The ROYAL MARSDEN
NHS Foundation Trust

PEAR

Phase I dose Escalation of pAlliative Radiotherapy with anti-PD1 antibody pembrolizumab in thoracic tumours

Statistical Analysis Plan

Version 3.1, 21/05/2024

Protocol Title and CCR number:	PEAR - Phase I dose Escalation of pAlliative Radiotherapy with anti-PD1 antibody pembrolizumab in thoracic tumours (CCR 4282)
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Sponsor:	The Royal Marsden NHS Foundation Trust
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Contents

List of Abbreviations

Abbreviation or special term	*Explanation*
AE	Adverse events
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computerised tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
ESMO	European Society for Medical Oncology
Gy	Gray
ICR	Institute of Cancer Research
irAE	Immune-related adverse events
MTD	Maximum tolerated dose
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death ligand-1
PFS	Progression free survival
PPSRC	Pembrolizumab Project Safety Review Committee
PR	Partial response
RECIST	Response evaluation criteria in solid tumours
RT	RT
SD	Stable disease
SRC	Safety Review Committee
TIL	Tumour infiltrating lymphocytes

Amendment history

Date	Version	Timing in relation to analysis	Brief description of change	Justification for change
02.05.2018	1.0	First draft, prior to an abstract submission	N/A	N/A
16.11.2018	2.0	Planned safety review meeting held in November 2018	Analysis of response rates for dose level 1 and dose level 2 in dose escalation phase (Part A)	Updated SAP version 1 to include analysis of response rates for dose level 1 and dose level 2 in Part A for the planned safety review meeting held in November 2018
11.01.2023	3.0	Final analysis	To reflect changes since protocol v3.0 and use SAP template version 5.1	Changes as per protocol amendments
16.05.2024	3.1 - Addendum	Ad-hoc analysis post final study report	To add exploratory ad-hoc endpoint to section 7.	Additional analysis request from chief investigator.

1. Trial Summary

This is a single centre non-randomised phase 1b open label trial of pembrolizumab given in combination with RT and will recruit up to 36 patients with lung cancer undergoing palliative RT to the lung.

Two dose levels of pembrolizumab (100mg & 200mg) will be studied to ensure tolerability of combining therapy with RT with the option after the first dose level to de-escalate (50mg) if DLTs are seen at dose level 1.

The study will be conducted in two parts; initially as a dose escalation phase (Part A), followed by an expansion stage (Part B). The expansion cohort will be with the higher dose radiotherapy group unless DLT was encountered in Part A. Dose of pembrolizumab will be the MTD.

In dose escalation (part A), patients will be recruited to a dose-escalation protocol of pembrolizumab in a 3+3 design in the two RT dose cohorts (high/low), each with 2 pembrolizumab dose levels (dose level 1 (100mg)) & dose level 2 (200mg)), and the first 3 patients will be recruited at dose level 1 (100mg) in each cohort.

Patients will be allocated to either low dose (20Gy in 5 fractions) or high dose (36Gy in 12 fractions) RT as standard of care and will be registered to receive pembrolizumab, in combination with their treatment. Both the low dose and high dose RT arms will run simultaneously. Two weeks after the completion of RT, if the patient is to continue on treatment, they will enter the maintenance phase and will receive 200mg of pembrolizumab alone every 3 weeks until disease progression, unacceptable toxicities, discontinuation for other reasons or withdrawal from the study.

The rate of entry and escalation to the next dose level will depend upon assessment of the toxicity profile of patients entered at the previous level. The DLT will be for a period of 2 months following the final fraction of RT (at the beginning of cycle 4), using CTCAE v4.0 for acute toxicity by the PPSRC before recruitment to the next dose level can begin.

All dose escalation and stopping rules used will be identical in both the low dose and high dose cohorts, respectively. However, the low and high dose RT arms are independent of each other running in parallel, the outcome from one is not expected to affect the decision-making process in the other. Dose expansion will be in the high dose RT arm, as the clinical data reviewed supports a higher dose being more immunogenic. However, the dose per fraction is higher in the low dose RT arm (4Gy/fraction) versus high dose RT arm (3Gy/fraction), and therefore the response rates during the dose escalation phase will have to be carefully considered by the PPSRC before confirming dose expansion. If in the event the high dose RT arm proves to be too toxic during dose escalation i.e. 2 or more DLTs in dose level -1, the dose expansion will occur, at the MTD defined, in the low dose RT arm only assuming it has not occurred at dose level -1 too.

2. Trial objectives

Primary objective

1. To determine the safety and tolerability of pembrolizumab in combination with RT to the lung
2. To describe the safety profile of pembrolizumab in combination with RT to the lung

Secondary objectives

1. To assess overall PFS and OS
2. To evaluate PFS and OS against PD-L1 expression
3. To assess overall response rates as per RECIST v1.1 and differential response rates in squamous versus non-squamous histological subtypes
4. To assess oesophagitis rates in this population

Exploratory objectives

1. To assess for evidence of abscopal response by individual lesion response (CR/PR/PD/SD) determined by RECIST v1.1
2. To identify biomarkers that correlate with immunological response to therapy

3. Trial Methods

3.1 Trial design

This is a single centre non-randomised phase 1b open label trial of pembrolizumab given in combination with RT for patients with lung cancer undergoing palliative RT to the lung. The study will be conducted in two parts; initially as a dose escalation stage (Part A), followed by an expansion stage (Part B). Patients will be allocated to either low or high dose RT as standard of care and will be registered to receive pembrolizumab, in combination with their treatment. The initial safety phase of the study has a 3+3 dose escalation design.

3.2 Randomisation

This is a non-randomised phase 1b open label trial.

3.3 Sample Size

This is a 3+3 design in two RT dose cohorts (high & low), each with two pembrolizumab dose levels (1 & 2) and the first 3 patients are recruited at dose level 1 (100mg) in each cohort. There will be a minimum of 6 and maximum of 12 patients in each cohort. This will give a total minimum of 12 and a maximum of 24 patients in the dose escalation phase. The expansion phase will then include an additional 12 patients receiving high dose RT and the recommended dose determined in the dose escalation phase. A maximum of 36 patients in total may be recruited depending on the dose levels tolerated.

3.4 Framework

This study is designed to assess that pembrolizumab can be safely administered in patients receiving palliative courses of RT to the lung.

3.5 Statistical Interim Analysis and stopping guidance

There is no formal interim analysis planned. However, in the dose escalation phase, after each dose level, safety data will be summarised for a Safety Review Committee (SRC) to evaluate the safety and tolerability of pembrolizumab in combination with palliative RT to the lung to decide the next dose level. The SRC will review and assess all available safety data once each dose cohort has completed the DLT period, to decide on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into consideration. A minimum of 3 patients or a maximum of 6 patients will be required per RT arm at each dose level.

No formal statistical method will be used for stopping the trial early. Stopping due to safety will be based on the recommendations from the SRC.

There are two conditions that will be criteria for the termination of the study. For this study a DLT would be regarded as any event of pneumonitis at ≥ grade 2. A 25% rate of ≥ grade 2 pneumonitis or more will be considered unacceptable.

In addition, if 1 patient with oesophagitis of ≥ grade 4 or 2 patients of myelitis of ≥ grade 2 occurred at dose levels -1 (50mg) and/or dose level 1 (100mg), these would be considered events on which the study would be terminated. However, if these adverse events occurred at dose level 2 (200mg), they would lead to dose de-escalation and cohort expansion.

3.6 Timing of Final Analysis

Final analyses can be performed once the last patient has completed one year of follow-up following the last dose of pembrolizumab or discontinued the study for other reasons.

Part A (dose escalation phase) can be analysed and reported after the last patient in each RT dose cohort (high and low), has completed DLT evaluation which will be for a period of 2 months following the final fraction of RT (i.e. at the beginning of cycle 4), using CTCAE v4.0 for acute toxicity. This includes the primary endpoint. For the primary end point, the results of each dosing level will be reviewed by the SRC before recruitment to the next dose level can begin and once the MTD has been determined the trial enters the expansion phase.

Secondary and exploratory endpoints can be analysed and reported after all patients have had at least one year of follow-up after the last dose of pembrolizumab or discontinued the study for other reasons.

3.7 Timing of outcome assessment

The expected study procedures and allowable visit windows are defined in the protocol. Patients will be followed up at regular intervals for PFS, OS and response.

4. Statistical Principles

4.1 Confidence Intervals and P values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided.

4.2 Adherence and protocol deviations

Details on treatment compliance (dose delays, reductions, interruptions, modifications) will be provided. Protocol deviations will be reported as recorded on the relevant case report form (CRF). The number (and percentage) of patients with protocol deviations will be summarised along with details of type of deviation provided. Any protocol deviations due to COVID-19 will also be summarised.

4.3 Analysis populations

Evaluable population: Will consist of all eligible patients who received at least one dose of Pembrolizumab and at least one fraction of radiotherapy. This population will be included for analysis.

5. Trial Population

5.1 Eligibility

The trial inclusion and exclusion criteria are specified in the protocol. The number of ineligible patients registered, if any, will be reported, with reasons for ineligibility.

5.2 Recruitment

A CONSORT flow diagram comprising the number of people screened, eligible, consented, received allocated treatment, withdrawing/lost to follow-up will be used to report patients' participation on the study.

5.3 Withdrawal/ Follow up – level of withdrawal

The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised.

5.4 Baseline patient characteristics

Baseline characteristics will be summarised descriptively for all eligible patients, both overall and separately by RT arm (high dose/ low dose).

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD and range if data are normal and median, IQR and range if data are skewed. Minimum and maximum values will also be presented for continuous data.

Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

6. Analysis

6.1 Outcome definitions

Primary outcome

1. To establish the MTD that can be safely combined with RT to the lung in the absence of DLT (Part A)
2. To measure the toxicity rate of DLTs assessed two months after the last fraction of RT has been administered (Part A)

DLT period is defined as the interval of 2 months following the final fraction of RT (at the beginning of cycle 4), using CTCAE v4.0 for acute toxicity. For this study a DLT would be regarded as any event of pneumonitis at ≥ grade 2.
Tolerability will be assessed by documenting all AEs and serious adverse events (SAEs). This is part of the safety endpoint to ensure that the combination regimen is tolerable and that there are no unexpected AEs when combining pembrolizumab with RT.

Secondary outcomes

1. To measure the PFS and OS at 6 months and 1 year (Part A and Part B)
2. To measure PFS and OS in PD-L1 strong population at 6 months and 1 year (Part A and Part B)
3. To measure the duration of clinical benefit (CR/PR/SD) using RECIST v1.1 including the different response rates between squamous and non-squamous histological sub-types at 6 months and 1 year (Part A and Part B)

4. To assess oesophagitis rates assessed at two months after the last fraction of RT has been administered (Part A and Part B)

Progression-free survival (PFS) will be measured from the start of RT until radiological or clinical evidence of progression or else death from any cause. Any progression free surviving patients will be censored at last follow-up date.

Overall survival (OS) will be measured from the start of RT until death from any cause; any surviving patients will be censored at last follow-up date.

Duration of clinical benefit will be assessed using duration of response (DOR) by RECIST v1.1. This will be measured from the date of first response (defined as CR or PR or SD) until evidence of progression or else death. Any patients not experiencing a response will not be included, and any progression free surviving patients will be censored at last follow-up date.

Response rates will be assessed by overall response rate (ORR) defined as (CR or PR) and disease control rate (DCR) defined as (CR or PR or SD), assessed using RECIST v1.1.

PD-L1 staining is referred to as tumour proportion score, reported as a percentage from 0–100%. It is classed as weakly positive (1 – 49%); strongly positive if >/=50%; and negative if <1%. A PDL1 strong population will be those who have a tumour proportion score of >/=50%.

Exploratory Outcomes

1. To evaluate the abscopal effect of pembrolizumab and RT measured by individual lesion response (CR/PR/PD/SD) determined by RECIST v1.1 (Part A and Part B)
2. Characterisation of TILs and tumour antigens in the tumour biopsies. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2 (Part A and Part B)
3. Analysis of research blood samples for ctDNA (Part A and Part B)

Abscopal response will only be evaluated on the scans acquired at cycle 2 and cycle 5. Any target lesion not irradiated at cycle 2 or cycle 5 that has gone into complete response (CR) may be deemed as an abscopal response i.e. disappearance of any lesions outside of the radiotherapy field.

Biomarker outcomes for translational research (exploratory outcomes 2 and 3) will be analysed by the ICR lab.

6.2 Analysis Methods

Primary outcome analysis

The maximum tolerated dose (MTD) that can be safely combined with RT in the absence of dose limiting toxicity (DLT) will be clearly stated.

The toxicity rate will be stated as the proportion of patients who have had a DLT calculated with a 95% confidence interval. Other toxicities will be tabulated with the proportions and frequencies of all grades described.

Tolerability will be assessed by recording toxicity. Acute and late toxicity data will be tabulated by grade.

Number and proportion of toxicity grades 1-4 and grade 3-4 will be reported. Toxicity data should include AEs, laboratory values, spirometry data, vital signs and irAEs.

Toxicity rates will be reported for both RT arms and by dose level, respectively.

Secondary outcomes analysis

Median PFS, OS and DOR will be calculated using Kaplan-Meier methods giving associated 95% confidence intervals, respectively. Survival rates at 6 months and 1 year for patients overall will be reported together with 95% confidence intervals. There will be no statistical comparison between RT arms or between dose levels.

PFS and OS will also be assessed for PD-L1 strong population. The effect of PD-L1 expression on survival will be assessed for PD-L1 strong and non-strong (>/=50% vs. <50%). DOR will also be assessed in the squamous and non-squamous cell histological sub-types. Any survival differences between groups will be compared using a log rank test. Survival rates at 6 months and 1 year for patients overall will be reported together with 95% confidence intervals. There will be no statistical comparison between RT arms or between dose levels.

Response rates (ORR and DCR) assessed for best overall response, will be calculated as proportions and compared by RT arms (high/low), in the squamous and non-squamous cell histological sub-types, and the PD-L1 strong and non-strong (>/=50% vs. <50%), respectively, giving associated 95% confidence intervals. Any difference in response rates (for ORR and for DCR) between responders and non-responders for these groups will be compared using a chi squared or Fisher's exact test as appropriate.

Oesophagitis rates will be tabulated by CTCAE v4.0 grade. Proportion of patients with oesophagitis grade 2+ will be summarised with associated 95% confidence interval by RT arm (high/low), and by dose level (100mg/200mg) per RT arm.

Exploratory outcomes analysis

The abscopal response rate will be calculated as those patients who have an abscopal response at either cycle 2 (week 9 ±3 weeks) or cycle 5 (week 18 ±3 weeks) scans. This will be presented as a proportion with

associated 95% confidence interval overall, by RT arm (high/low), and by dose level (100mg/200mg) in each RT arm.

Biomarker outcomes for translational research will be analysed by the ICR lab.

2. Adjustment for covariates

Not applicable.

3. Distributional Assumptions

Not applicable.

4. Sensitivity analyses

Not applicable.

5. Subgroup analyses

Not applicable.

6. Missing data

Not applicable.

7. Exploratory/ additional analyses (e.g. CACE analysis)

The following exploratory ad-hoc endpoint will be added to v1.3 of the study final report:

- To measure PFS and OS by the baseline neutrophils/lymphocytes ratio at 6 months and 1 year (Part A and Part B)

The effect of the neutrophils/lymphocytes ratio at baseline on survival will be assessed using methods of Kaplan Meir for each subgroup split into two groups by the median cut-off. Any survival differences between groups will be compared using median survival with 95% confidence interval and a log rank test. Survival rates at 6 months and 1 year for patients by group and overall will be reported together with 95% confidence intervals. There will be no statistical comparison between RT arms or between dose levels.

8. Safety

Toxicities will be assessed for safety as in the primary outcome analysis.

7. Statistical Packages

The analysis will be carried out using Stata version 17 or subsequent versions.

8. References

None.

9. Data Management & Central Statistical Monitoring Plan

This SAP was drafted in line with the Central Statistical Monitoring and Data Management Plans.

10. Appendix

Not applicable.

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Trial Statistician

21.05.2024

Laura Satchwell — Date

Peer Reviewer

Emily Greenlay — Date

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Chief Investigator

21/05/2024

Merina Ahmed — Date