writing and the withdrawal of consent should be documented by the in the patient's medical records and in the eCRF. However, data and samples collected up to the time of consent withdrawal will be included in the data reported for the trial.

If a patient does not return for a scheduled visit, and they have not stated that they would like to withdraw from the trial, a member of the trial team may contact their GP to check whether they would like to continue with the trial or withdraw. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator will enquire about the reason for withdrawal, request that the patient return for a final visit (if applicable) and follow-up with the patient regarding any unresolved Adverse Events (AE).

Patients will only be replaced in the trial if they are not evaluable for response to treatment at the 9-week assessment point. Patients who fail to start treatment for whatever reason will be replaced. Patients who start treatment but fail to complete 9 weeks due to symptoms/signs of disease progression, or death, will be classified as progressed and not replaced. Patients who start treatment and fail to complete 9 weeks due to other reasons (including toxicity, or patient choice) will be replaced.

9 Trial Treatments

9.1 Treatment Summary

For the purpose of this trial, both pembrolizumab and olaparib are considered to be Investigational Medicinal Products (IMP) conducted with a Clinical Trial Authorisation (CTA) in the UK. For detailed information, please refer to the PemOla Pharmacy Manual.

9.1.1 Name and description of IMP

Table 1: Summary of IMPs

IMP	Dosing	Route, Instructions of Administration & Formulation	Strength & How supplied	Storage Requirements
Pembrolizumab	200mg on Day 1 of each 3 week cycle	Solution for Intravenous infusion	100mg in 4ml vials (25mg/ml)	Store in the refrigerator between 2-8^{0}C in the original container.
Olaparib	300mg bd continuously	Oral for self-administration. Take at same time each day. Swallow whole, do not chew or crush the tablets.	100 & 150mg tablets	Store at room temperature below 30°C in original bottle.

9.1.1 Pembrolizumab description

Pembrolizumab is a highly selective IgG4-kappa humanised monoclonal antibody against PD-1 receptor. It was generated by grafting the variable sequences of a very high-affinity mouse antihuman PD-1 antibody onto a human IgG4-kappa isotype with the containing a stabilizing S228P Fc mutation.

9.1.2 Olaparib description

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP) developed as a monotherapy as well as for combination with chemotherapy, ionising radiation and other anti-cancer agents including novel agents and immunotherapy.

9.1.3 Legal status

Both IMPs pembrolizumab and olaparib are currently licensed within the EU for treatment of some cancers. Since this trial is evaluating both pembrolizumab and olaparib in an unlicensed indication, it is being carried out under a CTA. It is therefore only to be used by the named Investigators for the patients recruited onto this protocol, and within the trial.

9.1.4 Supply

Both pembrolizumab and olaparib are supplied free of charge for this trial by Merck Sharp Dohme Ltd (MSD). Both IMPs will be labelled by Merck Sharp Dohme Ltd (MSD) and distributed to each participating site for the duration of the trial by Eramol Ltd. The supply should be ring-fenced at the participating site for this trial and records retained in the Pharmacy Site File noting the location of the storage facility. Both IMPs will be distributed directly to site following confirmation that all necessary regulatory and ethical approvals are in place.

Please see the PemOla Pharmacy Manual for further information.

9.1.5 Packaging and Labelling

Olaparib tablets will be packed in high density polyethylene bottles with child resistant caps. Pembrolizumab solution for infusion will be supplied as 100mg/4ml vial. Both Olaparib and Pembrolizumab will be labelled in accordance with local regulations and Good Manufacturing Practice. An example of the label can be found in the PemOla Pharmacy Manual.

9.1.6 Storage conditions

All IMPs must be stored in a secure, limited-access location under the storage conditions specified on the label and must be used within the individual assigned expiry date. Note: Pembrolizumab must be stored in a refrigerator (2°C to 8°C). Neither the vial nor the diluted solution should be frozen. Do not shake the vial.
Prior to dilution the vial should be equilibrated to room temperature (temperatures at or below 25°C) and can remain out of refrigeration for up to 24 hours.

The site's Pharmacy Lead is responsible for ensuring that IMPs are stored appropriately prior to use and have not been the subject of a temperature excursion. Maintenance of a temperature log (manual or automated) is required, and any temperature deviations must be reported to the PemOla office immediately as detailed in the Pharmacy manual.

9.1.7 Maximum duration of treatment of a participant

The trial drugs will continue until disease progression, or for a maximum of 2 years. A patient

who, in the opinion of the local investigator, is clinically benefiting from treatment despite evidence of disease progression by RECIST1.1 criteria may be allowed to continue for as long as there is evidence of benefit, for up to 2 years. In this situation, the patient needs to be discussed with the Chief Investigator and the justification for continuing treatment documented.

Patients treated beyond progression should continue with trial-related assessments including repeat imaging as per the schedule of events. If the following scan shows further disease progression using RECIST 1.1 criteria compared with the previous scan, then trial treatment must be permanently discontinued.

9.1.8 Drug doses

Pembrolizumab will be given as a fixed dose of 200mg standard dose on Day 1 (+/-3 days) of every 3 weeks cycle, administered intravenously as an approximately 30 minute infusion, as per standard clinical practice.

Patients will self-administer olaparib. Olaparib dose is 300mg given orally, twice daily, from Day 1 to Day 21 continuously of each 3-week cycle.

9.1.9 Administration

9.1.9.1 *Pembrolizumab*

Pembrolizumab is to be administered intravenously every 3 weeks, as an approximately 30-minute infusion. It must not be administered as an intravenous push or bolus injection.

See the PemOla pharmacy manual for details about pembrolizumab preparation.

Pembrolizumab should be reconstituted and administered according to local institutional guidelines in line with the current SmPC.

9.1.9.2 *Olaparib*

Olaparib tablets should be taken TWICE a day at the same time each day approximately 12 hours apart. Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

Patients should be advised that the consumption of **grapefruit and Seville oranges** (as well as other products containing these fruits e.g., juice or marmalade), and St, John's Wort (tablet or tea) are prohibited while participating in the study. Otherwise, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting.

9.1.10 Known drug reactions

The full listing of ADRs can be found in the current IB of each study medication. See sections 9.2 and 11.2 of this protocol for more information.

9.1.10.1 *Olaparib*

Olaparib is generally well tolerated. Adverse drug reactions (ADRs) are usually mild or moderate without treatment discontinuation.

The most common ADRs are:

- Gastro-intestinal toxicities: nausea, vomiting, diarrhoea, decrease appetite, dyspepsia, abdominal pain, stomatitis and dysgeusia.
- General toxicities: dizziness, headache, fatigue, breathlessness, cough, increased creatinine level
- Haematological toxicities: mean cell volume elevation above baseline, anaemia, lymphopenia, neutropenia and thrombocytopenia

9.1.10.2*Pembrolizumab*

Common ADRs include:

- Fatigue, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, diarrhoea (colitis), breathlessness (pneumonitis), thyroid dysfunction, elevated liver enzymes and other immune-related adverse effects (IrAEs).

9.1.11 Dose modifications

There are no dose reductions planned for pembrolizumab.

Dose modifications are allowed for olaparib. The dose levels and the general approach to dose modification of olaparib are shown below:

Table 2: Olaparib Dose Levels

Drug	Protocol starting dose	Protocol Dose level-1	Protocol Dose Level -2
Olaparib	300mg bd	250mg bd	200mg bd

Once a dose reduction of olaparib has been made the dose should not be escalated during the trial treatment. If the dose of 200mg bd is not tolerated, olaparib should be permanently discontinued. Lower doses of olaparib may only be used if a patient requires treatment with a CYP3A4 inhibitor during trial participation (see section 9.2.3 below).

9.1.12 Dose Interruptions

Any toxicity observed during trial treatment can be managed by interruption of treatment, based on Investigator judgement. A dose reduction is only an option with olaparib, not with pembrolizumab. The Investigator will need to make an assessment regarding whether any toxicity is most likely to be due to pembrolizumab, or olaparib, or both drugs. Reasons for interrupting one or both drugs need to be documented.

In the event of immune-related adverse events requiring to interrupt, or stop, pembrolizumab permanently, olaparib can be continued.

If olaparib is interrupted or stopped permanently for toxicity, pembrolizumab may be continued.

See section 12.2 for management of drug-specific toxicity.

If treatment with olaparib is interrupted for more than 6 weeks, it should be stopped permanently, and the patient may continue on pembrolizumab. If treatment with pembrolizumab is interrupted for more than 12 weeks, it should be stopped permanently, and the patient may continue on olaparib. If both drugs are interrupted for more than 6 weeks at the same time, all trial treatment will be stopped permanently.

9.1.13 Missed dose of Olaparib

If a patient misses a scheduled dose (e.g., as a result of forgetting to take a tablet) or due to an hospital appointment the scheduled dose is taken earlier, the scheduled olaparib dose can be taken up to 4 hours before or after the scheduled dose time. If greater than 4 hours, the missed dose should not be taken. The patient should continue with the next dose at the scheduled time. Double doses must not be taken.

9.1.14 Dose replacement of Olaparib

If a patient vomits after taking the scheduled olaparib dose, a second dose must not be taken unless the swallowed tablet(s) are visible. The patient should continue with next dose at scheduled time. If no dose is scheduled, the dose will not be made up.

9.1.15 Procedures for monitoring treatment compliance

Patients will be asked to return any olaparib tablets that have not been taken or the empty container. The number of returned tablets will be recorded. Patients will be asked to keep a detailed record of the olaparib tablets taken in the PemOla trial patient diary. The date and time of olaparib administration, drug dose and number of tablets taken will be collected in patient diaries and returned to site team at the end of each cycle.

Olaparib and pembrolizumab treatment adherence data must be collected and recorded in the eCRF.

9.2 **Concomitant therapy**

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with local policies. All prescription concomitant medication will be recorded on the eCRF. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

All prescription concomitant medications received within 4 weeks before the first dose of study drug through to 4 weeks after the last dose of study drug should be recorded.

Anaphylaxis or hypersensitivity reactions can be treated or prevented according to local practice.

9.2.1 Supportive Care

No routine prophylactic anti-emetic treatment is required when starting pembrolizumab and olaparib; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Patients should also be supplied with an anti-diarrhoea medication (e.g., loperamide) for use in the event of diarrhoea, according to local practice.

9.2.2 Anticoagulant therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted and does not require blood monitoring.

Olaparib has the potential to interact with apixaban and can increase the risk of bleeding with apixaban. We therefore advise changing to alternative anticoagulant/or NOAC that has a lower potential to interact with olaparib. Fondaparinux, rivaroxaban, edoxaban all have potential to interact with olaparib however, risk is lower.

9.2.3 Prohibited therapies

- Chronic systemic corticosteroids (except for eligible patients with endocrinopathies requiring stable physiological doses of hormone replacement therapy such as hydrocortisone, for treating IrAEs, for the prevention of emesis, to treat COPD exacerbations, or to pre-medicate for IV contrast allergies)
- Immunosuppressive agents (except for those required for treating patients who develop IrAEs)
- Known strong CYP3A4 inhibitors (e.g Itraconazole, clarithromycin, protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A4 inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. For patients taking any of the above, the required wash-out period is 2 weeks prior to starting olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration as described in table 3. After the washout of the inhibitor is complete, the olaparib dose can be re-escalated. The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A4 inhibitor use.
  Note: a current list of strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Table 3: Dose Reduction of Olaparib with a Strong or Moderate CYP3A4 Inhibitor

Initial Dose	Strong CYP3A4 Inhibitor	Moderate CYP3A4 Inhibitor
300 mg bd	100 mg bd	150 mg bd

- Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A4 inducers (e.g., bosentan, efavirenz, modafinil) should not be taken with olaparib. For patients taking any of the above, the required wash-out period prior to starting olaparib is 3 weeks, and 5 weeks for phenobarbital.
- Radiotherapy is allowed for symptom control purposes only.
- No other chemotherapy, biological therapy, immunotherapy, hormonal therapy (except hormone replacement therapy (HRT) and stable treatment of >6 months with LHRH analogues, which are allowed), or other investigational product are permitted.

9.2.4 Vaccines

Live vaccines and attenuated live vaccines within 30 days prior to the first dose of study drug and 60 days of the last trial drug administration are not allowed. Covid-19 vaccinations are allowed throughout the course of the study. Covid-19 vaccination history prior to and during the study will be recorded in the eCRF.

9.2.5 Dietary restrictions

Grapefruit juice and its products are prohibited whilst on olaparib treatment.

9.3 Accountability and Dispensing

The IMPs should only be used as directed in this protocol. For further information, please refer to the PemOla Pharmacy Manual.

9.3.1 Pharmacy responsibilities

All pharmacy aspects of the trial at a participating site are the responsibility of the local site PI who will delegate this responsibility to the local pharmacist, or other appropriately qualified personnel. This delegation of duties must be recorded on the delegation log. The PI or a delegated individual (e.g., the trial pharmacist) must ensure that the trial medications are stored and dispensed in accordance with local practice, applicable regulatory requirements, and trial-specific prescriptions.

Olaparib tablets and pembrolizumab vials supplied for the PemOla trial should only be used for patients within the trial and not be used outside the context of this protocol. Dispensing should occur by the pharmacy at the participating site in accordance with the trial-specific prescription or as per local site-specific procedures. A prescription template will be provided, although sites will be permitted to use their own clinical trial template prescription if suitable. Refer to the Pharmacy Manual for details regarding ordering, stock levels, temperature monitoring and quarantine procedures.

9.3.2 Drug accountability

The site pharmacy must maintain accountability records for pembrolizumab and olaparib which includes receipt, dispensing, returned medication, storage conditions and destruction of returned/unused medication.

Records must also be kept for all IMP deliveries, and copies of the order/delivery note should be placed in the Pharmacy Site File (PSF) and kept within the pharmacy department as in routine practice.

Template accountability forms will be supplied by the lead site however, sites are permitted to use their own drug accountability records as long as the same information is recorded and is available to the Sponsor.

At the end of the trial, it must be possible to reconcile both IMPs supply and usage of stock. Account must be given of any discrepancies and certificates of delivery.

9.3.3 Returns and destruction

At the termination of the study or at the request of the sponsor, all unused drugs will be accounted for and destroyed locally at the study sites. Destruction documents should be retained in the PSF. Accountability records must be completed and any study drug remaining at the end of the trial must be destroyed according to the site's local standard procedures.

Details of IMP returns and destruction processes can be found in the Pharmacy Manual.

10 Procedures and Assessments

10.1 Participant Identification

Patients will be referred to clinics at the participating sites as per local practice. This could include identification via Multi-Disciplinary Team (MDT) meetings, screening of clinic lists as well as external referrals. Information regarding the PemOla trial will be made available on national clinical research (e.g., National Cancer Research Institute and Precision Panc) and pancreatic cancer-related (e.g. Pancreatic Cancer UK) websites, to raise awareness.

10.2 Consent

Potentially eligible patients (e.g. those who meet pre-screening initial eligibility requirements) will be approached by a member of their clinical team to explain the purpose of the trial and seek their interest to participate. REC approved patient information will be provided and the patient will be given sufficient time to consider whether they wish to take part.

The investigator or designee must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with their participation. In order to facilitate this, the REC approved Patient Information Sheet & Informed Consent Form (PIS & ICF) may be presented in alternative formats to patients with additional needs. The content of the PIS must remain the same, no changes to the content are permitted including the addition of images. However, the following formats are permitted in this trial - including but not limited to:

- Font changes – size, colour, style, spacing (including line spacing)
- Colour of paper
- Presentation in an electronic format (on screen)
- Being read aloud to patients with visual impairment, inability to read but understand spoken English in line with standard care practices for the patient
- Written language translation (back translation also required)

Regardless of how the Patient Information is presented (electronically etc), the patient must always be provided with a copy of the documentation for their future reference.

The PI or designee will obtain written informed consent from each participant before any trial-specific activity is performed. In exceptional circumstances where the patient (with mental capacity) is unable to fully sign the ICF by themselves or it is illegible due to an impairment, for example visually impaired patients, the consent process can be witnessed by an independent member of the care team with a handwritten annotation on the ICF in line with standard care practices for the patient. A file note should also be completed to document the additional signature and the reasons for this. This must be filed with the ICF. The Patient Information and consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The PI will retain the original of each participant signed informed consent form.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible.

10.3 Screening Evaluation

10.3.1 Pre-screening

The following can be undertaken prior the patient consenting to participate in the trial to determine initial eligibility:

- Confirmation of metastatic stage 4 PDA, based on prior histology or cytology and radiology, with measurable disease
- Confirmation that tumour tissue TMB is ≥4 mut/Mb or dMMR/MSI-H

Sites will be requested to provide the actual TMB measurement as well as information regarding the following specific gene/protein alterations, if tested for:

- ML1H1, MSH2, MSH6, PMS2 and EPCAM
- Lynch syndrome
- BRCA1 and BRCA2
- Other clinically relevant genes

In addition, sites will be asked to specify the molecular assay used for genomic testing.

10.3.2 Screening Assessments and trial registration

The following additional assessments and information are required after eligibility confirmation. If not already documented/performed during the Screening visit, these must be completed within 21 days prior to commencing trial treatment, unless otherwise specified.

- Medical history and demographics
- Baseline symptoms
- Concomitant medications review
- Performance status (see 10.4.2)
- Height and weight (see 10.4.4)
- Physical examination (see 10.4.3)
- Adverse event assessment – (see 10.4.6)
- Laboratory assessments (see 10.4.7)
- Pregnancy test for women of child-bearing and non-childbearing potential performed within 3 days prior to first treatment (see 10.4.7)
- Tumour assessment – CT scan confirming measurable disease, to be done within 30 days of planned treatment start date (see 10.4.11)
- ECG within 28 days of planned treatment start date (see 10.4.8)
- Completion of EORTC QLQ-C-30 and PAN26 questionnaires (see 10.4.12)

The results of the screening assessments must be documented in the registration eCRFs (see the eCRF and eCRF Completion Guidelines for registration instructions).

The patient must complete all screening assessments and registration before treatment can start.

If the patient meets all of the eligibility criteria, the patient will be registered by the CCTU-CT and assigned a unique Trial ID Number. Confirmation that eligibility requirements have been met must be documented in the eligibility eCRF and medical notes/records for the patient.

10.4 Trial Assessments

Trial specific assessments will only be conducted after patients have given written informed consent. Please refer to the Schedule of Events for timing of assessments (Section 10.9).

10.4.1 Demographics and medical history.

Demographics will include sex, ethnicity, age at consent. Medical history should include oncology history – initial date and TNM stage at diagnosis of PDA, any prior surgery, radiotherapy, chemotherapy for PDA; current TNM staging at trial entry; prior history of smoking and diabetes; relevant family history or other risk factors for PDA; any history of auto-immune disease; antibiotic use in the last 30 days.

10.4.2 Performance status

Assessment should include ECOG PS and Karnofsky Performance Status Scale (KPS) Clinical Frailty Score, body weight.

10.4.3 Physical examination

Comprehensive physical examination must be performed at screening. For all other visits (during treatment, and on follow-up), a physical examination only needs to be performed if clinically indicated.

10.4.4 Height and Weight

Body weight will be measured in kilograms. Height will be measured in centimetres.

10.4.5 Concomitant medication

Information on any concomitant treatment within the 4 weeks prior to starting trial treatment and all concomitant treatments given during the trial until 4 weeks after the last study dose must be documented. Concomitant medications include all prescription medications, and any other drugs taken for pain management on a daily basis. See section 9.2 for full concomitant medication details.

10.4.6 Adverse events

Recording of all clinically significant adverse events must start from the point of Informed Consent, regardless of whether a patient has yet received a medicinal product, until the end of treatment visit. See section 11 for full Adverse event details.

10.4.7 Laboratory assessments

Routine Laboratory assessments must include as a minimum:

- Full blood count (red blood cell count [including MCV, MCH, white blood cell count, neutrophils, eosinophils, lymphocytes, haemoglobin, platelets)
- Biochemistry (sodium, potassium, calcium, urea, creatinine, albumin, total protein, glucose [non-fasting])
- Calculated creatinine clearance (screening only, using Cockcroft-Gault)
- Liver function tests (AST or ALT [depending on local laboratory], ALP, total bilirubin)
- Thyroid function tests (including: TSH, free T4, free T3)
- Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody), based on local requirements only
- **Pre-cycle 1 treatment only (thereafter only if clinically indicated):** random cortisol; serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol (females) or testosterone (males), coagulation factors (PT or INR and aPTT/PTT) only in patients taking anticoagulation therapy

Tumour marker assessment:

- Ca 19.9

Pregnancy assessment:

- Test for women of child-bearing potential (WoCBP) should be performed as per local hospital procedure; either serum or urine β human chorionic gonadotropin (β-hCG) is acceptable.
- **WoNCBP** will require a non-childbearing status assessment unless there is documentation of either of the following:
    - Documented as postmenopausal (defined as aged ≥ 50 years and amenorrhoeic for ≥12 months following cessation of all exogenous hormonal treatments, and without an alternative medical cause).
    - Documentation of irreversible surgical sterilisation (excluding tubal ligation, radiation-induced oophorectomy) by:
    - hysterectomy or;
    - bilateral oophorectomy or;
    - bilateral salpingectomy with last menses >1 year ago

If WoNCPB do not meet either of the above criteria the following assessments must be performed during screening to confirm non-childbearing status:

- Serum follicle-stimulating hormone
- Luteinizing hormone
- Plasma oestradiol tests

If the non-childbearing status cannot be confirmed after the above assessments, then a pregnancy blood test will need to be performed and a negative result confirmed within 3 days prior to starting treatment. A pregnancy test will also performed within 30 days of treatment ending.

10.4.8 Resting 12-lead ECG

A standardised ECG machine should be used and the patient should be examined using the same machine throughout the trial, where feasible and as per local practice. 12-lead ECGs will be obtained with the patient resting in a supine or semi-supine position. An overall evaluation will be recorded prior to cycle 1 only. Subsequent ECGs will be undertaken only if the investigator requires it.

10.4.9 Research blood samples

A research blood sample will be collected prior to cycles 1, 2, 3, 6 and 9 (within 1 week prior to each new cycle) and on disease progression (within 28 days of confirmation), or at 1 year (+ 28 days), whichever is sooner.

Please refer to the PemOla Laboratory Manual for full details of sample handling and processing.

10.4.10 Archival tissue samples

The following will be requested/collected for analysis:
Archival tumour samples will be obtained from prior surgery, or from tumour biopsies associated with the diagnosis of PDA, both of which will be in the form of either FFPE blocks or slides.

Archival organ biopsies will also be obtained as part of investigation or treatment of immunotherapy-related toxicities.

No research biopsies are included in this protocol for the trial.

10.4.11 Tumour assessment – contrast enhanced CT scan & RECIST

Assessment for response by contrast-enhanced CT scans (chest, abdomen, and pelvis) will be done every 9 weeks for the first 9 x 3 weekly cycles (27 weeks), then every 12 weeks, until disease progression.

The baseline scan should be done within 30 days of starting treatment. The first scan after baseline should be done prior to cycle 4, at 8 weeks from treatment start date. Subsequent scans should be performed, at 17 weeks and 26 weeks and then every 12 weeks until disease progression. All CT scans after baseline can be undertaken with a window of +/- 7 days.

Scans should be performed using intravenous and/or oral contrast or as per local policy.

The primary endpoint will be evaluated using RECIST criteria version 1.1 and CT scanning every 9 weeks for the first 9 cycles (27 weeks), then 12 weekly. A trained radiologist should assess response using RECIST criteria version 1.1 (see Appendix 1).
In addition, response according to iRECIST criteria[53] will also be evaluated and compared with RECIST response, as an exploratory endpoint.

10.4.12 EORTC QLQC30 and PAN26 QoL questionnaires

EORTC QLQC30 and PAN26 QoL questionnaires will be completed prior to starting treatment (within 21 days), every 9 weeks (+/-1 week) for the first 27 weeks (coinciding with scanning dates), then every 12 weeks (+/-1 week), until death, loss to follow-up or maximum of 2 years (see 10.4.11 for clarification on timings)

10.4.13 Research urine samples

Research urine samples will be collected prior to cycles 1, 2, 3, 6 and 9 (within 1 week prior to each new cycle) and on disease progression (within 28 days of confirmation), or at 1 year (+ 28 days), whichever is sooner.

10.4.14 Research stool samples

Research stool samples will be collected prior to cycles 1, 2, 3, 6 and 9 (within 1 week prior to each new cycle) and on disease progression (within 28 days of confirmation), or at 1 year (+ 28 days), whichever is sooner.

10.5 **Timing of assessments while on treatment**

Patients should be assessed prior to each treatment cycle until 2 years, disease progression or unacceptable toxicity.

10.6 **Assessments at each time point**

All assessments should be carried out prior to the start of each cycle, unless otherwise specified. Cycle 1 treatment must start within 21 days of registration.

10.6.1 Remote visits

The first 27 weeks (up to cycle 9) will need to be face-to-face visits. From cycle 10, sites will have the option of moving to 6 weekly face-to-face visits with a 3-week virtual telephone check in between. In this case, olaparib compliance will be checked every 6 weeks and sites would be able to prescribe 6 weeks of olaparib at a time once the patient has stabilised, in

line with local policies. Patients will still need to attend for their laboratory investigations and research bloods at 1 year or disease progression.

10.6.2 Cycle 1 (1-3 weeks)

The following assessments are required within 1 week prior to starting cycle 1 unless otherwise specified.
(Please note: if the laboratory assessment, performance status, and tumour marker have been done as part of trial screening and are within the screening timeframe, they do not need to be repeated at cycle 1)

- Performance status (see 10.4.2)
- Weight (see 10.4.4)
- Physical examination (see 10.4.3)
- Concomitant medication review (see 10.4.5)
- Adverse event assessment – (see 10.4.6)
- Laboratory assessments (see 10.4.7)
- Tumour marker (see 10.4.7)
- ECG (see 10.4.8)
- Research blood sample (see 10.4.9)
- Urine sample (see 10.4.13)
- Stool sample (see 10.4.14)
- Tumour assessment - CT scan (chest, abdomen and pelvis) confirming measurable disease to be done within 30 days of treatment start date (see 10.4.11)
- Pregnancy test carried out within 3 days prior to starting treatment

10.6.3 Cycle 2 (4-6 weeks)

The following assessments are required within 1 week prior to starting cycle 2:

- Performance status (see 10.4.2)
- Body weight (10.4.4)
- Physical examination only if clinically indicated (see 10.4.3)
- Laboratory assessments – (see 10.4.7)
- Tumour marker (see 10.4.7)
- Research blood sample (see 10.4.9)
- Concomitant medication review (see 10.4.5)
- Adverse event assessment (see 10.4.6)
- Record of olaparib and pembrolizumab administered
- Olaparib compliance check
- Urine sample (see 10.4.13)
- Stool sample (see 10.4.14)

10.6.4 Cycle 3 (7-9 weeks) onwards till cycle 9 (25-27 week)

The following assessments are required within 1 week prior to the start of each cycle:

- Performance status (see 10.4.2)
- Body weight (see 10.4.4)
- Physical examination only if clinically indicated (see 10.4.3)
- Laboratory assessments - (see 10.4.7)
- Tumour marker (see 10.4.7)
- Research blood sample (cycle 3, 6 and 9 only) (see, 10.4.9)

- Concomitant medication review (10.4.5)
- Adverse event assessment (see 10.4.6)
- Record of olaparib and pembrolizumab administered
- Olaparib compliance check
- **Every 9 weeks for first 27 weeks:**
  - tumour assessment CT scan (chest, abdomen and pelvis), including RECIST (see 10.4.11)
  - EORTC QLQC30 and PAN26 QoL questionnaires (see 10.4.12)
- Urine sample (cycle 3, 6 and 9 only) (see 10.4.13)
- Stool sample (cycle 3, 6 and 9 only) (see 10.4.14)

10.6.5 Cycle 10 onwards until 2 years or disease progression or unacceptable toxicity

The following assessments are required within 1 week prior to the start of each cycle:

- Performance status (see 10.4.2)
- Body weight (see 10.4.4)
- Physical examination only if clinically indicated (see 10.4.3)
- Laboratory assessments (see 10.4.7)
- Tumour marker (see 10.4.7)
- Concomitant medication review (see 10.4.5)
- Adverse event assessment (see 10.4.6)
- Record of olaparib and pembrolizumab administered
- Olaparib compliance check (or every 6 weeks if moving to remote visits).
- **Every 12 weeks during treatment:**
  - tumour assessment CT scan (chest, abdomen and pelvis), including RECIST (see 10.4.11)
  - EORTC QLQC and PAN26 QoL questionnaires (see 10.4.12)

10.7 Sample collection at 1 year

Please note: these samples are only required for participants who remain on trial treatment and whose disease has not progressed at 1 year.

- Research blood sample (see 10.4.9)
- Urine sample (see 10.4.13)
- Stool sample (see 10.4.14)

10.8 Assessments at the end of trial visit

10.8.1 Disease progression assessments

These assessments should occur within 28 days after the date of protocol-defined disease progression (disease progression as per RECIST V1.1 criteria). If progression occurs beyond 1 year, the research blood, urine and stool samples do not need to be collected.

- Performance status (see 10.4.2)
- Physical examination only if clinically indicated (see 10.4.3)
- Laboratory assessments (see 10.4.7)
- Tumour marker (see 10.4.7)
- Research blood sample (see 10.4.9)
- Adverse event assessment (see 10.4.6)
- Urine sample (see 10.4.13)
- Stool sample (see 10.4.14)
- A pregnancy test should also be carried out 30 days after the end of treatment (see 10.4.7)

10.8.2 Follow-up assessments

10.8.2.1 *9 – 12 weekly follow-up (until disease progression)*

Patients who discontinue treatment due to toxicity, and/or meet any of the withdrawal criteria other than disease progression but remain on-trial will be followed up every 9 weeks (+/- 7 days) during the first 27 weeks and every 12 weeks (+/- 7 days) thereafter until disease progression. The following assessments will be undertaken:

- Performance status (see 10.4.2)
- Tumour marker (see 10.4.7)
- Tumour assessment CT scan (chest, abdomen, and pelvis), including RECIST, every 9 weeks during the first 27 weeks and every 12 weeks thereafter while on study until disease progression
- EORTC QLQC30 and PAN26 QoL questionnaires every 9 weeks during the first 27 weeks and every 12 weeks thereafter until death, lost to follow-up or maximum of 2 years

10.8.2.2 Survival follow-up

Participants that discontinue trial treatment or follow-up visits due to disease progression within 2 years from the start of trial treatment will only be followed up 2 years (+/- 28 days) from commencement of trial treatment:

- for survival (including date last known alive, or cause and date of death)
- to collate information of any treatment-related AEs until resolution to CTCAE $\leq$1
- any subsequent anticancer treatment will be documented.
- beyond disease progression, EORTC QLQC30 and PAN26 QoL questionnaires will continue to be collected every 9 weeks during the first 27 weeks and every 12 weeks thereafter until death, lost to follow-up or maximum of 2 years.

Details of the survival status will be obtained from the GP and/or source data (see section 16.2). No further follow-up visits are required.

10.9 Schedule of Assessments

Evaluations	Screening	Treatment period – first 27 weeks			Treatment period after 27 weeks	1 year	Follow-up		On PD (within 28 days +/- 7)
		Cycle 1 (1-3 weeks)	Cycle 2 (4-6 weeks)	Cycle 3 (7-9 weeks) onwards till Cycle 9 (25-27 weeks)	Cycle 10 Onwards[w]		9 -12 weekly Follow up visits[i]	Survival follow up	
Informed consent	X								
Eligibility confirmation	X								
Demographics[a]	X								
baseline symptoms and medical history[b]	X								
Performance status[c]	X	X[u]	X	X	X		X		x
Physical examination	X	X If clinically indicated							
Height	X								
Body weight	X	X	X	X	X				
Laboratory assessments[e]	X[F]	X[F,u]	X	X	X				x
CA19.9 Tumour marker	X	X[d]	X	X	X		X		x
WOCBP pregnancy test[g]	X[v]								X[t]
ECG	X[o]	X[o,d]	X[o] Only if the investigator requires it						
Research blood samples[h]		X	X	X		X			x
Research urine samples[q]		X	X	X		X			x
Research stool samples[r]		X	X	X		X			x
Adverse event assessments	X	X	X	X	X				x
Concomitant medications[p]	X	X	X	X	X				
CT & RECIST	X[j]	X[j]			X[j]		X[j]		
Olaparib dosing		Twice daily[s]							
Olaparib compliance check		At every visit							
Pembrolizumab administration[k]		X	X	X	X				

EORTC, QLQC30 and PAN26 QoL questionnaires	X	X[l]	X[m]		X[n]		
Survival status[i]						X	

a. Demographics will include sex, ethnicity, and age at consent.
b. Medical history should include oncology history – initial date and TNM stage of diagnosis of PDA, prior surgery, radiotherapy, chemotherapy; current TNM staging; prior history of smoking and diabetes; relevant family history or other risk factors for PDA; any history of auto-immune disease; antibiotic use in the last 30 days
c. Assessment should include ECOG, KPS Clinical Frailty Score, body weight.
d. Assessments are required, within 28 days prior to starting cycle 1 treatment. If they have been done as part of trial screening within this time frame, they do not need to be repeated
e. Routine Laboratory assessments must include as a minimum: Full blood count (total white blood count, neutrophils, lymphocytes, haemoglobin, platelets), Biochemistry (sodium, potassium, calcium, urea, creatinine, albumin, total protein), Liver function tests (AST and/or ALT (depending on local laboratory), ALP, total bilirubin), Calculated creatinine clearance (screening only, using Cockcroft-Gault)) and thyroid function tests (including: TSH, free T4, free T3)
f. **Pre-treatment only**: random cortisol, FSH, LH and oestradiol (females) or testosterone (males), random glucose; coagulation factors (PT or INR and aPTT/PTT) only in patients taking anticoagulation therapy
g. Test for WoCBP should be performed as per local hospital procedure (either serum or urine β human chorionic gonadotropin (β-hCG)). Repeat only if clinically indicated. WoNCPB that do not have documentation listed in section 10.11.1 must be performed during screening to confirm non-childbearing status Serum follicle-stimulating (FSH), Luteinizing hormone (LH) and Plasma oestradiol tests
h. Research blood to be collected pre-treatment, then prior to cycles 2, 3, 6, 9 and at disease progression or at 1 year, whichever comes first
i. Patients who discontinue treatment due to toxicity, and/or meet any of the withdrawal criteria other than disease progression but remain on-study will be followed up every 9weeks (+/- 7 days) during the first 27 weeks and every 12 weeks (+/- 7 days) thereafter until disease progression.
j. Contrast-enhanced CT scans (chest, abdomen and pelvis) will be done pre-treatment (within 30 days of treatment start date), then every 9 weeks for the first 9 x 3 weekly cycles (27 weeks), then every 12 weeks, until disease progression. Scans can be undertaken with a window of +/- 7 days.
k. Pembrolizumab will be given once every 3 weeks cycle, administered intravenously as a approximately 30 minute infusion, as per standard clinical practice
l. EORTC QLQC30 and PAN26 QoL questionnaires to be performed every 9 weeks during the first 27 weeks
m. EORTC QLQC30 and PAN26 QoL questionnaires to be performed every 12 weeks until death or maximum of 2 years
n. During the follow up EORTC QLQC30 and PAN26 QoL questionnaires will be completed prior every 9 weeks for the first 27 weeks (coinciding with scanning dates), then every 12 weeks, until death, loss to follow-up or maximum of 2 years.
o. ECG overall evaluation will be recorded prior to cycle 1 only. Subsequent ECGs will be undertaken only if the investigator requires it.
p. All prescription concomitant medications received within 30 days before the first dose of study drug through to 4 weeks after the last dose of study drug should be recorded. If the end of treatment visit is sooner than 4 weeks since last treatment, the local team should contact the patient to collect this data.
q. Research urine samples will be collected pre-treatment, then prior to cycles 2, 3, 6 and 9 and on disease progression, or at 1 year, whichever is sooner.
r. Research stool samples will be collected pre-treatment, then prior to cycles 2, 3, 6 and 9 and on disease progression, or at 1 year, whichever is sooner.
s. Olaparib to be administered twice daily, every day of each cycle.
t. To be performed 30 days after the last dose of treatment.
u. Assessments are required within 21 days prior to starting cycle 1 treatment. If they have been done as part of trial screening within this time frame, they do not need to be repeated
v. To be performed within 3 days prior to starting treatment

w. can be done every 6 weeks if sites decide to move to remote visits. Patients will still need to attend for their laboratory investigations and research bloods at 1 year

10.10 End of Trial Participation

The end of patient participation in this trial is defined as their last trial visit, which will be a maximum of 2 years after starting trial treatment.

There will be no provision for compassionate access to the trial IMP(s) once the participant has finished their participation in the trial. Trial participants will return to standard treatment.

10.11 Trial Restrictions

Patients must not enrol into any other investigational trial while enrolled in this trial. Co-enrolment in observational studies is allowed.

10.11.1 Contraception requirements

Women of childbearing potential (and their partners) are required to use adequate contraception during trial (from signing the informed consent until the last dose of the trial treatment) and for 150 days after the last dose of the trial treatment for women, and for 270 days after the last dose of trial treatment for men. Male participants must also refrain from donating sperm during this period. See section 10.4.7 for definition of Women of child-baring potential.

Acceptable non-hormonal birth control methods include:

- Intrauterine Device (IUD) PLUS male condom provided coils are copper-banded
- True abstinence (where the patient refrains from any form of sexual intercourse and is in accordance with the patient's preferred and usual lifestyle)
- Vasectomised sexual partner PLUS male condom (with patient assurance that the partner has received post-vasectomy confirmation of azoospermia)
- Tubal occlusion PLUS male condom

Acceptable hormonal birth control methods include:

- Hormonal shot or injection (e.g. Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g. Implanon, Norplant) PLUS male condom
- Intrauterine system (IUS) device (e.g. levonorgestrel releasing IUS – Mirena) PLUS male condom.

Men are required to use adequate contraception during the trial (from signing the informed consent form until the last dose of the trial treatment) and for 270 days after the last dose of the trial treatment. This includes:

- Barrier contraception (condom and spermicide) even if female partner(s) are using another method of contraception or are already pregnant (also to protect male partners from exposure to the trial IMPs etc)
- True abstinence (where this is in accordance with the patients preferred and usual lifestyle)

Female partners of male patients should also use a highly effective form of contraception during their partner's treatment and for 270 days after the last dose of trial treatment if they are of childbearing potential.

Women who are breast feeding are excluded from the trial.

11 Assessment of Safety

11.1 Definitions

11.1.1 Adverse event (AE)

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

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a participant has yet received a medicinal product.

11.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or The Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI).

When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant /event outcome or action criteria.

11.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatient´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect.
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was 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.

11.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

11.1.6 Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

The RSI is contained in a clearly identified section of the IB.

For this trial the Reference Safety Information is:

- Section 5.6 (table 64) of the latest Investigators Brochure for olaparib approved by the MHRA for this trial.
- Section 7.2 (table 62) of the latest Investigators Brochure for pembrolizumab approved by the MHRA for this trial.

11.1.7 Participant Reporting Duration

The Sponsor expects that AEs are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product

Recording and reporting of SAEs will start from the point of Informed Consent until 30 days after the last treatment date.

11.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 11.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 11.6.

11.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

For this trial the following adverse events must not be reported as SAEs, but must be recorded on the eCRF:

- Disease progression, or death as a result of disease progression
- Elective hospitalisation and surgery for further treatment of solid tumours.
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- Elective hospitalisation for trial therapy, disease-related procedures or placement of an indwelling catheter, unless associated with other serious adverse event.

11.4 Evaluation of adverse events

Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality) and severity.

11.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 11.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

11.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

11.4.3 Clinical assessment of severity

All events should be graded for severity according to the NCI-CTCAE Toxicity Criteria (Version 5.0) CTCAE v5.0, dated 27/11/2017 can be downloaded from the following URL:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

11.4.4 Recording of adverse events

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the CRF. Serious Adverse Events and Serious Adverse Reactions should be reported to The Sponsor as detailed in section 11.6.

11.5 **Reporting serious adverse events**

Each Principal Investigator needs to record all adverse events and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to The Sponsor immediately but not more than 24 hours of first notification. The Sponsor must keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial

- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

The Chief Investigator is also responsible for reporting serious adverse events to the IMP manufacturer (MSD) within 24 hours of awareness of first notification.

The completed SAE form should be emailed. Details of where to report the SAE's can be found on the PemOla SAE form cover page and the front cover of the protocol.

11.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 11.1.6 for the Reference Safety Information to be used in this trial.

11.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- competent authorities in the concerned member states (e.g. MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

11.6.2 When to report?

11.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 11.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

11.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 11.6.1 as soon as possible but no later than **15 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

11.6.3 How to report?

11.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

- A suspected investigational medicinal product

- An identifiable participant (e.g. trial participant code number)
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
- An identifiable reporting source

Also when available and applicable:

- A unique clinical trial identification (EudraCT number or in case of non- European Community trials The Sponsor's trial protocol code number)
- A unique case identification (i.e. The Sponsor's case identification number)

11.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

11.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to. A copy of the submitted report will be shared with MSD.

11.7 **Pregnancy Reporting**

All pregnancies within the trial (either the trial participant or the participant's partner) should be reported to the Chief Investigator and The Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/fetus. If the outcome meets the serious criteria, this would be considered an SAE.

The Chief Investigator is responsible for informing MSD of any notifications of pregnancy within two business days, but no longer than three calendar days, of receipt of information. Outcome of pregnancy also to be reported. A positive pregnancy test at the time of initial screening does not need to be reported to MSD.

12 Toxicity

12.1 **Known drug reactions**

For current information regarding any known interactions with other therapies, please refer to the most recent version of the pembrolizumab and olaparib IB. Prohibited medications and therapies are detailed in section 9.2 of the Protocol. Please also refer to the IB for the latest approved Reference Safety Information (RSI) for this trial. See section 11.1.6 of the Protocol for more information.

12.2 Management of Drug-specific Toxicity

12.2.1 Pembrolizumab-specific toxicity

Guidance regarding management of toxicity and supportive care for IrAEs is provided below, but Investigators can follow their own local guidelines, as appropriate.

Table 4: Pembrolizumab modifications

Toxicity	NCI CTCAE Grade	Dose modification
Diarrhea/Colitis	2-3	Hold the pembrolizumab until the toxicity resolves to grade ≤1- Administer tapering corticosteroids. Discontinue treatment if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Hold the pembrolizumab until the toxicity resolves to grade 1-0. Discontinue treatment if the toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue[(a)]
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Hold pembrolizumab until toxicity resolves to grade 1-0. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted Discontinue treatment if the toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Hold pembrolizumab until toxicity resolves to grade 1-0. Discontinue treatment if the toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
	1	Continue with infusion

Infusion Reaction [(b)]	2b	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue
Pneumonitis	2	Hold treatment until the toxicity has resolved to grade 1-0. Administer tapering corticosteroids Discontinue treatment if the toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue
Renal Failure or Nephritis	2	Hold treatment until the toxicity has resolved to grade 1-0. Administer tapering corticosteroids Discontinue treatment if the toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis	Withhold until etiology confirmed
	Grade 2, 4 or 4	Permanently discontinue
Neurological Toxicities	2	Withhold until etiology confirmed
	3 or 4	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Withhold until etiology confirmed
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
All Other Drug-Related Toxicity[(c)]	Persistent Grade 2	Hold treatment until the toxicity has resolved to grade 1-0.

	3	Hold treatment until the toxicity has resolved to grade 1-0. Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue

- Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life- threatening event.
- For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
- For patients with infusion reaction Grade 2, 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 subject should be pre-medicated for the next scheduled dose.
- Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 6 weeks of the last dose.

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). Patients should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

12.2.1.1 *Treatment for IrAEs*

Patients 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 aetiology are outlined below. Where appropriate, these guidelines include 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. 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 infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

12.2.1.2 *Pneumonitis*

For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

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

Nb. Pneumonitis may be associated with either olaparib, or pembrolizumab. For further guidance on managing pneumonitis, see section 12.2.3.

12.2.1.3 *Diarrhoea/Colitis*

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

All patients who experience diarrhoea/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 diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.

For Grade 2 diarrhoea/colitis that persists greater than 3 days, administer oral corticosteroids.

For Grade 3 or 4 diarrhoea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

When symptoms improve to Grade 1 or less, taper steroids gradually (usually over minimum 4 weeks)

12.2.1.4 *Hyperglycemia*

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.

12.2.1.5 *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 as the steroid dose is tapered.

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.

12.2.1.6 *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 3-4 hypothyroidism):

In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

Grade 3-4 hyperthyroidism Treat with an initial dose of IV corticosteroid 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.

12.2.1.7 *Hepatic*

For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly). Treat with IV or oral corticosteroids

For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

12.2.1.8 *Renal Failure or Nephritis*

For Grade 2 events, treat with corticosteroids.

For Grade 3-4 events, treat with systemic corticosteroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Nb. Renal toxicity is a rare event which may be associated with either olaparib, or pembrolizumab. For further guidance on managing renal toxicity, see section 12.2.4.

12.2.1.9 *Neurological Toxicities*

For Grade 2,3 and 4 events administer corticosteroids if required.

12.2.1.10 *Exfoliative dermatologic conditions*

For both suspected and confirmed SJS, TEN or DRESS administer corticosteroids if required.

12.2.2 Olaparib-specific toxicity

In case of toxicities presumed related to olaparib and not to immunotherapy, please follow the recommendations in the tables 5 and 6 below.

12.2.1.11 *Haematological toxicities*

Table 5: Management of olaparib haematological toxicity

Toxicity	**Dose modification**
Hb<100 and ≥80g/l CTCAE grade 2	Supportive treatment such as Transfusion If repeat Hb <90 g/l dose interrupt olaparib for maximum of 28 days until Hb ≥90 g/l.

	If repeat Hb ≥90 g/l restart at the same dose if this is the first occurrence of anaemia with no co-existent neutropenia or thrombocytopenia. If this is the second occurrence or it co-exists with neutropenia or thrombocytopenia reduce by 1 dose level.
Hb < 80 g/l CTCAE grade 3	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 28 days, until improvement to Hb ≥ 90g/l. Upon recovery to ≥90 g/l dose reduce by 1 level. If recurs, further dose reductions of 1 level will be required.
CTCAE ≥ Grade 3 Thrombocytopaenia and Neutropaenia	Dose interrupt until recovered to CTCAE grade 1 or better for a maximum of 28 days. With repeat CTCAE grade 3-4 occurrence, dose reduce to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg). If a further dose reduction is required, then reduce to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg).
CTCAE Grade 1-2 Neutropaenia and thrombocytopaenia	Investigator's clinical judgement will be used to decide whether to continue treatment or dose interrupt for a maximum of 28 days; appropriate supportive treatment and causality investigation is required.

12.2.1.12 *Non-haematological toxicities*

Table 6: Management of olaparib non-haematological toxicity

Toxicity	Dose modification
Pulmonary symptoms	An interruption in study intervention dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis. If no abnormality is observed on CT and symptoms resolve, then study intervention can be restarted.
Fatigue (Grade 2)	Consider short treatment break, initially 2-3 days, or longer-up to a maximum of 28 days Restart once resolves to <grade 2 at the same dose level if first occurrence, or dose reduce by 1 dose level if second occurrence.
Fatigue Grade 3 and 4	Stop olaparib for maximum of 28 days and once resolves to <grade 2 restart by reducing 1 dose level.
Nausea Grade 2 and 3	Consider short treatment breaks, initially 2-3 days, or longer-up to a maximum of 28 days. Restart once resolves to <grade 2 at the same dose level if first occurrence, or dose reduce by 1 dose level if second occurrence.

Nausea Grade 4	Discontinue Olaparib
Creatinine clearance between 31 and <50 ml/min	Reduce dose to dose level -2
Creatinine clearance <30 ml/min	Stop Olaparib

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). Patients should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

12.2.3 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. They are generally mild to moderate (CTCAE grade 1 or 2) in severity, intermittent and manageable on continued treatment.

Patients should receive appropriate anti-emetic treatment in accordance with local practice. Generally, a single agent antiemetic should be considered.

12.2.4 Pneumonitis:

During treatment, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e., episodes of transient or repeated dyspnoea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). **Nb. Pneumonitis may be associated with either olaparib, or pembrolizumab**.

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in both study drugs (pembrolizumab as well as olaparib) is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis.
If pneumonitis is suspected, it is recommended to interrupt all study treatment in the first instance.

Physical examination: Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed and SpO2 (saturation of peripheral oxygen) should be recorded. Any additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

12.2.5 Renal impairment

Renal dysfunction is a rare event reported both with olaparib and with Pembrolizumab. If subsequent to study entry and while still on study therapy, a patient's estimated creatinine clearance falls below the threshold for study inclusion (≥50 ml/min), retesting should be performed promptly.

A dose reduction of olaparib is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of Olaparib should be reduced to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg).

Because the creatinine clearance determination is only an estimate of renal function, in instances where the creatinine clearance falls to >31 and <50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of olaparib is warranted and whether also to consider interrupting and/or stopping pembrolizumab.

In patients develop severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; both olaparib and Pembrolizumab must be discontinued.

13 Evaluation of Results (Definitions and response/evaluation of outcome measures)

Details of the trial outcome measures and their definitions can be found in section 7.7.

Details of RECIST v1.1 can be found in appendix 1, section 29.

14 Analysis of Samples

All research samples for this trial must be handled, tracked, processed and stored according to the instructions provided in the PemOla Laboratory Manual.

14.1 Routine sample analysis

Routine blood samples taken will be analysed immediately as per local Hospital/Trust policy and will be destroyed once the analysis is complete.

14.2 Translational (exploratory) research

Blood and tissue samples will be collected for research as detailed below. Other analyses in this trial may be performed on the samples in line with the trial objectives.

We will collect and analyse the following samples as part of this trial:

- Tumour samples will be analysed for biomarker studies (% viable tumour, TIL response, PD-L1, HLA expression, GAS-STING pathway expression, immune signature expression using RNAseq, histology for immune cell profiling)
- Plasma samples (1 x 4mL EDTA tube and 1 x 10 mL PAXgene ccfDNA tube) will be collected for:
    - GTene panel testing of ctDNA: pre-treatment, prior to cycles 2, 3, 6, 9 and on disease progression or at 1 year, whichever is sooner
    - Cytokine analysis: same time points as for gene panel testing
    - PD/PK analysis
- Peripheral Blood Mononuclear Cells (PBMCs) (2 x 9mL CPDA tubes) for immunophenotyping using flow cytometry and T cell receptor (TCR) and B cell receptor (BCR) clonality analysis, pre-treatment and prior to cycles 2, 3, 6, 9, and upon disease progression, or at 1 year, whichever is sooner.
- Buffy coat will be collected to extract DNA at baseline only
- Urine samples for PD/PK analysis pre-treatment and prior to cycles 2, 3, 6 and 9 and upon disease progression, or at 1 year, whichever is sooner

- Stool samples for microbiome analysis pre-treatment and prior to cycles 2, 3, 6 and 9 and upon disease progression (+/- 1 week from study visit), or at 1 year, whichever is sooner

Please refer to the PemOla Laboratory Manual for details of sample collection, processing, storage procedures.

In cases of participant withdrawal from the trial, any data or samples already collected or results from tests already performed will continue to be used in the trial analysis unless explicitly requested by the participant for destruction.

15 Statistics

15.1 Statistical Methods

This study is designed to provide evidence that pembrolizumab plus olaparib is superior to optimal combination cytotoxic chemotherapy currently used to treat mPDA in either the first or second line setting, with an expected acceptable side effect profile and associated QoL.

This is a single arm open label clinical trial with a small sample size, using drugs with known side effect profiles. A Trial Steering Committee (TSC) will therefore be established to monitor patient safety, recruitment and efficacy outcomes at each stage of the trial.

15.2 Interim Analyses

The **first interim** analysis will be performed when 10 patients have been recruited and received at least 18 weeks treatment or progressed before 18 weeks. If there are at least 3 objective responses (defined as stable, partial or complete response by RECIST 1.1) and there are no safety concerns (no more than 2 patients hospitalised with grade 3+ drug-related AEs), the study will continue to recruit patients. If 2 or fewer responses are observed, and if the responses occurred only in patients with dMMR/MSI-H/TMB $\geq$10 mutations/Mb (true hypermutated) tumours, the trial will continue to recruit only patients whose tumours have TMB $\geq$10 mutations/Mb, assuming the prevalence of this higher TMB biomarker threshold makes continuation of the trial viable. Otherwise, the trial will be terminated.

In order to assess study viability, the TSC will be asked to review recruitment at the mid-point of the trial period, when the anticipated recruitment should be a minimum of 10 patients. It this target has been met or exceeded, the trial will be deemed viable and recruitment continued. If this target has not been met, the TSC will be asked to consider whether the trial should be terminated early, based on information regarding patient eligibility, rates of patients being screened and consented, monthly recruitment rate overall and by site, as well as consideration of alternative trial and non-trial treatment options available for these patients. The TSC will be minded to recommend early closure if recruitment within the planned timelines does not appear to be viable.

If recruitment and response rates are sufficient, then the trial will continue. A **second interim analysis** will be performed when 15 patients have been recruited and a minimum of 5 responses must have been achieved in order to continue the trial. If 4 or fewer responses are recorded, the trial will be terminated.

15.3 Participant Numbers

We have applied the Bayesian optimal phase 2 (BOP2) design[45] to have more flexibility for interim monitoring. It is anticipated that ORR of pembrolizumab plus olaparib will be at least

45% (H_1), while an ORR of 20% or less (H_0) will not be of clinical interest. While controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.05, assuming a vague prior (with prior effective sample size=1), the statistical design leads to the following stopping boundaries and yields a statistical power of 0.807 under H_1:

Table 7: Optimized stopping boundaries

# patients with response assessed	Stop if # responses <=
10	2
15	4
20	6

When the total number of patients reaches the maximum sample size of 20, we will only reject the null hypothesis and conclude that the treatment is effective if the number of responses is greater than 6.

Allowing for a non-compliance rate of 15%, we may need to recruit up to 24 patients over a maximum period of 45 months.

15.4 Final analysis

Should the trial have continued to recruit a total of 20 evaluable patients, the final ORR analysis will be performed, together with DOR, PFS and OS assessments.

The trial will have a 10% significance level (one-sided) and 80% power to detect an improvement in median PFS from 6 to 10 months. The trial is not powered for OS.

Statistical Assumptions

- Anticipated ORR of interest is ≥45%, as this matches the best ORR reported in randomised trials for unselected (30%[45-47]) as well as biomarker-stratified (45%[48]) mPDA populations receiving optimal chemotherapy. An ORR of ≤20% is not considered clinically of interest.
- Median PFS of 10 months is clinically of interest, when compared to median PFS reported with standard first-line (6 months [46],[47]) and second-line (3 months[48]) chemotherapy, as well as median PFS of 9.2 months reported for HA-high biomarker-selected patients in the HALO 202 trial [49]
- Median OS of 15 months is clinically of interest, when compared with median OS reported with standard first-line (<12 months[45] ,[46]) and second-line (6 months [48]) chemotherapy.

15.5 Additional pre-planned analyses

Stratification factors: Exploratory efficacy analyses will be performed for potential confounding variables, which will be included as stratification factors: true hypermutated (≥10 mutations/Mb) versus TMB 4-<10 mutations/Mb, and 1st versus 2nd line therapy.

In addition to the historical controls, we will seek to benchmark final outcomes against a number of contemporary groups, as follows:

- Previously untreated, unselected patients with mPDA receiving cytotoxic combination chemotherapy in the PRIMUS 001 trial, if the PRIMUS 001 trial has reported at the time of analysis
- Patients with MSI-H mPDA who have accessed treatment with nivolumab via the NHS England Cancer Drug Fund Covid-19 arrangements recently introduced in July 2020; we will request anonymised demographic and outcome data from NHS England, who oversee these data
- Those patients identified through the Precision-Panc platform to be dMMR, or MSI-H, but who for whatever reason fail to take part in this clinical trial. Reasons may include patient choice, or eligibility screen failure. We will seek to access anonymized patient information regarding any alternative anti-cancer treatment given, best response to that treatment as well as survival outcomes only.

15.6 Criteria for the Premature Termination of the Trial

The first interim analysis will be performed when 10 patients have been recruited and received at least 18 weeks treatment, or progressed before 18 weeks. If there are at least 3 objective responses (defined as stable, partial, or complete response by RECIST 1.1) and there are no safety concerns (no more than 2 patients hospitalised with grade 3+ drug-related AEs), the study will continue to recruit patients. If 2 or fewer responses are observed, and if the responses occurred only in patients with dMMR/MSI-H/TMB $\geq$10 mut/Mb tumours, the trial will continue to recruit only patients whose tumours have TMB $\geq$10 mut/Mb, assuming the prevalence of this higher TMB biomarker threshold makes continuation of the trial viable. If this target has not been met, the TSC will be asked to consider whether the trial should be terminated early, based on information regarding patient eligibility, rates of patients being screened and consented, monthly recruitment rate overall and by site, as well as consideration of alternative trial and non-trial treatment options available for these patients. The TSC will be minded to recommend early closure if recruitment within the planned timelines does not appear to be viable.

If recruitment and response rates are sufficient, then the trial will continue. A second interim analysis will be performed when 15 patients have been recruited and a minimum of 5 responses must have been achieved in order to continue the trial. If 4 or fewer responses are recorded, the trial will be terminated.

15.7 Procedure to account for Missing or Spurious Data

Protocol deviations will be reported throughout the trial and will be discussed at the Trial Management Group meetings.

The primary analysis will be performed based on all evaluable patients (see section 8.3). A non-compliance of 15% has been considered in the recruitment. All patients that meet the evaluable patient criteria will be included in the final analysis of the primary endpoint. All consenting patients will contribute towards assessment of the secondary endpoints. The reason for non-evaluable patients will be listed.

15.8 Definition of the End of the Trial

The end of trial will be the date of the last participant's last visit (LPLV).

16 Data Handling and Record Keeping

16.1 CRF

All data will be transferred into an eCRF by the participating sites with the exception of serious adverse events and pregnancies which will be reported to the CCTU-CT via email (see section 11.6 and 11.7). Data on the eCRF will be linked to the patient's data using their trial identifier and age at consent. All trial data in the eCRF must be extracted from and be consistent with the relevant source documents. The eCRFs will be completed and held in a secure electronic data capture system. It remains the responsibility of the investigator for the timing, completeness, and accuracy of the eCRF. The eCRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors, and Inspectors as required.

Completed CRF data should be entered into the database within two weeks of the participant visit being completed.
Paper CRF will be used as a backup system. All paper CRF pages must be clear and legible. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used. If paper CRFs are completed for any reason, they will require re-transcription onto the eCRF.

The PI will retain all copies of paper CRFs in the relevant sections of their Investigator Site File with any required de-identified background information from the medical records as required.

For further information please refer to the Electronic Case Report Form (eCRF) Guidelines document.

16.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms

Source data include, but are not limited to:

- Patient Medical Records
- Online Medical Records (e.g. medical records, prescribing records, results/reports from clinical investigations such as blood tests or scans)
- Signed and dated informed consent forms
- Pharmacy records
- Worksheets and forms for sample collection, processing storage and shipment
- Patient Diary Cards
- NHS databases e.g. NHS spine
- EORTC QLQC30 and PAN26 QoL questionnaires

16.3 Data Protection & Patient Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

In particular, investigators and site staff must ensure that no patient identifiable information (including name, address, and hospital number) is transmitted to the Coordination team or Sponsor. Every patient will be allocated a unique trial number that will link all of the clinical information held about them on the trial database. It will also be used in all correspondence with participating clinical trial sites. At no point in presentations or publications of trial data will individual patients be identified.

17 Trial Committees

A Trial Steering Committee (TSC) will be established to monitor patient safety, recruitment and efficacy outcomes at each stage of the trial.

Membership will be as follows:

- An independent Chair
- The trial Chief Investigator and Co-applicants (which include the trial statistician, CTU member and Patient and Public Involvement (PPI) member)
- Two independent Clinicians

As this trial is not blinded and the stop/go rules are set out at each stage (see section 15.3), there is no requirement for an independent statistician.

A Trial Management Group (TMG) will meet approximately monthly to oversee the running of the trial. TMG members will review SAEs and protocol non-compliances which have occurred during the trial, as well as recruitment. If there are specific safety concerns these may be escalated to the TSC.

18 Ethical & Regulatory considerations

18.1 Ethical Committee Review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

18.2 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

18.3 Heath Research Authority (HRA)

HRA approval is required for all UK trials prior to commencement.

18.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from The Sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

In the event of an urgent safety measure, the CI (or delegate) will cascade the information verbally and/or by email to each participating site within 24 hours. The Sponsor, funders, MHRA and REC will also be notified immediately (by telephone initially; written notification no more than 3 days after the event).

18.5 Peer Review

The trial protocol has been reviewed by the National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME) Programme.

18.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.7 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

19 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust. The trial will be funded by the NIHR EME Programme.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

20 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to The Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be routinely conducted for all participating sites. Additional scheduled monitoring visits to participating sites may be triggered based on data queries, SAE reporting or protocol deviation reports. Monitoring of participating sites should occur in line with the trial specific monitoring plan.

21 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and The Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to The Sponsor without any delay.

22 Vendors / Contractors

22.1 External Vendor / Contractors

MSD will manufacture both IMPs.

22.2 Central Facilities

-Eramol: Distribution
-Cambridge Molecular Diagnostics Lab: processing and analysis of blood samples, including but not limited to; PBMC isolation, processing of the plasma and buffy coat, and ctDNA and buffy coat analysis. Serum, plasma and urine samples will be stored here short-term.
-MRC-Toxicology: analysis of blood samples, including but not limited to immunophenotyping and TCR and BCR clonality analysis, and drug and metabolite analysis. Also drug and metabolite analysis on urine samples, and long-term storage of urine samples. Will also carry out microbiome analysis on stool samples and store them.
-Cancer Research UK-Cambridge Institute: Medium term storage of serum, plasma and PBMCs, and urine samples.
-University of Glasgow- Genomics Innovation Alliance: tumour analysis and storage.

23 Publications Policy

Ownership of the data arising from this trial resides with the PemOla Trial Management Group (TMG). On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

Any reported serious breaches will be detailed in all publications in line with regulatory requirements.

The main trial results will be presented at national and international conferences and published in a peer-reviewed journal, on behalf of all collaborators. All presentations and publications relating to the trial must be authorised by the TMG and funder.

The manuscript will be prepared by a writing group appointed from amongst the TMG and high-accruing investigators. The CCTU-CT, funder, Sponsor and all participating sites and Investigators will be acknowledged in publications and presentations. Senior authorship shall be shared between members of the TMG according to their leadership role in the trial. Priority will be given to the lead sites co-ordinating the trial, then to participating sites, ordered by recruitment.

In addition, patients who have consented to receive the results of the trial, will be provided with a summary of the results in lay terms at the end of the trial.

24 Data Transparency

24.1 Informing Participants of the Results of the Trial.

Patients who have consented to receive the results of the trial will be provided with a summary of the results in lay terms at the end of the trial.

25 Data and Sample Sharing

25.1 Data Sharing

De-identified datasets from the trial will be made available to the study funders and may also be made available to other researchers in line with national and international data transparency initiatives (using an open access model). This information is in the patient information sheet and consent will be provided for this.

25.2 Sharing Tissue Samples

Remaining de-identified tissue samples collected in this trial may be retained in a Human Tissue Authority licenced facility, pending ethical approval for use in another project. This information is in the patient information sheet and consent will be provided for this.

26 Archiving

As per current regulations, once the trial has come to an end and the analysis has been reported to the regulatory authorities, essential trial documentation as part of the TMF will be archived in keeping with The Sponsor’s policy and applicable regulations for a period of 5 years.

All trial related documentation and data as part of the investigator site file (including site level pharmacy file) will be archived in accordance with participating site's standard operating procedures and The Sponsor's timelines. These procedures state suitable locations to be specified at the time of archiving with limited access to named members of the research team only.

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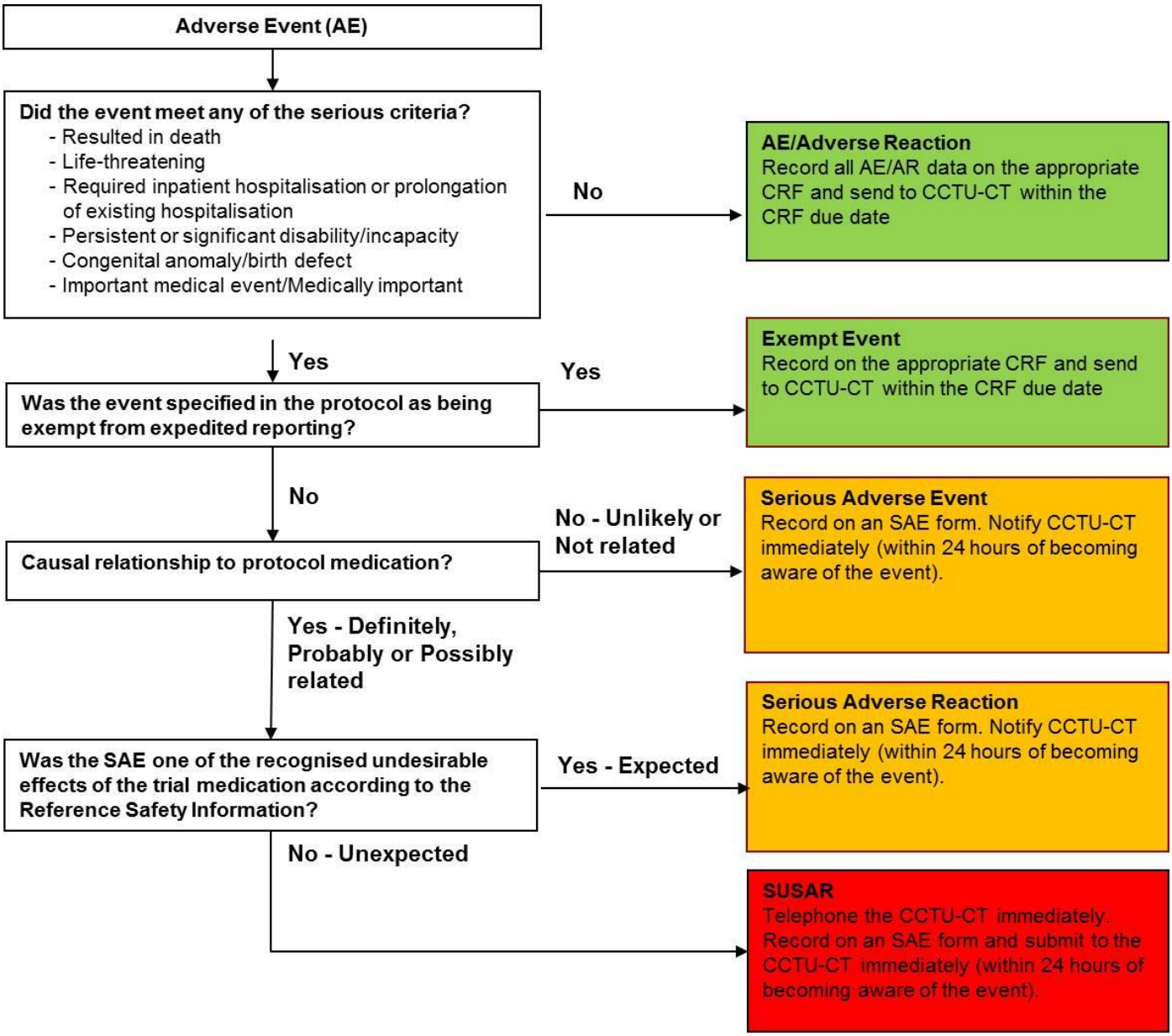
28 Safety Reporting Flow Chart



29 Appendices

29.1 Appendix 1 – RECIST Version 1.1

For the full RECIST version 1.1, please refer to:

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009).
New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). Eur J Cancer, 45, 228-247

Methods of Assessment
Tumour assessments for response and progression require CT scan (or MRI if allergic to intravenous contrast) of chest/abdomen/pelvis or measured by photography including a ruler. The same assessment technique should be used to characterise each identified and reported lesion at baseline and throughout the trial.

Measurable Disease
Patients will be classified as having measurable or non-measurable disease at baseline and at each imagining assessment.

Definition of Measurable Disease lesions
Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).

Cutaneous lesions measured by photography including a ruler to indicate size, must be a minimum of 10mm in diameter.

Malignant lymph nodes: To be considered pathologically enlarged and measured, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

Definition of Non-measurable lesions
Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Baseline Tumour Assessment
The baseline tumour assessment evaluation should be performed within 30 days of treatment start date.

Baseline Documentation of "Target" and "Non-Target" Lesions
Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible, repeated measurements.

- Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan.

Sum of the Diameters
Sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

Non-target Lesions
All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):
Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR):
At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD):
At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Evaluation of Non-target Lesions

Complete Response (CR):
Disappearance of all non-target lesions and normalisation of tumour marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR / Non-PD:
Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker levels above normal limits.

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

- When patient has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is not usually sufficient to qualify for unequivocal progression status.

- When patient has only non-measurable disease. There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

New lesions
- The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour, especially when the patient's baseline lesions show partial or complete response).

- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

- A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

Time Point Response
The table below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 7 Time point response: patients with target (=/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, and NE = inevaluable.

29.2 **Appendix 2- Performance status scales**

29.2.1 Table 8: Karnofsky Performance Status Scale[50]

Condition	**PS %**	**Comments**
Able to carry on normal activity and to work. No special care needed.	100	Normal. No complaints. No evidence of disease.
	90	Able to carry on normal activity. Minor signs or symptoms of disease.
	80	Normal activity with effort; Some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
	30	Severely disabled. Hospitalisation is indicated although death not imminent.
	20	Hospitalisation necessary, very sick; active supportive treatment necessary.
	10	Moribund. Fatal processes progressing rapidly.
	0	Dead

29.2.2 Table 9: ECOG Performance Status Scale[51]

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

29.2.3 Rockwood Clinical Frailty Scale [52]

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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29.3 Appendix 3 – NYHA Functional Classification

The **New York Heart Association (NYHA) Functional Classification**[40] provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

Table 10: NYHA functional classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

29.4 Appendix 4 – Authorisation of Participating Sites

29.4.1 Required Documentation

The following documentation must be in place prior to a site being opened to recruitment by the CCTU-CT trial team:

- Trial specific registration of interest form (identifying relevant local trial team)
- All relevant institutional approvals (e.g. local NHS confirmation)
- A signed participating site agreement (PSA) between the Sponsor and the relevant institution (typically the sites local NHS Trust)
- **A signed delegation log and signed CVs and dated and GCP certificates for the site trial team listed on the delegation log**
- An example of patient documentation (PIS/ICF etc) and GP Letter on local Trust-headed paper and with local contact details added.
- **Example of IMP prescription**
- Local Laboratory accreditation (or equivalent) and reference ranges for the protocol-specified parameters
- Completed and signed Trial Initiation Form
- **Confirmation of successful Out of Hours Medical Access testing**
- **Confirmation of receipt of the Investigator Site File and Pharmacy Site File**
- **Confirmation of local pharmacy green light**

The Principal Investigator (PI), other delegated site investigators and all staff involved in the conduct of the trial at site must be identified on the site delegation log held at site and copied to CCTU-CT prior to site activation.

29.4.2 Procedure for initiating/opening a new site

Once the trial team at CCTU-CT have performed the initiation meeting and confirmed that all documentation is in place, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

29.4.3 Patient registration procedure

Following confirmation of eligibility and completion of eligibility and registration eCRFs patients will be allocated a unique study ID number. Trial IDs will be allocated sequentially in the order in which the patients are enrolled.

Further details regarding the patient registration process are detailed in section 10.3.2.

29.4.4 eCRF completion & data management

Data will be collected using eCRFs. Data entry is the responsibility of the participating site. Please refer to the eCRF Completion Guidelines for full information.

Data protection/confidentiality

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited. See section 16.3 for further information.

29.4.5 Principal Investigator (PI) responsibilities

Once the site has been activated by CCTU-CT, the PI at each site is responsible for ensuring the following:

- Attendance at the site initiation meeting
- Adherence to the most recent version of the protocol
- All relevant staff are trained in protocol requirements
- Delegation of activities to appropriately trained staff (this must be documented on the delegation of responsibility and signature log)
- Appropriate recruitment and medical care of patients in the trial
- Timely completion of eCRFs and resolution of data queries raised by the CCTU-CT
- Accurate maintenance of the ISF
- Dissemination of all trial related information
- Ensuring appropriate attendance at the TMG teleconferences if required and ensure appropriate safety information is made available to the CCTU-CT in advance of the meeting.
- Dissemination of important safety or trial related information to all stakeholders at the participating site
- Safety reporting within the timelines and assessment of causality and expectedness of all SAEs
- Timely completion of any remote or on-site monitoring activities
- Assistance with any on-site monitoring activities organised by the CCTC-CT
- Archiving of the ISF upon confirmation of CCTU-CT post end of trial

29.4.6 Trial documentation & archiving

- Each participating site is responsible for archiving their own trial data (including source data, the Investigator Site File (ISF), Pharmacy Site File (PSF)) for the appropriate time period as determined by the regulations governing clinical trials in place at the time of archiving.
- The archiving facility may be at the participating site or at another appropriate location off-site as per local policy. The CCTU-CT will advise when the site may commence archiving.
- The site will need to provide the name and address of the archival facility to the CCTU-CT.
- In case of audit or inspection following archival, the participating site will be expected to retrieve the relevant documentation within a reasonable timeframe.