

Full title: A Phase II: Two-Stage Trial of Pembrolizumab in Cancer of Unknown Primary




CUPem

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Statistical Analysis Plan

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Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
CI	Chief Investigator
CNS	Central Nervous System
CR	Complete response
CRUK	Cancer Research UK
CSR	Clinical study report
CT	Computerised tomography
CTAAC	Clinical Trials Awards and Advisory Committee
CTCAE	Common Terminology Criteria for Averse Events
CTS	Clinical Trials Section
CTU	Clinical Trials Unit
CUP	Carcinoma of unknown primary
DCR	Disease Control Rate
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EUDRACT	European Clinical Trials Database
ECI	Event of Clinical interest
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GMC	Genomic Medicine Centres
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
IB	Investigator Brochure
ICD	International Classification of Disease
ICHTB	Imperial College Healthcare NHS Tissue Bank
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IUD	Intrauterine Device
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

INR	International normalized ratio
IRB	Institutional Review Board
ir-RECIST	Immune-related
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
JRO	Joint Research Office
LDH	Lactate dehydrogenase
mAb	Monoclonal Antibody
MDT	Multidisciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHSE	National Health Service England
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
APTT	Activated Partial Thromboplastin Time
QLQ	Quality of Life Quotient
QoL	Quality of Life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Stable disease (RECIST)
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Bacillus Tuberculosis
TILs	Tumour-infiltrating lymphocytes
TMG	Trial Management Group
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
WBC	White Blood Cell
WGS	Whole Genome Sequencing

1. Introduction

Carcinoma of unknown primary (CUP) is one of the ten most frequent cancer diagnoses and the 5th commonest cause of cancer death in the UK (CRUK mortality data for 2012 (ICD-10 codes C77-80)). Every day in the UK alone, 30 people die from CUP. The ICD-10 (C77-80) coding data show that since 2010, the incidence and mortality have remained static at 9,500 to 10,500 per year. Despite improving diagnostic techniques, only a 13% decline in mortality was achieved in the 6 years between 2006 and 2012. CUP remains a poor prognosis cancer, with median survivals of 8 months from diagnosis and a one year survival probability of 15-35%. Despite this, there are very few randomised clinical treatment studies and therefore little consensus on the optimal treatment regimens. There is no established second-line treatment regimen. The highly metastatic clinical presentation and heterogeneity of CUP at the clinical and pathological level, as well as the possible overlaps with some known primary solid cancers, has also been a practical and intellectual hindrance to the successful classification and treatment strategies.

In 2009/2010 CRUK funded the CUP-ONE Trial (EUDRACT ref 2008-000657-35) which was the first prospective clinico-translational study of cancers of unknown primary with the aim of collecting tissue biopsies in consenting patients and developing (with industry partners) the best rapid molecular classification for carcinomas of unknown primary, initially as a diagnostic validation, and correlation with clinical outcomes. (Wasan HS: CUP-ONE phase II clinico-translational study of Cancers of unknown primary – CRUK project grant C18607/ TRICC grant A7967 & CTAAC grant C18607 Glasgow CTU C18607).

The recruitment in the UK between 2010 and 2014 has led to a successful collaboration between many Cancer Networks and a comprehensive clinical and tissue database of 640 tissue samples. These data are currently being analysed. Preliminary data from the clinical treatment outcomes of the CUP-ONE Trial has been presented (Wasan HS, J. Paul, M.C. Nicolson et al Ann Oncol (2014) 25 (suppl 4): iv397. doi: 10.1093/annonc/ndu345.8) and demonstrates that two-thirds of patients do not have any treatment offered because of a combination of performance status, lack of efficacy and toxicity of current cytotoxic regimens. Of the treated patients only about a third

responds, with a median survival of 8 months for all the treated patients. There is thus a significant unmet need to change the treatment paradigm in CUP.

There has been recent agreement (March 2017) from UK NHSE to prospectively (deep) whole genome sequence 750 genomes from 250 patients within the 100k-genome project. The combination of this and integration with global projects (see below) will allow a more detailed understanding of the biology of CUP, which should apply in a tumour agnostic manner, potentially to all solid cancers that are highly metastatic at presentation. Within the NHS 100k genomes project, there is the ability to link the data to therapeutic interventions including clinical trials.

In addition, (Wasan HS) is a co-applicant in the current Australian Study (SUPER: Solving Unknown Primary cancer; Professor David Bowtell, and Penny Schofield, are PI's for the Australian CUP genome sequencing project APP1048193– SUPER 2013 to 2016 Funding from Cancer Australia)), which have and are developing tools that might better assess this sensitively in a way that is meaningful to patients with one of its co-primary aims being a comprehensive psychosocial analysis of CUP Patients. We are thus working on better QOL tools for CUP patients.

There are no established standards of care, consensus, or known benefits to second or more lines of therapy in CUP. Hence a new standard of care needs to be established which is well tolerated and beneficial. Any objective responses or disease control of any significant duration, seen in second line or further are rare so the simple observation of Pembrolizumab (as the test drug here) demonstrating any clinical benefit, where there are no other known treatment options would be an important step in further investigating this strategy in the first line setting.

Initially conceived as a two-cohort study, recruitment had proved challenging for cohort 2 (due to COVID issues). A decision was made in January 2021 for a substantial amendment to lift the recruitment cap in cohort 1 as the minimum effect in > 1 participant had been observed and that, as there was no standard of care treatment worldwide for second-line CUP, there would be major interest in understanding meaningful standard of efficacy in cohort 1, as well as in cohort 2 for immunotherapy strategies.

Since this amendment recruitment continued to be difficult, and a new substantial amendment in January 2022 has formally closed the second cohort, due the effect of ongoing COVID-19 pandemic as well as associated clinical factors.

Following the closure of the second cohort, the first cohort sample size is now expanded to a range of 31-67 patients with recruitment to complete at the end of December 2022. The precise statistical implications of the eventual recruitment total are detailed in full within section 3.

2. Study Objectives and Hypotheses

2.1 Primary Objectives

Objectives:

Overall response rates by immune-related (irRECIST) and RECIST criteria:

Disease Control Rate (DCR), Overall Survival (OS) & Progression Free Survival (PFS).

Hypothesis:

Pembrolizumab has Efficacy in CUP:

- as a second-line treatment in terms of Response which translates into improved PFS and OS.
- and treatment leads to rapid improvement in QOL in high metastatic disease burden.

2.2 Secondary Objectives

Objective:

- Incidence of adverse events up to 8 weeks after the last dose of Pembrolizumab.
- Incidence of adverse events up to 8 weeks after the last dose of Pembrolizumab in Performance Status 2 (PS2) patients.

Hypothesis:

- Pembrolizumab is much better tolerated than conventional chemotherapy in CUP patients and PS2 patients may also benefit.

2.3 Exploratory Objectives

Objective:

- Identification of genomic biomarkers predictive of immune response to Pembrolizumab.

Hypothesis:

- CUP patients have identifiable biomarkers predictive for Pembrolizumab efficacy.
- CUP patients have high mutational loads and this correlates with increased efficacy with Pembrolizumab.

- CUP patients have high mutational loads and this correlates with increased efficacy with Pembrolizumab

(Note: Results for the exploratory objective will not be included in the Clinical Study Report (CSR) but will be reported separately according to standard ethical and regulatory guidelines.)

3. Design

3.1 Study Design

An open label, non-randomised, single arm, sequential phase (two sequential cohorts) study, evaluating the preliminary efficacy of Pembrolizumab in Cancer of unknown Primary (CUP).

A substantial amendment in January 2022 has formally closed the second cohort, due to the significant challenges in recruitment caused by the ongoing COVID-19 pandemic as well as associated clinical factors.

Cohort 1:

Cohort 1 will enrol a minimum of 31 patients and a maximum of 67 patients, who have had at least one prior line / regimen of chemotherapy (at least 2 cycles) appropriate for CUP and who have not had a RECIST response to first-line chemotherapy, or are progressing after an initial response, or are treatment intolerant to first-line chemotherapy, due to unacceptable toxicity.

Cohort 2:

Cohort 2 is now formally closed. This cohort had sought to enrol patients who are chemo-naïve (first-line setting) for CUP, with a PS 0-2.

Patients will undergo screening procedures during a standard 28-days time window from initiation of the study, under standard GCP and informed consent. Restaging will be performed by computerized tomography using ir-RECIST criteria at 3 months from initiation of systemic treatment and on an 8 weekly basis thereafter until radiological proven disease progression or intolerance or patient choice.

The EORTC QLQ-C30 questionnaire (to assess the quality of life) will be done at baseline after 3 months and then at discontinuation of study treatment.

Correlative translational study samples (blood) and tissue (used for histological confirmation and to document PD-L1 expression) will be collected at baseline, and blood and serum samples monthly (after an informed optional consent and banked for retrospective immune-modulating and other biomarkers for future research and analysis).

Patients will also be separately consented to the NHSE CUP 100K genome project that will be running in the UK by 2018, for deep sequencing of tumor tissue and germline, in centers participating in, or with access to the UK framework for this programme.

3.2 Study Treatment

The treatment to be used in this trial is outlined below in Table 1, further details can be found in Section 6 of the study protocol.

Table 1: Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on the day of study entry (screening and consent completed) or as close as possible to the date on which treatment is allocated.

3.3 Study Population

This trial will be performed at three investigational sites in England, and recruit patients who were histologically confirmed with cancer of an unknown primary. See full eligibility criteria below.

3.4 Eligibility Criteria

Inclusion Criteria

Patients who meet all of the following inclusion criteria will be considered eligible for this study:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Be willing to provide consent for archival tumour (in the form of formalin fixed paraffin embedded (FFPE) block) or fresh tumour material (if judged technically feasible by radiologist) is mandatory for diagnosis and biomarker analysis.
5. Have a performance status of 0-2 on the ECOG Performance Scale.
6. Have had at least one prior line / regimen of chemotherapy appropriate for CUP (at least 2 cycles). Either did not have a RECIST response to first-line chemotherapy or progressing after an initial response, or are treatment intolerant to first-line chemotherapy due to unacceptable toxicity.
7. Adequate organ and bone marrow function (all screening tests should be performed within 10 days of treatment initiation):
 - a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - b. Platelets $\geq 100 \times 10^9/L$
 - c. Haemoglobin ≥ 9 g/dL (≥ 90 g/L) without transfusion or EPO dependency (within 7 days of assessment)
 - d. Serum creatinine $\leq 1.5 \times$ Upper Limit of Normal (ULN) or Creatinine clearance* ≥ 60 mL/min for patients with creatinine levels $> 1.5 \times$ ULN
* Creatinine clearance should be calculated per institutional standard
 - e. Serum total bilirubin $\leq 1.5 \times$ ULN or direct bilirubin \leq ULN for patients with total bilirubin levels $> 1.5 \times$ ULN
 - f. Aspartate aminotransferase [AST] $\leq 2.5 \times$ ULN ($< 5 \times$ ULN if liver metastases are present)
 - g. Alanine aminotransferase [ALT] $\leq 2.5 \times$ ULN ($< 5 \times$ ULN if liver metastases are present)
 - h. Albumin ≥ 2.5 g/dL
 - i. International Normalized Ratio (INR) or Prothrombin Time (PT) $\leq 1.5 \times$ ULN (unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants)

- j. Activated Partial Thromboplastin Time (APTT) $\leq 1.5 \times \text{ULN}$ (unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants).
- 8. Female subject of childbearing potential should have a mandatory negative serum pregnancy within 72 hours prior to receiving the first dose of study medication.
- 9. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 6.9.2 – Contraception, for the course of the study through 120 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
- 10. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 6.9.2 - Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible for this study:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or any of its excipients
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent

- Note: Subjects with \leq Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
 - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
 8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
 9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
 10. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis
 11. Has an active infection requiring systemic therapy
 12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
 13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)
17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)
18. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.5 Sample Size

1) In the first cohort 20 second-line (or more) patients will be accrued; if no responses or benefit is observed in 20 assessable patients, accrual of the whole trial will stop at this point. “Assessable” is defined as patients who have had at least 2 cycles of Pembrolizumab and are assessable for response at a minimum of 6 weeks post-study start.

2) The study statistics were originally modelled on the UK CUP-ONE trial based on the primary study endpoint of response in cohort 2.

An interim futility analysis was originally pre-planned after recruiting 24 (out of 57) patients in Cohort 2 and a final analysis after 77 participants completed the study (20 for Cohort 1 and 57 for Cohort 2). ≥1 documented response in Cohort 1 was achieved in May 2020, enabling Cohort 2 to open and Cohort 1 to close once sufficient evaluable participants had been enrolled. Due to the unexpected challenges recruiting study participants outlined in the Trial Summary and sections 1.3.1 and 3.1, particularly for Cohort 2, Cohort 1 was reopened and expanded and the initial version 7.0 of the protocol has formally closed Cohort 2 with approval from the TMG, MSD and combined

TSC/IDMC. Cohort 1 (pre-treated patients) remains a crucial area of unmet need with no standard of care treatment existing.

The sample size has thus been recalculated to accommodate the shift of focus to assessing PFS and OS in Cohort 1 and complete removal of Cohort 2. The sample sizes were recalculated based on the Brookmeyer-Crowley test for median survival time (Brookmeyer R and Crowley JJ. A confidence interval for the median survival time. Biometrics. 1982: 38, 29-41).

Assuming a historic null PFS of 2 months and an alternative PFS of 4 months, the minimum required sample size to determine the median PFS for the study cohort is 46 (at 0.05 level of significance, one-sided, 90% power). For the OS, assuming a null OS of 4 months and an alternative OS of 7 months, the required minimum sample size is 67 with the same level of significance and power. Therefore, the final sample size needed to determine both the median PFS and OS is 67 (the higher sample size). In the event that this sample size will be difficult to recruit within the additional accrual period of 12 months, a sample size of 31 will still be able determine the median PFS and 45 the median OS with a power of 80%.

Power	Null Median Survival	Alternative Median Survival	Min N
0.80	2 months PFS	4 months	31
0.90	2 months	4 months	46
0.80	4 months OS	6 months	83
0.80	4 months	7 months	45
0.90	4 months	6 months	122
0.90	4 months	7 months	67

The study will therefore aim to recruit between 31 and 67 patients to Cohort 1 within the allotted study period. This sample size range is estimated to have a power of 80% to 90% in determining the PFS and/or the OS of the study cohort.

As for DCR, the minimum range of this sample size (i.e. 31) would require ≥ 10 DCR to recommend Pembrolizumab for further evaluation, assuming an unacceptable DCR of $\leq 20\%$ (P0) vs the desired rate of $\geq 40\%$ (P1). This Fleming single-stage design would provide a one-sided alpha of 8% and a power of 86%. Different simulations for the minimum DCR needed ($H_0: P \leq 0.2$ vs $H_1: P \geq 0.4$) given a one-sided alpha $\leq 10\%$ and power $\geq 80\%$ are presented below:

Power	N	Alpha	Minimum DCR needed
0.80	35	0.03	12
0.86	31	0.08	10
0.90	47	0.04	15
0.91	42	0.06	13
0.91	36	0.09	11

3.6 Schedule of Time and Events

Table 3 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. Treatment is divided into cycles of 21 days, with visits and assessments specified according to the relevant cycle.

Unless otherwise indicated, scheduled assessments may take place within ± 3 days of the specified visit. Assessment days are relative to the start of study treatment i.e. Cycle 1 Day 1.

If a patient has a treatment break, please contact the Clinical Trials Section (CTS) for advice regarding the timing of research blood assessments. All other assessments, including laboratory safety assessments, vital signs and radiological imaging should continue to be performed.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or MSD for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

During the COVID-19 pandemic, patients whom are under ongoing treatment can be offered longer intervals of 1 to 2 weeks between treatment to avoid peak COVID-19 capacity issues.

Table 2: Schedule of Assessments

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Study Screening	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Administrative Procedures													
Pre-screening Visit													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Trial Treatment Compliance		X	X	X	X	X	X	X	X				
Quality of Life Questionnaire (EORTC QLQ-C30)	X					X				X			
Post-study anticancer therapy status											X	X	X
Survival Status		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X ^a	X			X				X	X	X		
Directed Physical Examination	X ^a	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight	X ^a	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X ^a	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment		
		1	2	3	4	5	6	7	8		Safety Follow-up	Follow Up Visits	Survival Follow-Up
Treatment Cycle/Title:	Study Screening												
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Pregnancy Test –Serum β-HCG	X ^b		X ^c		X ^c		X ^c		X ^c				
PT/INR and aPTT	X ^d	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	X	X	
CBC with Differential	X ^d	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	X	X	
Comprehensive Serum Chemistry Panel including full or directed tumor marker panel (+/- NET serum markers)	X ^d	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	X		
Urinalysis	X ^d	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	X		
T3, FT4 and TSH	X ^d	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	X	X	
Efficacy Measurements													
Tumor Imaging	X ^f					X ^g			X	X (if not done within 12 weeks prior)		X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection	X ^h												
Correlative Studies Blood & Urine Collection	X		X		X		X		X	X	X		

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Study Screening	1	2	3	4	To be repeated beyond 8 cycles				Safety Follow-up	Follow Up Visits	Survival Follow-Up	
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	Discon	Every 8 weeks post discon	Every 12 weeks	
aIn circumstances where screening assessments are conducted within 3 days prior to treatment initiation these can be used to cover both screening and C1D1.													
bMandatory negative blood serum pregnancy test at screening for patients of childbearing potential.													
cIn patients of childbearing potential: <ul style="list-style-type: none">Mandatory negative serum pregnancy test within 72 hours prior to receiving study treatmentMandatory negative urine pregnancy test result available prior to receiving study treatment													
d Lab tests (blood samples for haematology, clinical chemistry and urinalysis) for screening should be performed within 10 days prior to the first dose of treatment. In circumstances where blood samples for haematology and clinical chemistry and urinalysis fulfils both the timeline of day -10 to 0 and 72 hours prior to C1D1 dosing these can be used for both screening and C1D1.													
eOn dosing days for all cycles, samples must be taken pre-dose (up to 72 hours prior to dosing).													
f Baseline assessment should be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of the study treatment.													
gSubsequent tumour assessments will be conducted every 12 weeks, with window for each assessment is ± 7 days.													
hTumour blocks / slides should be made available within 60 days of patient enrolment.													

4 Population of Analysis Sets

Unless otherwise stated, all analyses will be performed using the Intention-to-Treat (ITT) population which includes all study participants taking part in the trial regardless of whether they dropped out, fully adhered to the treatment or switched to an alternative treatment. A Per-Protocol (PP) population is additionally defined for the purpose of ad hoc or exploratory analyses.

4.1 Intention-to-Treat (ITT) Population

The Intention-to-treat population includes all enrolled patients eligible for the study.

4.2 Safety Population

The Safety Population is defined as all patients who received at least one dose of Pembrolizumab.

4.3 Per-Protocol (PP) Population

The Per-Protocol Population includes enrolled patients who are assessable for the primary endpoint. Assessable patients are those that have received at least 2 cycles of Pembrolizumab and are assessable for toxicity.

5 Variables of Analysis

5.1 Primary Efficacy Endpoint

The overall response to treatment is assessed using RECIST v1.1 and immune-related (irRECIST). Appendices A and B in the protocol present the guidelines for evaluation of objective tumour response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) or immune-related RECIST. The disease control rate will be calculated.

Disease Control Rate (DCR) - is defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) for at least 12 weeks in either RECIST or irRECIST criteria.

Overall Survival (OS) - defined as the length of time from study enrolment until death, withdrawal of consent, last follow-up date if lost to follow-up or the end of the study, whichever occurs first.

Progression Free Survival (PFS) – is defined as the length of time from study enrolment to first evidence of progressive disease identified at follow-up or confirmed disease progression at the end of the trial or death. Patients will be censored at the last follow-up date if they are lost to follow-up, withdrawn from the study or have not progressed at the end of study. Median PFS and its 95% confidence interval will be reported. Kaplan-Meier survival curves will also be plotted.

Quality of Life (QOL) is measured as scores from the EORTC QLQ-C30 version 3 questionnaire which will be administered at baseline, after 3 months and then at discontinuation of study treatment.

5.2 Secondary Efficacy Endpoints

- The incidence of adverse events up to 8 weeks after the last dose of Pembrolizumab will be noted.
- Incidence of adverse events up to 8 weeks after the last dose of Pembrolizumab in Performance Status 2 (PS2) patients.

5.3 Safety variables

Adverse Event (AE) - is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the study treatment, is also an adverse event.

Details to be collected in the eCRF for each AE will include:

- AE description
- Date of onset and date of resolution
- Severity
- Seriousness
- Relationship to study treatment
- MedDRA codes and terms according to system organ class, high level term, low level term and preferred term

Severity and Seriousness of Adverse Events

Severity is a measure of intensity whereas seriousness is defined by the criteria in section 7.4 of the protocol. Severity will be assessed using the grading scales found in the National Cancer Institute CTCAE version 4.03 (June 2010) for all adverse events with an assigned CTCAE term. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>). Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event eCRF. All adverse events regardless of CTCAE grade will also be evaluated for seriousness.

Causality of Adverse Events

The causal relationship between the study treatment and each AE will be assessed as follows:

Unrelated: No evidence of any causal relationship

- Unlikely: There is little evidence to suggest there is a causal relationship (e.g. event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
- Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

Serious Adverse Event (SAE) - is defined as any event that:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Is another important medical event (that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

N.B. In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes:

- A new cancer (that is not a condition of the study);
- Is associated with an overdose (whether accidental or intentional)

* “Life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** “Hospitalisation” means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

SAEs, including death that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment will also be followed and recorded.

Serious Adverse Reaction (SAR) - is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.

Suspected Unexpected Serious Adverse Reaction (SUSAR) - any SAR that is NOT consistent with the applicable product information as set out in the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC). SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.

Other safety variables – this includes pregnancy and lactation which are not considered adverse events is defined as a SAE that is judged to be related to any dose of study drug administered to the subject. Pregnancies and lactations that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations

that occur from the time of treatment allocation through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor, who will then report to Merck Global Safety within 2 days.

5.4 Demographic Variables

Demographic variables include patient's age, gender and race/ethnicity which will be collected at screening.

5.5 Medical History

Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered clinically significant by the investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

5.6 Clinical Assessments

Physical examinations will be done at baseline and other time points to assess the general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen and neurological characteristics of the patient. The result of the physical examination is recorded as normal, abnormal (clinically significant or not clinically significant) or not done. Clinically significant abnormal findings should be recorded as medical history.

Vital signs including height, weight, blood pressure, body temperature, pulse and respiratory rate will be measured as indicated in assessment schedule. Vital signs may be assessed at any time during the visit; however, supine blood pressure and

pulse should be measured after 10 minutes rest. Height will be measured at initial screening visit only.

Performance status will be assessed according to ECOG (Eastern Cooperative Oncology Group) criteria as follows:

- 0 Fully active, able to carry on all pre-disease activities without restriction
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, 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 50% or more of waking hours
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 Death

5.7 Laboratory Evaluations

The following laboratory variables will be measured in the study at designated time points in Table 2:

- Biochemistry: Sodium [Na], potassium [K], chloride [Cl], bicarbonate [CO₂], Uric Acid, calcium, phosphate, glucose), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase, albumin, Lactate dehydrogenase (LDH), total bilirubin, direct bilirubin (If total bilirubin is elevated above the upper limit of normal)), total protein, magnesium and Blood Urea Nitrogen
- Haematology: White blood cell count (WBC) with differential (to include neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count haemoglobin (Hgb), haematocrit (Hct), Absolute neutrophil count (ANC), Absolute lymphocyte count (ALC) and platelet count.
- Coagulation: PT/INR and aPTT
- Urinalysis: Macroscopic assessment of the amount of protein, glucose, white blood cells and blood if they are present (levels should be recorded

if available) and microscopic analysis should be performed if an abnormality is noted.

- Pregnancy test for patients of child bearing potential (If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required). Serum β -human chorionic gonadotropin (β -hCG) for patients of child bearing potential
- Thyroid: Total triiodothyronine (T3), Free thyroxine (FT4), Thyroid stimulating hormone (TSH)
- Tumour Markers for CUP +/- any serum markers deemed to be relevant to disease monitoring, e.g. PSA, b-HCG, CEA, Ca19.9, Ca125, Ca153, AFP, NSE, SCC, S100, and Chromogranin A and B.
- ‡ If considered standard of care in your region.

Laboratory values that have changed significantly from baseline and are considered to be of clinical concern will be recorded as an adverse event and followed up as appropriate.

5.8 Prior and Concomitant Medications Review

Prior Medications - include prior medication use, including any protocol-specified washout requirement, and prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication

Concomitant Medications - medications, if any, which are taken by the subject during the trial and 30 days after the last dose of trial treatment. All medications related to reportable SAEs and ECIs will be recorded as defined in Section 7 of the protocol.

The following details will be collected: drug name, reason for therapy, therapy dosage / units, frequency of therapy, route of administration, start and end date of therapy.

5.9 Disease Details and Treatments

Prior Cancer Treatments - include systemic treatments, radiation and surgeries.

Post Study Anti-Cancer Therapy Status - all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

Treatment Compliance - is detailed record of the date and time of administration and drug dose all study treatment that are captured in the patient diary. The number of missed or delayed doses will be reported for each patient and compliance will be reported as the percentage of treatment delays.

5.10 Exploratory Variables

Exploratory variables include genomic biomarkers predictive of immune response to Pembrolizumab. Genomic sequencing will be done within the 100K-genome project, the data from which can be linked to this and other CUP trials. This is not costed in this application and the analysis will not be included in this statistical analysis plan.

6 Statistical Methodology

The study data will be summarised using standard descriptive methods by cohort and as combined data. Histograms and box-plots will be used to assess the distributional assumptions and to check for possible outliers. Mathematical transformations will be applied, where appropriate, in order to render variables normally distributed. Continuous variables that follow an approximately normal distribution will be summarised using the mean and standard deviation (StDev). Skewed continuous variables will be summarised using the median and inter-quartile range (IQR). Categorical variables (binary, ordered and multinomial) will be presented in terms of frequencies and percentages.

The primary outcome and secondary outcome will be tested using a two-tailed hypothesis test with a 5% significant level.

6.1 Patient Flow

Details about patient screening, enrolment and assessment are provided in the following diagram:

CUP Patient Identification

- Potentially eligible patients identified at Local CUP or specialist CUP MDT or in clinic suitable for conventional first-line chemotherapy
- Progression or intolerant of first or more lines of conventional chemotherapy potentially eligible

Patient Consent and Screening

- Patients considered potentially eligible provided with Patient Information Sheet
- Patient Informed Consent
- Screening assessments

Registration (n=31-67)

Trial procedures summary

- Pembrolizumab 200 mg given in 3 weekly cycles until one or more protocol discontinuation criteria apply
- Radiological imaging every 12 weeks (4 cycles)
- Translational sample collection every 6 weeks (2 cycles)

End of treatment visit(30 days after discontinuation)

Follow Up if no PD on treatment (8 weekly with 12 weekly radiological imaging)

Survival Follow Up (12 weekly until death, withdrawal of consent or end of study)

6.2 Baseline Characteristics

Baseline characteristics including demographics, medical history, prior and concomitant medication, quality of life, vital signs and weight, ECOG performance status and laboratory evaluations will be summarized by cohort group using appropriate descriptive statistics.

6.3 Primary Efficacy Analysis

The overall response rate will be calculated as the proportion of patients who have a complete response (CR) or partial response (PR) to treatment as assessed by the objective tumour response criteria: RECIST v1.1 **or** immune-related (irRECIST). The response rate and its 95% confidence interval (CI) will be presented for each cohort. As previously described, the response rate is the primary efficacy variable that will be used to decide whether the study will stop or continue accrual in both cohorts.

Disease Control Rate (DCR) will be calculated for each cohort as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) for at least 12 weeks in either RECIST **or** irRECIST criteria.

The Overall Survival (OS) and Progression Free Survival (PFS) will be summarized descriptively using the median and Kaplan-Meier graph for each cohort.

The Quality of Life (QOL) in each cohort will be assessed using mean or median scores from the EORTC QLQ-C30 (version 3) questionnaire administered at baseline, after 3 months and then at discontinuation of study treatment. The QOL scores between visit dates will be compared using Repeated Measures ANOVA or Friedman's Test on the per-protocol population who completed the baseline and at least one follow-up QoL assessment. The type of statistical test to be used will depend on the characteristic of the data distribution. Adjustment for multiple testing will be applied. The Tukey post-hoc method or the Wilcoxon signed-rank test will be used for pairwise comparisons. Profile plots and longitudinal plots will also be presented.

6.4 Secondary Efficacy Analysis

Incidence of adverse events up to 8 weeks after the last dose of Pembrolizumab will be measured.

6.5 Safety Analysis

The safety data which include adverse events (AEs) and serious adverse events (SAEs) will be tabulated for the two cohorts. AEs and SAEs will be summarised by description, frequency, outcome, severity, seriousness and relationship to study treatment. Additionally, SAEs will also be summarised by SAE reason. Serious Adverse Reaction (SAR), Suspected Unexpected Serious Adverse Reaction (SUSAR) and other safety variables (e.g. pregnancy and lactation) and their frequencies, if any, will also be reported.

6.6 Secondary Analysis

The analysis of efficacy variables, clinical and laboratory measurements will be done using all the measurement points or visit dates.

Compliance with the study medication will be assessed based on patient diaries. Compliance will be measured by the percentage of treatment delays noted in each patient. The median and range of the compliance measure will be reported.

Data on concomitant medications will be summarized by: drug name, reason for therapy, therapy dosage / units, frequency of therapy and route of administration.

6.7 Data Management

Data management will be performed by CCTS using the InForm electronic data capture (EDC) and management system. The system allows for real time oversight of trial activity including adverse event reporting, rapid data validation and data aggregation.

6.8 Missing Data

No imputation for missing data will be undertaken. The number of missing observations for each variable will be reported.

6.9 Withdrawal from the Study

Withdrawal can occur at any time according to the following reasons: patient decision; lost to follow-up; death, pregnancy or administrative reasons. Patients who withdraw from the study before having at least 2 cycles of Pembrolizumab or before having follow-up tumour or QoL assessment will be excluded from the Quality of Life analysis and some secondary analyses.

6.10 Deviations from the SAP

Any deviation(s) from the final statistical plan in the final analysis will be described and the justification be given in the final report.

6.11 Tables to present

Table 1. Patient Baseline Characteristics *

	Cohort 1 n = 20	Cohort 2 n = 57
Age (yr)		
Sex		
Male		
Female		
Weight (kg)		
Height (m)		
BMI (kg/m²)		
Ethnicity		
White		
Mixed		
Asian		
Black		
Other		
Cell Type of Tumour		
Adenocarcinoma		
Squamous cell carcinoma		
Neuroendocrine		
Poorly differentiated carcinoma		
Poorly differentiated neoplasm		
Histopathological types of CUP		
Well or moderately differentiated adenocarcinomas		
Undifferentiated or poorly differentiated adenocarcinomas or carcinomas		
Squamous cell carcinomas		
Undifferentiated neoplasms		
CUP Subtypes		
Poorly differentiated carcinoma, predominantly nodal disease		
Poorly differentiated neuroendocrine carcinomas		
Peritoneal adenocarcinomatosis of a serous papillary histological type in females		
Isolated axillary nodal metastases in females		
Squamous carcinoma involving non- supraclavicular cervical lymph nodes		
Metastases in bone adenocarcinoma and elevated serum PSA in males		
Poor-risk visceral CUP		

* Data are presented as frequency (percentage) for categorical variables and median [IQR] for continuous variables

Table 2. Concomitant medical conditions at baseline*

Medical condition	Cohort 1 n =	Cohort 2 n =
Medical condition 1		
Medical condition 2		
Medical condition 3		
Medical condition 4		
Medical condition 5		
Medical condition 6		
Medical condition 7		
Medical condition 8		

** Data are presented as number of patients having the medical condition.
A patient may have more than one concomitant medical condition.*

Table 3. Concomitant medications at baseline*

Drug Name and Dose	Cohort 1 n =	Cohort 2 n =
Medication 1		
Medication 2		
Medication 3		
Medication 4		
Medication 5		
Medication 6		
Medication 7		

** Data are presented as number of patients taking the medication. A patient may have more than one concomitant medication.*

Table 4. Summary of Tumour Assessment based on RECIST (irRECIST)

	Baseline	Cycle 5	Cycle 8	Discon	Post Discon
Sum of the diameters for all target lesions (mm)[†]	## (##-##) [n=##]	## (##-##) [n=##]	## (##-##) [n=##]	## (##-##) [n=##]	## (##-##) [n=##]
Proportion of Tumour size change^{†‡}		## (##-##) [n=##]	## (##-##) [n=##]	## (##-##) [n=##]	## (##-##) [n=##]
Overall response (n=)					
Complete response		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Partial response					
Stable disease					
Progressive disease					
Progression before scan					
Withdrawn before scan					
Missing					

[†] Data are presented as median (IQR)

[‡]Proportion change in the sum of the diameters for all target lesions at that follow-up time (or progression if prior to that follow-up time) compared to baseline

Table 5. EORTC QLQ-C30 scores

A. Cohort 1

Scales	Baseline		Month 3		Discon		p-value
	Mean Median	StDev Range	Mean Median	StDev Range	Mean Median	StDev Range	
GHS							
Physical functioning							
Role functioning							
Emotional functioning							
Cognitive functioning							
Social functioning							
Fatigue							
Nausea and vomiting							
Pain							
Dyspnea							
Insomnia							
Appetite loss							
Constipation							
Diarrhea							
Financial difficulties							

B. Cohort 2

Scales	Baseline		Month 3		Discon		p-value
	Mean Median	StDev Range	Mean Median	StDev Range	Mean Median	StDev Range	
GHS							
Physical functioning							
Role functioning							
Emotional functioning							
Cognitive functioning							
Social functioning							
Fatigue							
Nausea and vomiting							
Pain							
Dyspnea							
Insomnia							
Appetite loss							
Constipation							
Diarrhea							
Financial difficulties							

Table 6. Summary of Adverse Events (AEs)*

	Cohort 1		Cohort 2	
	No. of Events	No. of Subjects [†]	No. of Events	No. of Subjects [†]
Total Number of AEs	##	##	##	##
Severity				
Grade 1	## (##.##%)	##	## (##.##%)	##
Grade 2				
Grade 3				
Grade 4				
Grade 5				
Missing				
Relation to study medication				
Definitely				
Probably				
Possibly				
Unlikely				
Not related				
Not assessable				
Missing				
AE expectedness				
Expected				
Unexpected				
Missing				
AE classification				
Not serious				
Serious				

* Data are presented as frequency (percentage) for categorical variables

[†] A patient may have more than one AEs.

Table 7. Severity of AEs*

A. Cohort 1

	Grade					Total
	1	2	3	4	5	
MedDRA 1						
MedDRA 2						
MedDRA 3						
MedDRA 4						
MedDRA 5						
Total†						

B. Cohort 2

	Grade					Total
	1	2	3	4	5	
MedDRA 1						
MedDRA 2						
MedDRA 3						
MedDRA 4						
MedDRA 5						
Total†						

*Data are presented as number of AEs (number of patients having AEs); A patient may have more than one AE in any category and a patient is only shown once in each category, but may have AEs in more than one category.

†Each patient is counted only once in the total for the number of patients

Table 8. Relationship of AEs with study medication*

A. Cohort 1

	Relationship with study medication	
	Possible/ Probable/ Definite	Unassessable/ Unrelated/ Unlikely
MedDRA 1		
MedDRA 2		
MedDRA 3		
MedDRA 4		
MedDRA 5		
Total†		

B. Cohort 2

	Relationship with study medication	
	Possible/ Probable/ Definite	Unassessable/ Unrelated/ Unlikely
MedDRA 1		
MedDRA 2		
MedDRA 3		
MedDRA 4		
MedDRA 5		
Total†		

*Data are presented as number of AEs (number of patients having AEs); A patient may have more than one AE in any category and a patient is only shown once in each category, but may have AEs in more than one category.

†Each patient is counted only once in the total for the number of patients.

Table 9. Summary of Severe Adverse Events (SAEs)*

	Cohort 1		Cohort 2	
	No. of Events	No. of Subjects [†]	No. of Events	No. of Subjects [†]
Total Number of SAEs	##	##	##	##
Reasons for SAE				
Resulted in death	## (##.##%)	##	## (##.##%)	##
Inpatient hospitalisation/ prolongation of existing				
Severity				
Mild				
Moderate				
Severe				
Life threatening				
Death				
Causal relationship to study drug				
Definitely				
Probably				
Possibly				
Unlikely				
Not related				
Outcome				
Resolved				
Persisting				
Fatal				

* Data are presented as frequency (percentage) for categorical variables

[†] A patient may have more than one SAEs.

Table 10. Severity of SAEs*

A. Cohort 1

	Severity					Total
	Results in death	Life threatening	Requires hospitalisation or prolongation of hospitalisation	Results in persistent or significant disability	Medically significant	
MedDRA 1						
MedDRA 2						
MedDRA 3						
MedDRA 4						
MedDRA 5						
Total†						

B. Cohort 2

	Severity					Total
	Results in death	Life threatening	Requires hospitalisation or prolongation of hospitalisation	Results in persistent or significant disability	Medically significant	
MedDRA 1						
MedDRA 2						
MedDRA 3						
MedDRA 4						
MedDRA 5						
Total†						

*Data are presented as number of SAEs (number of patients having SAEs); A patient may have more than one SAE in any category and a patient is only shown once in each category, but may have SAEs in more than one category.

†Each patient is counted only once in the total for the number of patients

Table 11. Relationship of SAEs with study medication*

A. Cohort 1

	Relationship with study medication	
	Possible/ Probable/ Definite	Unassessable/ Unrelated/ Unlikely
MedDRA 1		
MedDRA 2		
MedDRA 3		
MedDRA 4		
MedDRA 5		
Total†		

B. Cohort 2

	Relationship with study medication	
	Possible/ Probable/ Definite	Unassessable/ Unrelated/ Unlikely
MedDRA 1		
MedDRA 2		
MedDRA 3		
MedDRA 4		
MedDRA 5		
Total†		

*Data are presented as number of SAEs (number of patients having SAEs); A patient may have more than one SAE in any category and a patient is only shown once in each category, but may have SAEs in more than one category.

†Each patient is counted only once in the total for the number of patients.

Table 12. Haematology Data*

	Baseline n=	Visit 1 n=	Visit 2 n=	Visit 3 n=	Visit 4 n=	Visit 5 n=	Visit 6 n=	Visit 7 n=
Haemoglobin (g/dl)								
Haematocrit (g/dl)								
RBC ($10^{12}/L$)								
Platelets ($10^9/l$)								
WBC ($10^9/l$)								
Neutrophils ($10^9/l$)								
Lymphocytes ($10^9/l$)								
Monocytes ($10^9/l$)								
Eosinophils ($10^9/l$)								
Basophils ($10^9/l$)								
Coagulation (PT/INR)								
Coagulation (aPTT)								

*Values are presented as median (IQR).

Table 13. Biochemistry Data*

	Baseline n=	Visit 1 n=	Visit 2 n=	Visit 3 n=	Visit 4 n=	Visit 5 n=	Visit 6 n=	Visit 7 n=
Sodium (mmol/L)								
Chloride (mmol/L)								
Bicarbonate (mmol/L)								
Uric acid (μmol/L)								
Blood urea (mmol/L)								
Alanine aminotransferase (ALT) (U/L)								
Aspartate amino- transferase (AST) (U/L)								
Alkaline phosphatase (ALP) (U/L)								
Total bilirubin (μmol/L)								
Direct bilirubin (μmol/L)								
Lactate dehydrogenase (LDH)								
Total protein								
Calcium (mmol/L)								
Potassium (mmol/L)								
Magnesium (mmol/L)								
Glucose (mmol/L)								
Phosphate (mmol/L)								
Albumin (g/L)								

Baseline n=	Visit 1 n=	Visit 2 n=	Visit 3 n=	Visit 4 n=	Visit 5 n=	Visit 6 n=	Visit 7 n=
Free triiodothyronine 3 (FT3) (pmol/L)							
Free triiodothyronine 4 (FT4) (pmol/L)							
Thyroid Stimulating Hormone (TSH) (mIU/L)							

*Values are presented as median (IQR).

Table 14. Urinalysis Data

	Baseline n=	Visit 1 n=	Visit 2 n=	Visit 3 n=	Visit 4 n=	Visit 5 n=	Visit 6 n=	Visit 7 n=
Glucose	0 + ++ +++ >+++							
Total Protein	0 + ++ +++ >+++							
Blood	0 + ++ +++ >+++							
White Blood Cells	0 + ++ +++ >+++							
Dipstick	Normal Abnormal - not clinically significant Abnormal - clinically significant							

Table 15. Other Safety Assessments

	Baseline n=	Visit 1 n=	Visit 2 n=	Visit 3 n=	Visit 4 n=	Visit 5 n=	Visit 6 n=	Visit 7 n=	Visit 8 n=	Visit 9 n=	Visit 10 n=	Visit 11 n=
Vital Signs												
Pulse					Median [IQR]							
SBP					Median [IQR]							
DBP					Median [IQR]							
Temperature					Median [IQR]							
Respiratory rate					Median [IQR]							
ECG												
Normal					n (%)							
Abnormal – not clinically significant					n (%)							
Abnormal – clinically significant					n (%)							
BMI												
Raw value					Median [IQR]							
Obese					n (%)							
Normal					n (%)							
Undernourished					n (%)							
ECOG												
0					n (%)							
1					n (%)							
2					n (%)							
3					n (%)							
4					n (%)							
5					n (%)							
Pregnancy					n (%)							
Lactation					n (%)							

Table 16. Treatment Compliance summary

	Cohort 1	Cohort 2
Number of patients with delayed treatments		
Percentage of patients with delayed treatments		
Mean number of delayed treatments among patients		
Mean percentage of delayed treatments among patients		

6.12 Figures to present

Figure 1. Kaplan-Meier curve showing overall survival for the whole cohort.

Figure 2. Kaplan-Meier curve showing progression-free survival for the whole cohort.

Figure 3. Distribution of tumour size change proportion at different follow-up periods

Figure 4. Waterfall plot base on best overall response by patient and maximal percentage of tumour reduction

Figure 5. EORTC QLQ-C30 Profile Plots at Different Visits

References

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